Ümit H. Kartoğlu

It is not an overstatement to say that VVM is one of the most important recent innovations in the area of public health, providing health workers with advisable and dependable means of ensuring that the administered vaccine has not been damaged by heat. Without a VVM, the only reference available at point-of-use is the expiration date. But, if a vaccine has not expired, does this mean it is always safe to use? Vaccines exhibit no visible change with exposure to heat. Before the development of the VVM, health workers had no means of identifying whether vaccine had suffered damage from heat exposure at any point during transportation and/or storage. Nowadays the administration of safe life-saving vaccines is much less a matter of chance. With VVM, health practitioners in the field can focus on delivering an efficient care and treatment service without needing to be concerned about medicine viability.

THE BOOK OF VVM

Yesterday-today-and-tomorrow

Moreover, VVM renders immunization operations much more effective. It allows programmes to exploit the stability of each vaccine to the greatest possible extent, it minimizes distribution costs, and it increases flexibility in the handling of vaccines in the field. Immunization outreach is also boosted with immunization access and coverage increased. VVM helps to pinpoint cold chain problems and facilitates the efficient management of vaccine stocks. Countries adopting VVM-based vaccine management can now make informed decisions with the help of VVM readings. Although VVM was developed as a time and temperature integrator, it also made a significant contribution to the reduction of inadvertent vaccine freezing. VVM facilitated the extension of the cool-chain concept by removing the ice that is a common source of freeze damage. This helped health workers to better understand the heat stability of vaccines and accept the fact that freezing is a greater danger than mild heat exposure. Today, VVM continues to evolve to address emerging needs in immunization programmes. Incorporating a threshold indicator into VVMs (VVM+ or VVM-TI) and integrating VVM into 2D barcodes are the most recent examples of this evolution. This simple, yet elegant tool, which has sold over eight billion units by 2018, has played a decisive role in saving millions of children's lives across the planet.

Extensio et Progressio

THE BOOK OF VVM

Yesterday-today-and-tomorrow

Extensio et Progressio

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THE BOOK OF VVM

Yesterday-today-and-tomorrow

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to Nellie,
the love of my life,
my VVM - always lighter than the outer circle...

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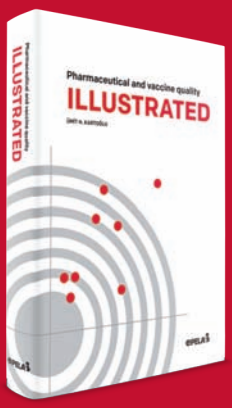

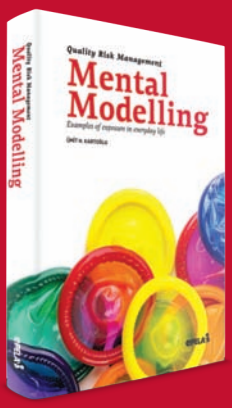

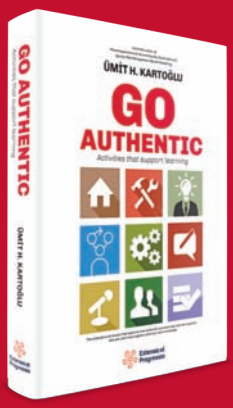

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Foreword

The impact of vaccine vial monitors (VVMs) on global immunization is significant. These simple labels have both prevented unnecessary vaccine wastage and helped to ensure the effectiveness of vaccines that have been delivered to billions of individuals throughout the world. VVMs have also changed the way that vaccines are handled and this has been especially useful in situations where war, environmental disaster, challenging geography, and lack of infrastructure make vaccination difficult. Their availability has facilitated new World Health Organization (WHO) policies allowing opened vials of certain vaccines to be used for more than one day thereby stretching valuable vaccine supplies and allowing a relaxation of the temperatures that vaccines must be kept at thereby extending vaccine outreach.

VVMs were first applied to oral polio vaccine and have been instrumental in the progress made to eradicate polio. More than 8 billion have been distributed to date and they are present on nearly every type of vaccine.

The vision was provided by U.S. scientists who conceived and developed the concept of miniature time temperature indicators for vaccines using solid state polymerization technology and by a WHO consultant who was independently advancing a similar concept. Eventually they all contributed to making their separate visions into one reality. The science was supplied by the chemists at Allied Chemical and Temptime Corporation (previously LifeLines Technology Inc.) who identified and formulated the materials that could react to heat in a similar way to vaccines. PATH, at the time a relatively new non-profit organization with a focus on health technology, brought ingenuity in co-designing the indicators with

end-users and advancing both the original indicators based on Allied Chemical technology and the VVMs of today from Temptime. Back in the 1980s, the type of private-public sector collaboration between Temptime and PATH was a novelty and would not have been possible without core support from the United States Agency for International Development. The false starts were many and numerous as the technology shifted, vaccine suppliers objected, and Temptime nearly dropped out given the delays and complexities. Yet the VVM succeeded due to the perseverance of a core group of champions, WHO's essential convening and policy making role, a committed manufacturer, and a cast of thousands who helped to fund, assess, improve, manufacture, and launch the technology through design trials, country evaluations, laboratory studies, policy formation, procurement specifications, regulatory issues, industry adoption, training, and introduction. This pioneering technology also served as a catalyst to evolve and improve how global immunization stakeholders work together and helped to create a roadmap for the vaccine technologies that followed.

The Book of VVM is a compelling case study of the forty-year history of this technology and the enormous effort it took to bring the VVM to fruition. I have had the privilege of being involved in this global effort for thirty years and of working with Dr. Ümit Kartoğlu during the eighteen years he led the VVM work at WHO. It took dedicated champions to get the VVM to where it is today and Ümit has been one of the most passionate and productive advocates of the technology. He has masterfully harnessed his technical, public health, artistic, training, and communications skills in the effort as is evidenced by this book. Read on for a detailed and colorful account of all things VVM.

Debbie Kristensen
Director of Vaccine Technology, Strategy, and Policy
Medical Devices and Health Technologies
PATH

Behind the pages

We may ask ourselves where humanity might be without some of the greatest inventions that have come to pass. Great ideas have continuously changed the path of human civilization over time with vaccination being widely considered one of the greatest medical achievements of modern civilization. Many commonplace and preventable childhood diseases are now increasingly rare because of vaccines. The concerted human effort to bring the vaccines to the ones who need them at the right time is remarkable.

Just one example of the dedication and self-sacrifice involved was the 1925 'Serum Run' between the settlements of Nenana and Nome in Alaska also known as the Great Race of Mercy. This involved a famously grueling winter expedition across the frozen Alaskan interior using dog-sled relays to take diphtheria antitoxin to the beleaguered township of Nome where an outbreak of diphtheria was threatening around 10,000 local Alaskan natives who had no natural immunity to this lethal disease. The epic journey took 20 mushers and about 150 sled dogs just five and a half days to cover the 1,085 km route. This display of bravery and determination was how the small town of Nome and the communities surrounding it were saved from an incipient epidemic. Balto, the lead sled dog on the final leg into Nome, became the most famous canine celebrity of the era. Balto's statue became a popular tourist attraction both in New York City's Central Park and downtown Anchorage in Alaska.

The vaccine vial monitor (VVM) is one of the most important inventions of the last century; one that has dramatically changed vaccine management practices and continues to shape the cold chain. In 1996, when VVMs started to get to countries with the oral polio vaccine (OPV), I was the health officer for the UNICEF

Shooting the "Five Senses",
Ümit Kıvanç, Gençer Yurttaş and Ümit Kartoğlu in Kalimantan island, Indonesia, 2007

Central Asian Republics and Kazakhstan Area Office. I remember one particularly cold night going to the airport in Almaty at 03.00 am to receive the very first shipment of OPV with VVMs. For years, I was a humble VVM user and advocate in the field. Things started to change when I was hired by the WHO Headquarters 'Access to Technologies' team in 2001 and VVM became one of my prime responsibilities. That was at a time when vaccine manufacturers were dragging their feet about incorporating VVM onto vaccines other than OPV. My brief was to overcome this resistance from the manufacturers, an objective that formed the basis for my plans for the historic 2002 VVM technical consultation meeting.

In 2007, I immensely enjoyed organizing the event to celebrate the 10th year anniversary of VVM introduction. Visiting Niger, Indonesia, and Vietnam for the shooting of the "Five Senses" video is full of cherished moments.

Towards my retirement in August 2018, I conceived the idea of writing this book. I was one of the few people who had witnessed the decades-long programme of VVM development from its birth to its maturity. I had worked with sweat and tears to get VVMs onto all vaccines as well as tirelessly helping vaccine managers and health staff to excel in using the VVMs to their utmost potential. Today, it is a great pleasure to see one of my e-VVM based vaccine management course graduates (2015), Junaidu Adamu Barde from Nigeria, working for the Clinton Health Access Initiative, using the course learning materials to duplicate efforts in his country.

I worked on this book from September 2018 to August 2019. I went through every single published and unpublished work on VVMs, watched all available videos about VVMs and the early contending products, talked to key people, some face to face, others over the phone. I visited the U.S., Albania, Burkina Faso, and Sierra Leone. Unfortunately, there were some people I just could not reach despite all my efforts with email and phone messages. And, although I considered myself highly knowledgeable about VVM, I was simply amazed at the volume of new information I discovered and the knowledge I gained.

I had originally wanted this book to be a concise, structured, globally-relevant manual that provided comprehensive information on a wide scope of issues; in other words, an 'A-Z of VVM'. In the event, it turned out to be more voluminous than I thought. I did not want to restrict myself when there are so many clever, dedicated and selfless individuals that have made this near-miraculous innovation a reality and in doing so contributed to saving, literally, the lives of millions.

So, I am happy that it became a celebration of all the efforts of individuals, organizations, agencies, donors, and manufacturers involved in the development, scaling, applying, advocating for, enforcing, helping health workers to excel in their practice, and using it.

As with my previous books, I have again licensed this work under the Creative Commons (CC) Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0). The book can be reproduced, remixed, tweaked or built upon non-commercially.

I am grateful to Temptime Corporation, and especially to Renaat Van den Hooff and Ted Prusik for sponsoring the creation of this book. I thank Emily Moore for the VVM literature list she put together, it eased my search enormously. I also thank all the individuals I have interviewed for their time and everything they have shared with me. I am thankful to all my colleagues who sent me photographs, and documents. Gençer Yurttaş deserves a special thank you for his immaculate VVM photography. I deeply appreciate Alan Kennedy for his editing work, and Ümran and Gökhan Akaalp's help in developing the book's website. I am grateful to my wife Nellie and daughter Deniz Nala who supported me with love. Deniz Nala was already helping me at the age of 14 measuring VVMs with a spectrodensitometer and entering data into an Excel sheet to calculate optical density differences during a VVM based vaccine management eLearning course.

I never imagined that for something only 0.38 cm^2 in size that I could write a book of 424 pages. This 'little big thing', now reinventing itself with the incorporation of a peak threshold indicator as well as entering the digitized supply chain with the integration of 2D barcodes, never ceases to amaze me.

Ümit H. Kartoğlu, MD, DPH
Collonge-Bellerive
July 2019

Contents

Abbreviations

°C	degree Celsius
°F	degree Fahrenheit
µm	micrometer
$	(U.S.) Dollar
¥	(Japan) Yen
2D	two-dimensional
AD	auto disable
AFRO	Regional Office for Africa (WHO)
AMRO	Regional Office for the Americas (WHO)
ANMAT	National Administration of Drugs, Foods and Medical Devices (Argentina)
AQL	acceptance quality limit
ARICC	African Regional Inter-Agency Coordination Committee
BCG	bacilli Calmette-Guérin (tuberculosis vaccine)
CBV	community-based volunteers
CCL	cold chain logistics
CCM	cold chain monitor (card)
CCSP	Cold Chain Support Package (UNICEF)
CCT	controlled cold temperature
CDC	Centers for Disease Control and Prevention (U.S.)
CFR	Code of Federal Regulations
cm	centimeter
CRT	controlled room temperature

CTC	controlled temperature chain
CVI	Children's Vaccine Initiative
DDL	digital data logger
DFID	Department of International Development (U.K.)
DT	diphtheria tetanus (vaccine)
DTP	diphtheria tetanus pertussis (vaccine)
EEFO	earliest-expiry first-out
EPA	Environmental Protection Agency (U.S.)
EPELA	Extentio et Progressio, Authentic eLearning
EPI	Expanded Programme on Immunization
EVM	effective vaccine management
EVSM	effective vaccine store management (initiative)
FIFO	first-in first-out
Gavi	Gavi the Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunization)
GLO	Global Learning Opportunities
GMP	good manufacturing practices
GMT	geometric mean titre
GPV	Global Programme for Vaccines and Immunization
GSK	GlaxoSmithKline
HbSAg	surface antigen of the hepatitis B virus
HepB	hepatitis B (vaccine)
Hib	*Haemophilus influenza* type b (vaccine)
HPV	human papilloma vaccine
ICCPE	The International Commission for the Certification of Poliomyelitis Eradication
IDRC	International Development Research Centre (Canada)
IFPMA	International Federation of Pharmaceutical Manufacturers Association
IPAC	Immunization Practices Advisory Committee (WHO)
ISO	International Organization for Standardization
JICA	Japan International Cooperation Agency
JICS	Japan International Cooperation System
LMIS	logistics management and information system
m	meter
MCH	mother and child health
MD	medical doctor
MDVP	multi-dose vial policy
MKT	mean kinetic temperature

MMR	mumps-measles-rubella (vaccine)
MOH	Ministry of Health
MR	measles-rubella (vaccine)
MSF	Médecins Sans Frontières (Doctors Without Borders)
NID	national immunization day
NIOSH	The National Institute for Occupational Safety and Health (CDC)
NIST	National Institute of Standards and Technology (U.S.)
OAS	Organization of American States
OCC	out of cold chain
OD	optical density
OPV	oral polio vaccine
PCM	phase contrast microscopy
PDA	Parenteral Drug Association
PDF	portable document format
PIACT	Program for Introduction and Adaptation of Contraceptive Technology
PhD	Philosophiae Doctor (doctor of philosophy)
PQS	Performance, Quality and Safety
Q&A	questions and answers
QA	quality assurance
QC	quality control
R&D	research and development
PTS	p-toluene sulfonate
RFP	request for proposal
SAGE	Strategic Advisory Group of Experts (WHO)
SD	Supply Division (UNICEF)
SEM	scanning electron microscopy
SII	Serum Institute of India
SOP	standard operating procedure
TACRO	The Americas and Caribbean Regional Office (UNICEF)
TAG	Technical Advisory Group
TCSA	Toxic Substances Control Act (U.S.)
Td	tetanus toxoid and diphtheria (reduced component) vaccine
TechNet	The Technical Network for Strengthening Immunization Services
TI	threshold indicator
TIP	Technology Introduction Panel (UNICEF)
TLAC	Technologies and Logistics Advisory Committee (WHO)
TT	tetanus toxoid (vaccine)
TTI	time-temperature integrator

TTSPP	time and temperature sensitive pharmaceutical product
UID	unique identification number
U.K.	United Kingdom
UN	United Nations
UNET	United Nations Eastern Team
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
U.S.	United States
USA	United States of America
USAID	United States Agency for International Development
USD	United States dollar
USP	United States Pharmacopoeia
VAR	vaccine arrival report
VFC	Vaccines for Children (programme)
VM	vaccine management
VMTC	Vaccine Management Training Cluster (WHO)
VSQ	Vaccine Supply and Quality (unit)
VVM	vaccine vial monitor
VVM+	combined vaccine vial monitor and peak threshold indicator (Also called VVM-TI)
WIIFM	what's in it for me
WHO	World Health Organization
YF	yellow fever (vaccine)

Glossary

The *italic* references in parenthesis indicate the original source of the definition. Author's own or modified definitions do not have such indications.

Accelerated stability studies: Studies designed to determine the rate of change of vaccine properties over time as a consequence of the exposure to temperatures higher than those recommended for storage. These studies may provide useful support data for establishing the shelf-life or release specifications but should not be used to forecast real-time, real-condition stability of a vaccine. They could also provide preliminary information on the vaccine stability at early developmental stages and assist in assessing the stability profile of a vaccine after manufacturing changes. *(WHO)*

Accelerated testing: Studies designed to increase the rate of chemical degradation and physical change of an API or FPP by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. *(WHO)*

Acceptable temperature range (for refrigerators): The acceptable temperature range for storing vaccine is +2°C to +8°C. However, WHO PQS prequalification programme indicates that transient excursions outside this

range will be tolerated, within the following limits:

No excursion must exceed +20°C.
No excursion must reach 0°C.

The cumulative effect of any excursions within the above range is assessed over the five-day period of the day/night test. For this test, the calculated mean kinetic temperature (MKT) must remain within the range +2°C to +8°C when the default activation energy is set at 83,144 kJ per mol. using the recorded temperature data, an MKT figure is calculated for each sensor. The worst-case result determines the outcome of the test. Excursions in other tests are noted and must not exceed the defined upper and lower limits. *(WHO)*

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of test results. *(ICH Q6A)*

Adjuvant: Substance that is intended to enhance relevant immune response and subsequent clinical efficacy of the vaccine, but does not in itself confers immunity. Adjuvants help activate the immune system, allowing the antigens - pathogen components that elicit an immune response - in vaccines to stimulate a response that leads to long-term protection. Most common adjuvants used in vaccines are aluminum hydroxide and aluminum phosphate. *(WHO)*

Advance shipping notice: A notification of pending deliveries, similar to a packing list, usually sent in an electronic format. It provides information to the destination's receiving operations well in advance of delivery, and tends to impact logistics in reducing receiving cost, confirming accuracy and bringing flexibility. *(WHO)*

Antigen: Fragments or safe forms of pathogens that are used in vaccines, substances capable of stimulating an immunological response, such as the formation of antibodies. They may be proteins, polysaccharides, or complex lipids e.g., bacterial walls, the surface of erythrocytes, the protein capsule of viruses, the exotoxins and endotoxins of bacteria. The word "immunogens" reflects the fact that vaccines cause immune responses, not disease. Antigens responsible for initiating allergic reactions are called allergens.

Batch: A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval. *(ICH Q7)*

Batch number (or lot number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. *(ICH Q7)*

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. *(ICH Q7)*

Chemical indicators: (also called markers or phase-change indicators), are generally impregnated onto a paperboard substrate. These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. Chemical temperature threshold indicators are irreversible and are suitable for high or low temperatures. Temperature threshold indicators show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature. *(WHO)*

Cold: The condition or subjective perception of having low temperature. Though some define cold as the "absence of heat" it is not fully correct since temperature relates to the thermal energy held by an object, which is the kinetic energy of the random motion of particle constituents of the object, an object will have less thermal energy when it is colder. Absence of heat is only possible at the "absolute zero" point at -273.15°C (zero kelvin) where all motion of the particles are ceased and completely at a resting state.

Cold chain: The entire chain of storage facilities and transportation links through which supplies move from manufacturer to consumer, including port facilities, the primary store, intermediate stores, all service delivery points, equipment and transport vehicles. *(WHO)*

Cold life: Cold life is measured from the moment when the container lid is closed until the temperature of the warmest point in the vaccine storage compartment first reaches +10°C, at a constant ambient temperature of +43°C. Cold life applies when fully frozen water-packs are used as the coolant; these will continue to be used for transporting OPV and single antigen freeze-dried (lyophilized) vaccines. *(WHO)*

Cold room: A purpose made insulated enclosure fitted with refrigeration equipment which maintains a set temperature above 0°C. *(WHO)*

Cold store: A facility where the cold room/freezer room or other refrigeration equipment are located, including a packaging area. *(WHO)*

Combined vaccine: A vaccine that consists of two or more antigens, combined by the manufacturer at the final formulation stage or mixed immediately before administration. Such vaccines are intended to protect against either more than one disease, or against one disease caused by different strains or serotypes of the same organism. *(WHO)*

Conjugated vaccine: A vaccine produced by covalently binding an antigen to a carrier protein with the intention of improving the immunogenicity of the attached antigen. This technique is most often applied to bacterial polysaccharides for the prevention of invasive bacterial disease.

Cool: Fairly low temperature.

Cool life: Cool life with cool water-packs at +5°C: Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the vaccine storage compartment first reaches +20°C, at a constant ambient temperature of +43°C. Cool life applies when cool water-packs are used. *(WHO)*

Cool life test: The empty passive container is stabilized at +43.0°C and loaded with cool *water-packs* which have been stabilized at + 5.0°C for a minimum of 24 hours. Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the storage compartment first reaches +20.0°C, at a constant ambient temperature of +43.0°C. *(WHO)*

Cool water-pack: A water-pack cooled to a temperature of between +2.0°C and +8°C before use. *(WHO)*

The only way to eliminate the freezing risk entirely is to transport liquid vaccines, other than OPV, in cold boxes lined with cool water-packs which have been precooled in a refrigerator to a temperature of +2°C to +8°C. Where it is essential to transport OPV, liquid and freeze-dried vaccines in a single carrier, experiments have shown that cool water-packs may safely be used provided the cool life of the carrier is not exceeded. Changing over to the use of cool water-packs involves significant changes in practice. In addition, there are equipment implications because additional refrigerators will be needed at primary and sub-national level to cool the water-packs in bulk.

Coolant: Ice, water, water-based gel, phase-change material, dry ice, or other substance, typically encapsulated in a rigid or flexible plastic container, used to maintain a predefined temperature range inside a passive container during transport operations. *(WHO)*

Cooling: The process of removing heat from a system by exposing it to an environment (or another system) that is at lower temperature. Cooling occurs through the transfer of thermal energy through radiation, convection and conduction.

Diluent: A liquid used to reconstitute lyophilized (freeze-dried) vaccines for administration. Diluents are not just for dissolving vaccines, they are designed to meet an individual vaccine's specific requirements in terms of volume, sterility, pH and chemical balance. Certain vaccine diluents include adjuvants and/or some antigens that are components of the final vaccine. For example, the diluent for Meningococcal A conjugate vaccine lyophilized (MenAfriVac) from Serum Institute of India Ltd., contains aluminium phosphate as adjuvant and thiomersal as preservative.

Diluents are not interchangeable. Each lyophilized vaccine must be reconstituted with its own diluent that is provided together with the vaccine. Using the wrong diluent, substituting normal saline, or using sterile water makes the vaccine ineffective and less able to provide protection against disease. Fatal AEFI cases have been reported due to incorrectly use of medications for reconstitution.

Earliest expiry first out (EEFO): Material requirements are serviced in the order of items with the earlier date of consumption regardless of the date of entry or acquisition. FEFO (first expiry, first out) is also used with the same meaning, however, since it reminds FIFO (first in, first out), to prevent any confusion, EEFO is the preferred acronym. In vaccine vial monitor (VVM) based vaccine management systems, some vaccines with later expiry may be dispatched prior to earlier expiry vaccines if the VVM indicates that the vaccine may become unusable before the next dispatch period.

Eradication (of disease): Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed *(WHO)*. In 1979, a global commission certified that smallpox had been eradicated, and this certification was officially accepted by the 33rd World Health Assembly in 1980. Currently, dracunculiasis and polio are the two eradication programmes sanctioned by WHO.

Expiry date: The date given on the individual container (usually on the label) of a final product up to and including which, the product is expected to remain within specifications, if stored as recommended. It is established for each batch by adding the shelf-life period to the date of manufacture or the starting date of the last potency test.

First in first out (FIFO): Material requirements are serviced in order of items with the date of entry or acquisition. FIFO does not take into account the expiry date of the product; it assumes the expiry date of a latest arrival of a product will have longer expiry date compared to earlier arrival of the same product - which is not the case always. Because of this reason, with the increasingly complex supply provi-

sions, EEFO (earliest expiry, first out) is now the preferred way to manage stocks.

Freeze indicator: Go/no-go type indicator providing a signal only when exposed to temperatures lower than a predetermined threshold temperature. They could be chemical or electronic. Electronic ones have better accuracy compared to its chemical versions. Threshold temperature for freeze indicators are usually set as to 0°C while WHO prequalified models have -0.5°C as threshold to cover all alarms under the 0°C (with +/-0.5°C accuracy).

Gold standard: A diagnostic test or benchmark that is the best available and current preferred method of diagnosing a particular condition (disease). All other methods available and new tests developed to diagnose the same condition should be validated against the gold standard. For example, "phase control microscopy" was used as a "golden test" for validating the "shake test" in diagnosing the freeze damaged aluminium adjuvanted vaccines.

Hazard: The potential source of harm. *(ISO 14971:2000)*

Heat: A form of energy that flows from a warmer to a cooler environment through either a direct (radiation and/or conduction) or an indirect path (convection).

Ice-pack: A water-pack that has been frozen to a temperature between –5.0°C and –25.0°C before use.

Intermediate vaccine store: A secondary store or substore that receives vaccine either from a primary vaccine store or another intermediate vaccine store and distributes vaccine to lower levels. *(WHO)*

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e., all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution. (WHO)*

Label: All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information *(WHO)*:

- the name of the drug product;
- a list of the active ingredients (if applicable, with the International Nonproprietary Names (INNs)), showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, mass or volume;
- the batch number assigned by the manufacturer;
- the expiry date in an uncoded form;
- any special storage conditions or handling precautions that may be necessary;
- the directions for use, and any warnings and precautions that may be necessary;

- the name and address of the manufacturer or the company or person responsible for placing the product on the market.

Written labels on the packaging permit the follow-up of a specific medicinal product by means of the batch number on the labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient with the aim of locating and identifying products that are of potential risk (e.g. blood products, blood-derived products). They also mask the real identity of the medicinal product in clinical studies. *(WHO)*

Last mile: Last mile is the final leg of the supply chain that is between a service point and a customer, as it is often the least efficient link in the supply chain. By definition, it does not need to be a mile. For example, when you order a product from an online distributor located in another country and the product is sent directly to you, this is the last mile. In another example, when you ask your pharmacy for your prescription to be delivered to your home, this is the last mile. In health services, two approaches are used in last mile; active and passive. Immunization programme uses an active approach, when a child does not come for a scheduled vaccination session, the programme follows the person to reach and vaccinate. On the contrary, retail pharmacies use passive approach, they wait for patients to come with their prescriptions.

Long-term stability studies: Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions. For APIs with a proposed re-test period or shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed re-test period or shelf-life. *(WHO)*

Mean kinetic temperature (MKT): A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation. *(ICH Q1A/R2)*

Optical density (OD): The degree to which a refractive medium retards transmitted rays of light.

Potency: The measure of biological activity, using a suitable quantitative biological assay, based on the attribute of the product that is linked to the relevant biological properties. *(WHO)*

Public private partnership: A partnership between the public sector and the private sector for the purpose of delivering a project or a service traditionally provided by the public sector (EU). Some so-called public-private partnerships could be more accurately described as public sector programmes with private sector participation (WHO). Some examples of public private partnerships for health include Roll Back Malaria, Safe Injection Global Network, and Stop TB (all of which have secretariats in WHO).

Qualification: Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification. *(WHO)*

Risk: The combination of the probability of occurrence of harm and the severity of that harm *(ISO 14971:2000)*. Also defined as the effect of uncertainty on objectives (ISO 3100).

Shelf-life: The period of time during which a product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch. Shelf-life is used for the final product; storage period is used for the intermediates. *(WHO)*

Shipping indicators: (Electronic) Shipping indicators are single-use devices designed to monitor vaccine temperature during international shipment from the manufacturer to the primary store. Although as a general category, damage indicators including threshold indicators are also considered as shipping indicators, WHO recommends use of 10- or 20-day electronic shipping indicators in each and every shipping carton. These devices serve as a quick reference to help recipient countries determine whether the shipment – or parts of the shipment – have been exposed to temperatures at which vaccines could have been damaged; and help the procurement agency determine when, where, and to what extent temperature limits have been exceeded. *(WHO)*

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufactur-

er and approved by regulatory authorities. *(ICH Q6A)*

Stability: The ability of a product to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf-life. *(WHO)*

Temperature-controlled: Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits. *(WHO)*

Temperature excursion: An event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data. In situations in which cool water-packs are used for vaccine transport, an excursion up to a maximum of +20°C is acceptable. *(WHO)*

Threshold indicator: Indicators providing a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature.

Time-temperature integrators (TTIs): Are generally chemically impregnated onto a pulp or paperboard substrate. Their reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (see *chemical indicators*). The reactions are irreversible - once a color change, color development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state. They change color, or are marked by a hue progression in intensity (generally from light to dark) in response to cumulative changes in temperature, such as heat, at a rate dependent on the Arrhenius equation. A TTI accumulates all of the temperature conditions experienced by the product to which it is affixed. The color development can be customized based on the known stability of the product, and in much the same way that most biologicals and pharmaceuticals degrade when exposed to heat - faster at higher temperatures, and slower at lower temperatures.

Time and temperature sensitive pharmaceutical product (TTSPP): Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended. *(WHO)*

Traceability: The ability to identify and trace the history, distribution, location, and application of products, parts, materials, and services. A trace-

ability system records and follows the trail as products, parts, materials, and services come from suppliers and are processed and ultimately distributed as final products and services. *(ISO 9000:2015)*

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria. *(PDA)*

Introduction: the revolution

"Sometimes it's the simple ideas that make all the difference. Making it super easy for a rural health worker to know whether a vial of vaccine is still effective by scaling up the VVMs has saved hundreds of thousands of lives."
Bill Gates[1]

Stanley Kubrick in his epic science fiction film **2001: A Space Odyssey** explored one of the most fundamental concepts of what it means to be a human, in other words, what distinguishes us from the animals with which we share our planet. In his watershed movie, Kubrick explored the distinguishing qualities of humanity through a genius analysis of three distinct species: Pre-human ape, human, and post-human star-child.

The opening *dawn of man* sequence starts with the sun rising over a mysterious Black Monolith that is radiating ghostly cosmic energy across a prehistoric landscape inhabited by packs of scavenging apes. Somehow triggered by the unnatural artifact one of the hominids gazes at an old bone and, tilting his head from side to side to the triumphant strains of the fanfare from *Thus spoke Zarathustra (Also sprach Zarathustra)* op. 30, picks it up and starts to wield it as a tool to smash other bones. Suddenly realizing the potential of tools, the ape jubilantly throws the bone into the air – the cue for one of the most celebrated fast-forwards in the

1 Quoted from David S & Schifrin D. (2017). *Vaccine vial monitors: "The little big thing": Taking social innovation to scale.* The Stanford Graduate School of Business case study

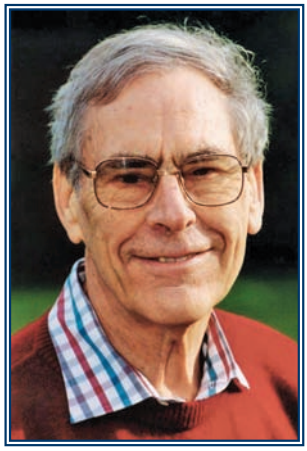
history of cinematography as the bone metamorphoses into a futuristic satellite orbiting the Earth.

Humans are an inventive species. Ever since extant homo sapiens appeared on Earth, they have excelled in dreaming up and creating amazing things that have changed our lives. Although each of us would make a different list of inventions that have had the greatest impact on human life, most would agree on some fairly obvious ones such as the wheel, the printing press, the internal combustion engine, the telephone, the light bulb, penicillin, contraceptives, and the internet. On the other hand, few would include the humble nail or the simple flushing toilet as groundbreaking creations. And yet, without nails, civilizations would crumble and in the absence of sanitary toilet facilities (which over two billion people still don't have), many people continue to die from preventable diseases.

Edward Jenner injecting vaccine into his son by Giulio Monteverde

Vaccination is another invention which might not appear on many people's lists but it is another invention that has saved innumerable lives. Vaccinations have been responsible for completely eradicating deadly smallpox virus from the face of this planet for good, and are today controlling many diseases and extending the human lifespan. The first vaccine for smallpox was developed by Edward Jenner in 1796, followed by Louis Pasteur who produced a rabies vaccine in 1885. It is Pas-

teur who generally gets the credit for making vaccination the major part of medicine that it is today.



Professor David Morley

All vaccines are temperature sensitive. They need to be protected from exposures to heat and cold, and to be kept within a certain temperature range during transportation and storage, the so-called 'cold chain'. However, the vaccine cold chain did not come into existence together with the vaccines. Before the cold chain, vaccines and medicines were shipped without any temperature control. Fortunately, some individuals were blessed with a resourceful imagination. Knowing that chocolate melts at around 30°C, they started to insert small chocolate bars inside the transport boxes – on the basis that if the chocolate melted (or became soft) they could be certain that the contents of the box were exposed to temperatures above 30°C.

Following the establishment by WHO of the Expanded Programme on Immunization (EPI) in 1974 with the goal of making vaccines available to all children, it was to take another two years for a proposal to reach WHO for the development of a vaccine cold chain. It was to be Dr. David Morley of the Institute of Child Health, London, who raised three critical concerns that seemed to be restraining this ambitious EPI project within WHO. The absence of systems to monitor the temperature of thermosensitive vaccines was at the top of Dr. Morley's priority list along with the need for appropriate equipment to store and transport vaccines, and the insufficient number of adequately trained staff to handle the vaccines. He suggested that WHO establish a team within the EPI to address these three critical issues.

The first director of the WHO/EPI, Dr. Rafe Henderson, willingly accepted Dr. Morley's proposal and asked WHO consultants to develop an appropriate strategy paper and plan of action to address the issues raised in Dr. Morley's proposal. John Lloyd was among the ones contacted in May 1976. Lloyd, originally an architect, an unorthodox thinker, believed that the main problem with vaccine distribution was that there was no visual way of determining whether a vaccine had been heat damaged. In his quest for such a reactant, Lloyd went to Malmö, Sweden to meet up with professor and biochemical engineer M. Tiru of Kockums Chemicals. This was a new chemical company that had been formed by the long-established Kockums's ship-building firm that was seeking to restructure its operation into new areas. M. Tiru showed John his enzyme indicator of time and temperature for the food industry with the comment: *"this is the nearest, that we can get to a visible change to show the effect of exposure to heat"*. The indicator was a small pouch of

plastic full of a liquid which, when exposed to time and temperature, gradually changed color. It started as a mauve color and changed progressively to a yellow color. Armed with this knowledge, Lloyd prepared his proposal[2] for WHO, a vaccine cold chain based on the one found in the food industry.

The fulfillment of John Lloyd's dream was initiated by WHO in 1979, and a long marathon commenced to bring the vaccine vial monitoring concept to life, with a first appearance being on oral polio vaccine (OPV) in 1996.

At the very time when WHO were receiving a letter from Dr. Morley requesting that a temperature monitoring system be established for thermosensitive vaccines, another doctor in a different part of the world, had already started his own assiduous campaign for vaccine time and temperature integrators. After graduating from the University of Miami, Miller School of Medicine, another John – Dr. John Allegra – took up an appointment in the Republic of Malawi. *"There I saw what was happening,"* says Dr. Allegra, *"drugs were being kept in really hot temperatures, and suffering thermal abuse"*. Being a close friend of Ray Baughman, and being aware of him conceiving early diacetylene-based time-temperature integrators [before 1975], John strongly believed that these indicators could be the answer if applied onto vaccines. Ray and John were to spend endless efforts to find customers to their technology, but in the end, these endeavors did not turn into any real opportunities. It was not until the Program for Appropriate Technology in Health (now called PATH) approached Allied Chemical[3] (where Baughman was heading a research group) that things started to change.

With funding from non-USAID sources, PATH was able to develop first generation prototypes for measles vaccine using a chemical licensed from Allied Chemical. Once the Technologies for Health (HealthTech) programme of the United States Agency for International Development (USAID) was started in 1987, one of the initial subprojects was to identify an appropriate indicator technology for OPV, as the chemical PTS (p-toluene sulfonate) diacetylene was not sufficiently responsive for the extremely heat sensitive OPV along with some other limitations. Under the HealthTech programme, a new core technology was discovered that used diacetylene polymers. Unlike the PTS solution, this new technology which was originated by Allied, but owned by LifeLines Technology, Inc., (now Temptime Corporation in New Jersey, USA), was found to be applicable to all vaccines and easier to manufacture.

PATH/HealthTech worked with LifeLines Technology, Inc., to successfully modify their proprietary technology for use with all the vaccines being used in developing-country immunization programmes. The resulting product became ge-

2 Lloyd SJ. (1977) Improving the cold chain for vaccines. *WHO Chronicle.* 31(1):13-18
3 Allied Chemical later became Allied Corporation, then AlliedSignal and then Honeywell

nerically known as 'VVM'. The LifeLines' product was branded HEATmarker®, and this brand-name also became a trademark of Temptime Corporation. HEATmarkers became commercially available in 1991 and are now a standard feature of all vaccines purchased through United Nations (UN) agencies, and in many countries that are purchasing their own vaccines.

Like the invention of the humble metal nail with its huge significance for humanity, the invention of the VVM was to result in the gradual transformation of the vaccines cold chain bringing huge benefits in terms of cost control, logistics efficiency and, of course, increased safety in vaccine use. None of the other temperature monitoring devices and/or systems regardless of how technically sophisticated they were, could manage to do what this particular *'little big thing'* was capable of.

It is not an overstatement to say that VVM is one of the most important recent innovations in the area of public health, providing health workers with advisable and dependable means of ensuring that the administered vaccine has not been damaged by heat. Without a VVM, the only reference available at point-of-use is the expiration date. But, if a vaccine has not expired, does this mean it is always safe to use? Vaccines exhibit no visible change with exposure to heat. Before the development of the VVM, health workers had no means of identifying whether vaccine had suffered damage from heat exposure at any point during transportation and/or storage.

Nowadays the administration of safe life-saving vaccines is much less a matter of chance. With VVM, health practitioners in the field can focus on delivering an efficient care and treatment service without needing to be concerned about product viability.

Moreover, VVM renders immunization operations much more effective. It allows programmes to exploit the stability of each vaccine to the greatest possible extent, it minimizes distribution costs, and it increases flexibility in the handling of vaccines in the field.

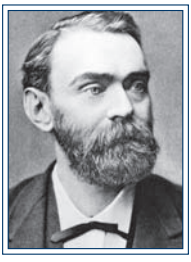
Immunization outreach is also boosted with immunization access and coverage increased. VVM helps to pinpoint cold chain problems and facilitates the efficient management of vaccine stocks. Countries adopting VVM-based vaccine management can now make informed decisions with the help of VVM readings.

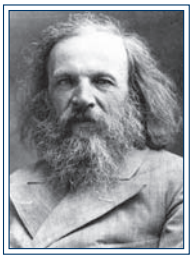
Although VVM was developed as a time and temperature integrator, it also made a significant contribution to the reduction of incidents involving the inadvertent freezing of vaccines. VVM facilitated the extension of the cool-chain concept by removing the ice that is a common source of freeze damage. This helped health workers to better understand the heat stability of vaccines and accept the fact that freezing is a greater danger than mild heat exposure.

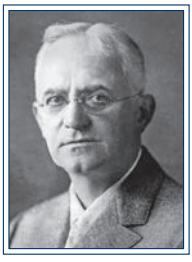
Today, VVM continues to evolve to address emerging needs in immunization programmes. The incorporation of a threshold indicator into VVMs (VVM+® or VVM-TI) and integrating VVM into 2D barcodes are the most recent examples of this evolution. This simple, yet elegant tool, which has sold over eight billion units by 2018, has played a decisive role in saving millions of children's lives across the planet.

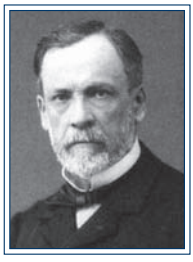
History unfolded

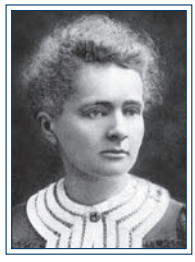
We all associate certain people as the pioneers, inventors or discoverers of landmark products, concepts, tools, or elements. Most of us immediately associate Alfred Nobel's name with dynamite, that of Dmitri Mendeleev with the periodic table, George Eastman with roll film, Louis Pasteur with pasteurization, Marie Curie with radium, and so on.


Alfred Nobel


Dmitri Mendeleev


George Eastman


Louis Pasteur


Marie Curie

But if we need to put a name against the discovery of VVM, who would that be? It is difficult to point to one single person since there were more than one midwife involved in the birth of VVM, although the initial thinking behind the use of chemical indicators for the temperature monitoring of vaccine vials be-

longs to John Allegra and Ray Baughman. The development of the concept of VVM goes way back to the 1970s when, in two different locations and completely independently, the idea was conceived.

The journey of two friends with miniaturized time-temperature integrators

Ray Baughman refers to John Allegra as "his brother"; one of his best friends in life. The two initially met at Harvard during their PhD programmes, Baughman reading materials science and Allegra reading physics (although after completing his PhD at Harvard, Allegra decided to become a medical doctor). As well as the science that brings these bright young minds together, they spend time going scuba diving along the coast of Massachusetts, and share many adventures exploring exotic places in South America, the Caribbean and around the world.

John Allegra in one of his last missions to Nigeria, 2006

After obtaining a PhD at Harvard, Baughman joined the Allied Chemical Corporation in 1971 and his appointment marked the start of solid-state polymerization work at Allied Chemical. Following Anthony F. Preziosi's synthesizing of the very first diacetylene monomer at Allied, on 28 December 1976, Baughman and two of his friends at Allied, Gordhanbhai N. Patel and Anthony F. Preziosi, filed a U.S. patent for a diacetylene time-temperature indicator:

United States Patent [19]

Patel et al.

[11] **3,999,946**

[45] **Dec. 28, 1976**

[54] **TIME-TEMPERATURE HISTORY INDICATORS**

[75] Inventors: **Gordhanbhai N. Patel,** Morris Plains; **Anthony F. Preziosi,** Ledgewood; **Ray H. Baughman,** Morris Plains, all of N.J.

[73] Assignee: **Allied Chemical Corporation,** Morris Township, N.J.

[22] Filed: **Feb. 23, 1976**

[21] Appl. No.: **660,562**

[52] **U.S. Cl.** ..... **23/253 TP;** 426/88

[51] **Int. Cl.**[2] **G01N 31/22**

[58] **Field of Search** ..... 23/253 TP; 426/87, 88; 73/356; 116/114 AM

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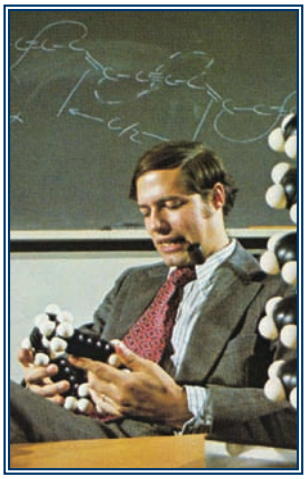
Primary Examiner—Robert M. Reese
Attorney, Agent, or Firm—David W. Collins; Ernest A. Polin

[57] **ABSTRACT**

Compositions containing at least two conjugated acetylene groups (-C ≡ C-C ≡ C-) are suitable as integral time-temperature history indicators. These compositions exhibit sequences of irreversible color changes at combinations of times and temperatures specific to each composition. Thus, when supported on the surface of a product or on a substrate affixed to a product, they are useful for indicating whether a perishable (e.g., foodstuff, pharmaceutical, chemical, etc.) has been exposed to an undesirable time-temperature history that results in substantial degradation of the perishable or whether a product has been exposed to a desirable time-temperature history during processing (e.g., the sterilization of a foodstuff or biomedical material).

19 Claims, 2 Drawing Figures

The topochemical polymerization of certain crystalline diacetylenes (converting a monomer single crystal to a polymer single crystal) was discovered by Gerhard Wegner. Baughman says that while earlier work by other pioneers had noticed this solid-state reaction, and its associated dramatic color changes, the nature of this reaction and its ability, in some instances, to convert a monomer single crystal to polymer single crystal was not previously understood. Motivated by the tensile strength and modulus theoretically obtainable for polymer single crystals, Baughman started to work on a route to strong single crystal polymer fibers. With the introduction of inks made of diacetylene crystal powders, offering wonderfully color-responsive materials that are suitable for inexpensive and reliable time-tempera-



Ray Baughman in early 1970s

ture integrators, Baughman proposed the use of the diacetylene reaction to make printable time and temperature integrators. The rate of polymerization reaction matches the rate of product degradation, making the time-temperature integrator color changes consistent with the way that this exposure effects the quality of perishable products like food and temperature sensitive pharmaceuticals.

After qualifying as a medical doctor, Allegra went to Malawi to work through the Catholic Medical Mission Board. He was always in touch with Baughman and kept himself abreast of all the exciting developments with diacetylene monomers. In Malawi Allegra was witnessing first-hand the considerable handling problems associated with the management of vaccine and other temperature-sensitive medicines in the field, and came up with the notion that printable monomer technology could be an answer to this problem by attaching an indicator on every vial. On his return to the U.S. together with Baughman, he went on a campaign, visiting both food and pharmaceutical companies to explain their technology to potential customers. During their presentations and discussions with the industry while on this journey, Baughman and Allegra focused on four main advantages of the technology:

- More dramatic color changes were obtainable,
- The existence of convenient methods for both initiating and terminating indicator activity,
- The range of activities and temperature dependencies available match particular industry needs,
- Small indicator dimensions can readily be achieved.

However, despite some initial enthusiasm, none of the initial interest led to any real opportunities, at least for the time being.

Declining ship building industry, vaccine stability and the need for a time and temperature integrator

While Baughman and Allegra were trying to find customers for their technology in the U.S., interesting developments were taking place in Europe, where WHO had been approached by Professor David Morley concerning the necessity of establishing of a system to monitor the temperature of thermosensitive vaccines.

Meanwhile, John Lloyd and James Cheyne, another two close friends from their time together as students of architecture, were busy designing and building hospitals in Africa. Both had seized an opportunity from the King's Fund, a London-based charitable organization, to take a sabbatical for six months, to work on

the decentralization, resources and the impact of decentralization on the primary health care system; a challenge that, in fact, had little to do with vaccines and cold chain. The two friends arrived in Tanzania, when there had just been a measles campaign involving some very unstable vaccine. *"After the vaccination campaign there was an unexpected and exceptional measles outbreak,"* recalls Lloyd, *"which took place equally in children who had not been vaccinated and in children who had been vaccinated. So, people were very unsettled. They've just completed this work and it has gone wrong. Everyone was talking about it and we ended up getting very involved and interested in the issue. From the outset we recognized that the fundamental problem related to the inherent instability of the vaccines and that there was no way of recognizing when the vaccine had been compromised and had lost its potency. We conjectured that it would be wonderful if we could simply look at the vaccine and see if it had changed color or something like that. This was around 1974."*

The following year, when the pair returned to the U.K., Lloyd joined an intermediate technology development group in London. This was a voluntary group, working with research charity the Wellcome Trust. John started as part of the health group in that organization, and he immediately started thinking about how to get this project off the ground by getting some money together and approaching WHO to see if the cold chain could be improved.

In fact, Lloyd asked Professor Morley in 1976 to approach WHO with a proposal to support the EPI that had just started in Ghana as a project. Dr. Morley's proposal embraced three major areas of improvement to the cold chain, with the main one, the establishment of systems to monitor handling temperature of the thermosensitive vaccines, receiving a warm welcome by Dr. Henderson, director of the EPI. Lloyd elaborates:

"I'd been reading up this field, the cold chain field, although, to be honest, there was not much to read those days. But there was certain activity. What I found interesting was that a company called Kockums AB, which was a ship building organization in Sweden, were concerned at the time about the slowdown in ship building and were looking to diversify. As part of their search Kockums had employed a biochemical engineer called Mr. Tiru, who knew a lot about enzymes. So, I travelled to Malmö where this man showed me how enzymes could be made to imitate the degradation of vaccines. It was an exciting moment. It was being set up for completely a different reason: Kockums believed the cold chain for food was extremely weak in many countries and that the control of food quality in Europe and the U.S. was going to be made a lot tighter. Mr. Tiru claimed that these improvements would be greatly facilitated with this type of technology. What he was showing to me was something like a big label 1.5 to 3 cm, he said we could attach to our packages. But I knew that a typical pharma package would not survive intact all the way to the remote villages at the end of the cold chain. Tiru did his best to make the

smallest indicator he could, but in the end, it was still almost the size of the vial. Well, it worked, but it was quite expensive."

Subsequently, on 11 May 1976, John Lloyd approached WHO with his historic proposal, a draft review of the available technology relevant to the cold chain. It is historic from the perspective that it is the very first technical document suggesting solid solutions to improve the temperature monitoring of vaccines as well as addressing issues around the cold chain equipment. Quite simply, it was the first document bringing a discipline to the cold chain. In his document, Lloyd describes a combined defrost and heat indicator. Although not exactly what the VVMs (unit level indicators) are today, Lloyd's thoughts were the stimulus for WHO to engage in looking for solutions to monitor the temperatures of vaccine packets (secondary packages) all the way from the point of manufacture to point of use.

Because of its historic value, we reproduce the introduction to Lloyd's 25-page proposal and the sections covering the need for a time/temperature indicator:

DRAFT REVIEW OF THE TECHNOLOGY RELEVANT TO THE COLD CHAIN

John L Lloyd
London, 11 May 1976

INTRODUCTION

Choosing the most appropriate technology for the cold chain can only, at best, tackle half of the problem successfully preserving vaccines. Refrigeration is inescapably a relative sophisticated technology in most areas of a developing country and the process of distributing vaccines is a relatively complex organizational problem. Both of these aspects require efficient and effective management, which is the other half of the solution to the problem. However, technology can, and often does, complicate and obstruct the management process so the objective of selecting technology must be to promote and support simplest, and therefore the best, system of management.

This paper, in spite of the title, is not an exhaustive analysis of all worldwide manufacturers of cold storage products; it cannot be inclusive, nor would it be readable, or I submit useful, if it was. Rather, it aims to provide a 'bench mark' of categories of technology related to stages of the cold chain against which the performances of new products can be compared. Therefore, the paper is structured around the chart shown on Table 0.1 which identifies the most probable areas for discussion, but not all areas for thought.

The term 'cold chain' is misleading in that it suggests continuity – a repetition of the same technology from beginning to the end. A glance at the chart will show that, of course, application of technology changes throughout the cold chain, responding to different conditions. Until now, the vaccine itself has been the only 'continuous' element in the process. This fact has given rise to the single largest problem – that the time/temperature history of a vaccine has not been recorded continuously throughout the cold chain.

Table 0.1
Cold Chain Technology Chart

STAGES OF THE COLD CHAIN	Power availability	Breakdown of stages	Cold store	Deep freeze	Chart temp recorder	Insulated packaging	Cold pack buffers	Refrigerators: Compression	Refrigerators: Adsorption	Thermometers	Cold box	Temperature indicator
1. International Air transit						8	10			11		●
2. Airport customs store	▨		11	11	11	8	10	10				●
3. Vehicle transit						8	10			11		●
4. Central store	▨		11	11	11			10				●
5. Vehicle transit							13			15	13	●
6. Regional store	▨				14			14		15		●
7. Vehicle transit	▨						15			15	15	●
8. Static unit	▨								17	15	17	●
9. Mobile teams	▨						21	21		21	21	●
10. Ambulant teams							22			22	22	●
11. Temporary Vaccination Sta	▨						21		21	21	21	●
12. Assay transit to central lab	▨					22	22	22		22	22	●

Cold Key to Power Availability	
Mains – central standby	▨
Mains – local standby	▨
12v electricity generated	▨
Gas, kerosene, etc.	▨
None	

The vaccinator cannot know what margin of safety he has before a vaccine batch should be re-assayed because he has no way of knowing its time temperature history. Table 0.1 therefore indicates the continuous involvement of time temperature measurement.

First, the paper discusses the need for an availability of a time-temperature indicator. Second, the paper discusses, stage by stage, the broad functional requirements of the cold chain, and how available products meet these requirements. The paper concludes with a summary chart of the ideas discussed and recommended for consideration.

Table 0.1 tabulates the stages of the cold chain against the different technological considerations. Therefore, for each stage in the Cold Chain the circled cells indicate the page number on which each aspect of technology is discussed. E.g. Cold boxes are first discussed on page 13 during transit between the central and regional store. (The black spots indicate the discussion in section 1.0)

VACCINE STABILITY – THE NEED FOR A TIME/TEMPERATURE INDICATOR

Comparing the stability characteristics of live viral vaccines from different manufacturers is difficult to do with any great confidence of accuracy. Temperature degradation tests are not always thorough, nor are tests comparable in procedure between manufacturers. There is an arguable case for standardization of test procedures and levels of accuracy.

The results of these tests, altered to include a wide margin of safety, give the fieldworker a false impression of the resilience remaining in a vaccine. 'X' number of safe days at an ambient of 'Y' may be reduced by mishandling earlier in the cold chain to a fraction of the published figures by the time the vaccine reaches the immunization station set up in the village.

A simple color/tone change indicator attached to packs of vials could provide the following information:

i) the pack has been frozen (for triple vaccine)

ii) the pack has been brought out of freezing

iii) the pack has none, ¼, ½, ¾ or all of its storage life remaining – before the batch needs an assay.

The information provided does not need to describe the state of the vaccine precisely, but the quality of handling the batch. This would enable a rotation of stock, not on the basis of date of arrival alone, but also based on the standard of handling history.

Two types of indicator are required, the enzymatic time/temperature integrator and the defrost indicator. Both these types exist and have been subject to extensive tests in the frozen food industry.

Time/temperature indicators

The Bio-Medical Science Inc. and 3 M Co. (see Table 1.1) both manufacture time temperature indicators which show a scaled track set on a flat card. The length of the track represents the total life of the indicator – so notionally a color change advanced to cover half the track indicates half the storage life remaining, since the scale is linear. However, the progressive color change is achieved by migration, the effects of which slow with age. Therefore, the last portion of the scale, on a product nearing the end of its storage life is covered in a slow and erratic way. A linear scale is highly misleading therefore.

Table 1.1
Time Temperature Indicator Availability

COMPANY	ADRESS	SHELF LIFE	MODELS	PRICE US$*
DEFROST INDICATORS				
Artech Corp.	2816 Fallfax Drive Falls Church, VA 22042 USA	L.T. 1 yr @ 75°F 1 yr @ 32°F	8	0.08 – 1.00
Check Spot Inc.	P.O. Box 1825 Vancouver, Wash. 98663	6 mo. @ 75°F 3 mo. @ 45°F	4	0.20
Tempil	Hamilton Boulevard So., Plainfield, N.J 07080 USA	3 mo. @ 75°F	4	0.25 – 1.25
TIME/TEMPERATURE INTEGRATORS				
I-point AB (Kockums Chemical)	Nya Agnesfridsvagen 181 S-213 75 Malmö, Sweden	1 mo. @ 75°F 6 mo. @35°F	2	0.01 – 0.05
TIME/TEMPERATURE INDICATORS				
Bio-Medical Science Inc.	140 New Dutch Lane Fairfield, N.J 07006 USA	Over 1 yr @ 75°F	4	0.15 – 1.00
3M Co.	3M Center St. Paul, Minn. 55101 USA	1 yr. @ 75°F	14	0.25 0 -0.50

*Price varies with both model and quantities.

The I-point has the advantage over the previous two indicators that it integrates the effect of both time and temperature onto a single go/no go spot of

color. There is no judgement needed as to 'proportion of scale colored', it is simply 'yes or no'. The same information on proportion of life exhausted can still be achieved of course, for example, by four indicators with 'staggered' design – so that two color changes out of four would indicate half-life. The cost of the I-point indicator is also considerably less than its rivals. Color recognition is not necessary to read the indicator – it is mounted on a card which matches tones to each other.

Tests on the I-point indicator have been carried out and are published by the Swedish Institute for food preservation research. Further tests on the performance of the indicator with Measles vaccine are planned by the National Bacteriological Laboratory., Stockholm who expect to complete them in June this year.

In summary the SIK report[1] stated:

"Storage tests at constant temperatures revealed that a very good degree of uniformity in indicator color-change was obtained at the higher temperature, +20°C. At the lower temperatures, -5°C and -20°C, a maximum error in the time to color-change of 5-10% of the rated time was observed. The standard deviation amounted to approximately +3% of rated time at -5°C and ± -5°C of rated time at -20°C. The Q_{10} of the indicators varied between 2 and 3."

The Q_{10} factor signifies the proportional increase in storage life when the temperature is lowered by 10°C, and is thus a measure of the slope of the time-temperature tolerance curve. (The curve indicates the rate of quality deterioration at different temperatures).

The Q_{10} factor therefore needs to be established from accelerated degradation tests previously mentioned. A crude estimate for Burroughs Wellcome Polio vaccine, for example, 2.2 and for measles 3.0 – factors well within the design abilities claimed by Kockums Chemicals, the manufacturers of I-point.

Defrost Indicators

The Artech Corporation indicator has been extensively tested and shown[2] to have the following problems:

i) activation at very low temperatures inconvenient and inconsistent. One third of indicators tested by one firm failed to activate at the manufacturers recommended temperature

ii) the indicators are vulnerable to mechanical damage and resultant seepage of eutectic salts onto the indicator paper turning it partially or completely red

iii) a proportion of indicators change color slightly before the design temperature has been reached

These indicators are very costly (for this application) and are unlikely to prove economic, even if they can be shown to be reliable, to attach to vaccine packages.

'Tempil' have failed to respond requests for information so far – nor has it been possible to find tests carried out on the indicator. The indicator is, again, an expensive alternative. Check Spot Inc. market at least expensive alternative with good performance. The following comments[3] were made of tests carried out:

i) indicators responded for variable temperatures with good agreement between claimed and observed response temperatures
ii) the indicators had a response failure rate at the design temperature of 0%
iii) all sample indicators discolored almost instantaneously at the design temperature

Indicators available for 3, 13, 20 and 32°F @ 0.20 US $ each.

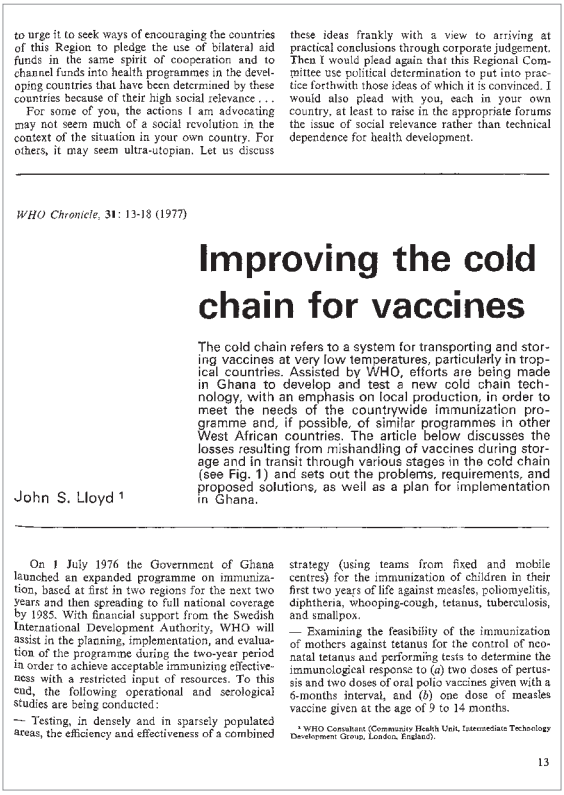
These indicators are activated by at least 1 hour at 0°C which may not be sensitive enough for DTP vaccine which may be damaged by periods of flash freezing of less than 1 hour.

Although tests for both types of indicators could arguably not be entirely relevant to the vaccine storage field, there are sufficiently good results in the frozen field to warrant extensive field tests for the cold chain. The largest single improvement in the cold chain may well be the recording of handling history for a vaccine packet from point of manufacture to point of use.

1 OLSSON, Par. Storage tests of time-temperature indicators in the temperature range for +20°C to -20°C, Swedish Institute for food preservation, June 16, 1975

2 SMITH, D.A. Irreversible warm up indicators (I.W.I) for use with frozen foodstuffs. Unpublished mimeographed report by Research and Development Department – Metal Box Co.

3 KAN-ICHI HAYAKAWA et al. Performance of frozen food indicators subjected to time variable temperatures. ASHRAE Journal, Apr. 1974, USA



to urge it to seek ways of encouraging the countries of this Region to pledge the use of bilateral aid funds in the same spirit of cooperation and to channel funds into health programmes in the developing countries that have been determined by these countries because of their high social relevance . . .

For some of you, the actions I am advocating may not seem much of a social revolution in the context of the situation in your own country. For others, it may seem ultra-utopian. Let us discuss these ideas frankly with a view to arriving at practical conclusions through corporate judgement. Then I would plead again that this Regional Committee use political determination to put into practice forthwith those ideas of which it is convinced. I would also plead with you, each in your own country, at least to raise in the appropriate forums the issue of social relevance rather than technical dependence for health development.

WHO Chronicle, **31**: 13-18 (1977)

Improving the cold chain for vaccines

The cold chain refers to a system for transporting and storing vaccines at very low temperatures, particularly in tropical countries. Assisted by WHO, efforts are being made in Ghana to develop and test a new cold chain technology, with an emphasis on local production, in order to meet the needs of the countrywide immunization programme and, if possible, of similar programmes in other West African countries. The article below discusses the losses resulting from mishandling of vaccines during storage and in transit through various stages in the cold chain (see Fig. 1) and sets out the problems, requirements, and proposed solutions, as well as a plan for implementation in Ghana.

John S. Lloyd [1]

On 1 July 1976 the Government of Ghana launched an expanded programme on immunization, based at first in two regions for the next two years and then spreading to full national coverage by 1985. With financial support from the Swedish International Development Authority, WHO will assist in the planning, implementation, and evaluation of the programme during the two-year period in order to achieve acceptable immunizing effectiveness with a restricted input of resources. To this end, the following operational and serological studies are being conducted:

— Testing, in densely and in sparsely populated areas, the efficiency and effectiveness of a combined strategy (using teams from fixed and mobile centres) for the immunization of children in their first two years of life against measles, poliomyelitis, diphtheria, whooping-cough, tetanus, tuberculosis, and smallpox.

— Examining the feasibility of the immunization of mothers against tetanus for the control of neonatal tetanus and performing tests to determine the immunological response to (*a*) two doses of pertussis and two doses of oral polio vaccines given with a 6-months interval, and (*b*) one dose of measles vaccine given at the age of 9 to 14 months.

[1] WHO Consultant (Community Health Unit, Intermediate Technology Development Group, London, England).

13

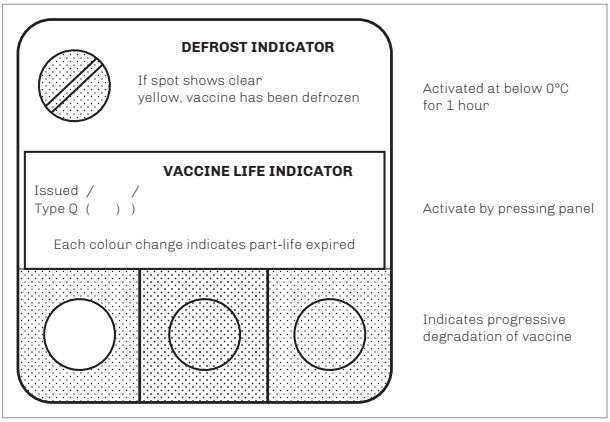
The following year, Lloyd published a technical manuscript detailing the temperature monitoring part of his proposal in the *WHO Chronicle*. In this article, Lloyd gives an illustration of the suggested combined defrost and vaccine life indicator. At this point it is worth reiterating that the temperature monitoring solution suggested at this point is for the secondary packaging of the vaccines (i.e. the protective, consolidation packaging such as a cardboard box that is not directly in contact with the vaccine), as described in the article *"it is probable that each 100-dose package of vaccine will be fitted with such an indicator"*. The main reason for this decision can probably be attributed to the sheer size of the enzyme indicator available from Kockums.

Lloyd explains the device as follows:

"The three windows at the base of the indicator are mechanically activated by pressing the pad in the centre. Once activated, the windows will turn to a dark tone identical with the surrounding card. As the life span of the vaccine becomes reduced, the window will change color, one by one, to a bright light tone. In this way, the windows show diminishing proportions of the remaining, based on the integration of both time and temperature. The window at the top of the paper is designed to change color irreversibly and very quickly as a result of sudden defreezing; this will give an indication of those vaccines that might have accidently been frozen. This indicator is activated by freezing below 0°C for one hour: so, it is also useful to show instances where diphtheria-pertussis-tetanus (DTP) vaccine might have been exposed to periods of freezing in excess of one hour.

"If these indicators prove to be a success, they could be fixed to the vaccine packets on the date of issue and remain attached until the vaccine is used. Fieldworkers and storekeepers can use the color changes both as a basis for stock rotation and for batch assay or rejection."

In this design, Lloyd also foresees the importance of such an indicator as a stock management tool.



John Lloyd's time-temperature integrator

At this point, before describing how global health organization PATH enters the picture, I would like to briefly discuss the defrost indicator suggested by John Lloyd. It is important to understand that at the time of Lloyd's paper, the physical damage to aluminum adjuvanted vaccines as a result of actual freezing had not come to light. So, it was not possible for Lloyd to have included such an argument at the time of his proposal.

Ümit Kartoğlu with John Lloyd, Washington D.C., USA, 2007

Aluminum adjuvanted vaccines are sensitive to freezing and when this occurs they lose their protective features with the damage being irreversible. In this sense, the freezing impact on freeze-sensitive vaccines is considered as a "single" event, while heat exposure is always cumulative. This is why freeze indicators are all dichotomous type "go/no go" or "yes/no" type of indicators. The major problem in attaching freeze (or defreeze) indicators to vaccines is that the triggering point of the indicator is insufficient evidence on which to base a final safe/not safe decision. This is because, being exposed to freezing temperatures and being actual-

ly frozen (solid frozen) are two different concepts. No freeze-sensitive vaccines freeze with exposure to 0°C for an hour, a temperature which would trigger the indicator. And today, we have a validated 'shake test' that helps us to distinguish whether a freeze-sensitive vaccine has been affected by freezing. In the validation study of the shake test, it was shown that vaccines exposed to -2°C for 24 hours were found to be identical to vaccines kept at 2°C to 8°C range, meaning that the physical structure of the vaccines remain intact unless they are frozen solid. In this regard, an activated freeze/defreeze indicator will not be able to indicate whether vaccines really have been frozen solid and irretrievably damaged by freezing. Since the final decision will always be taken by conducting the shake test, you can have a vial with a freeze/defreeze indicator that has been activated and yet passes the shake test. If so the vaccine can be safely used. Go/no go type of indicators will work only if the decision of using or not using is taken based on the indicator status.

Following the success of today's VVM, discussions have arisen about the possibility of incorporating vial-mounted freeze indicators. For the above reasons WHO have not supported nor endorsed any of these proposals with the recommendation being to continue investing in freeze-preventative measures.

Infinite enthusiasm and infinite patience: PATH changes the course

In 1980, three good friends, Richard Mahoney, Gordon Perkin and Gordon Duncan came together and launched PATH. All three had extensive experience in international health, especially in family planning, and they founded the organization to help meet the need for contraceptive technologies in the developing world.

PATH cofounders Rich Mahoney (left) and Gordon Perkin (middle) and Gordon Duncan (right)

Michael Free worked at the Columbus, Ohio-based Battelle institute alongside Gordon Duncan. He was part of the early conversations around PATH and helped build the proto-programme before the organization was formally launched (Known at that time as the Program for Introduction and Adaptation of Contraceptive Technology - PIACT).

"You have to understand the culture of PATH at that time." explains Free, *"This was the first 30 years of the organization, and it was not prone to pessimism. If it launched in to something, it launched in to it with infinite enthusiasm and infinite patience. PATH was formed basically as a very early organization with the aim of fostering partnerships between public and the private sector. It was all about climbing mountains, and it was as if we had come from another planet since there was very little understanding of the idea of a nonprofit, nongovernment organization being involved with technology development. And indeed, even at WHO we were kept in the "Industry File" right up to the mid 90s. They could not understand. In fact, there was a case where we were actually presented with some technologies that had been selected by WHO committees for further development only for them to discover that both technologies concerned came from PATH. We were hauled upstairs and they were in a state of hyper embarrassment apparently because we had helped to organize the meetings. But this was all about auto disable (AD) syringes, not VVM."*

Dr. Gordon Perkin became PATH president in 1980. Perkin explains his story that links Ray Baughman (Allied Chemical) and PATH:

"PATH was quite new, I had come in as President in 1980 from an assignment in Mexico with the Ford Foundation. We were looking for opportunities to demonstrate what we were all about. I recall being in a dentist office waiting for the appointment and picking up a copy of what I think was a popular science magazine. In it was an interesting article on how Allied Chemical was developing a chemical that could be used as a food freshness indicator for perishable products like chicken which may have to travel long distances to market possibly out of the cold chain. This indicator would be able to indicate a perishable product's freshness on store arrival before it was sold and consumed. I was aware of the fact that vaccines were also a perishable product and there could be interest in providing a similar type of indicator that could be used for vaccines to indicate whether they had in exposed to too much heat in transit. So, I called Allied Chemical, was put in touch with Ray Baughman who was head of the project, and we (Patrick Tam from PATH and myself) subsequently met."

Perkin tells me that he was not actually the first, but one of the first to suggest this to Allied as a potential product development project.

"There was another MD, John Allegra, who was a friend of Ray Baughman, and had gone to undergraduate school at Harvard with him, who went onto medical school, and subsequently worked in Africa on vaccines. He had brought to Ray's attention the possi-

Michael Free, Gordon Perkin and Ümit Kartoğlu, Seattle, December 2018

bility of some indicator for vaccine exposure and its integration. So, that's where it started and PATH was looking for an opportunity like this to demonstrate what it was all about."

PATH, in its search for funds to support the project, ended up going to Alberta in Canada, and managed to secure a small contribution from a private foundation there which was subsequently matched by the Alberta government, and by the IDRC, the International Development Research Centre in Ottawa. Most importantly, PATH was able to get a royalty-free license from Allied to work on the development of the PTS (p-toluene sulphanate derivative of a diacetylene monomer) compound for application on vaccine vials as monitors.

Ümit Kartoğlu with Vivien Tsu at PATH, Seattle, December 2018

Perkin continues: *"We came up with a model marker targeting measles vaccine which indicated over time the heat exposure, the cumulative heat exposure and would turn black at the point where the vaccine was no longer effective. The chemical was manufactured by Raylo Chemicals in Edmonton and was the original compound that the VVMs started out with."*

PATH and WHO subsequently tested the prototype measles vaccine model marker in the field. Vivien Tsu of PATH was coordinating the field studies and takes up the story:

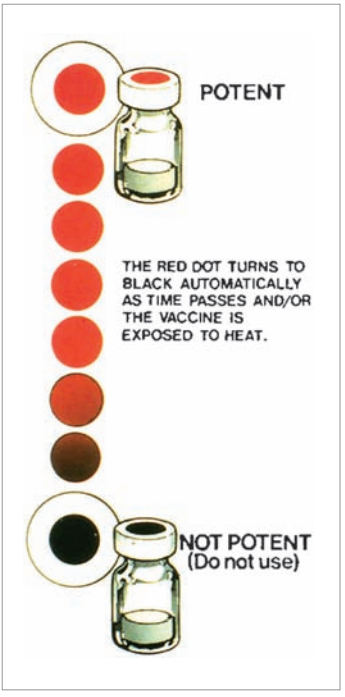
"When we started I was a very junior programme person, I came to PATH in 1981, pretty much fresh out of Public Health School. The project was well underway in terms of developing the actual stickers, and we then had this opportunity to do the field evaluation. At the time people were very skeptical about whether health workers would be able to recognize the indicator's color difference, and also whether their usage might undermine staff training. These were the big questions even when I came into the program in 1981, and what we debated with the folks in EPI, which in those days was John Lloyd and James Cheyne. The brief was to 'take it out to the field and see'. That was why we got

this small grant to go to these 10 different countries in different regions and see what the reaction was."

PTS technology PATH prototype VVMs go to field for trials

The first VVM design field trials were conducted by PATH in Mexico and Philippines in 1981. Following these two trials, PATH refined the measles VVM prototypes based on PTS technology and produced them for validation field trials. Between 1982 and 1984, field trials were conducted in the cold chain systems of 10 countries (Argentina, Brazil, Egypt, Kenya, Nepal, Pakistan, Peru, Philippines, Yemen and Zimbabwe) to determine the efficacy, interpretability, physical integrity and acceptability of PTS technology based VVM prototypes.

The active indicator material p-toluene sulfonate, when exposed to heat for a certain time, transformed quickly from a monomer state, in which it was red, to a polymer state in which it was black. The material was printed, using a standard flexographic process with multiple passes, onto a strip of treated paper. Following air drying, it was then covered with a laminate of transparent polyester before being punched into discs 0.5 mm in diameter. Production was quite complex. The time to full color change for the raw indicator formulation before printing and drying was 11 days ±5% at 37°C. The method of applying the chemical onto a treated paper in those days reduced this period to 9.5 days. Indicators were then taken to be heat treated at 80°C to reduce their life to 8 days ± 8 hours at 37°C, all verified by a control scanner. The indicators were then manually applied to the top of the vial cap for the study purposes.



Validation field studies indicated a number of limitations. These were summarized in a WHO report on "measles vaccine indicator study" published in October 1984 (WHO/EPI/CCIS/84.7). Although the results demonstrated the ability of the indicator in routine management to detect specific cold chain failures and identify usable vaccine after such failures, recent laboratory studies of the most widely used freeze-dried measles vaccines have revealed that the stability of these vaccines has improved significantly since the instigation of the indicator study. This has led to the indicator color change no longer corresponding to a critical fall in the potency of most vaccines. Even if the color change were

corrected to reflect the current stability levels of measles vaccines, these levels were generally so far above those of certain vaccines used in the EPI that further development of a specific measles vaccine indicator was not considered a practical solution. Nevertheless, the study pointed the way to two possible applications. Meanwhile, during these ongoing studies a number of toxicology issues came up. Tsu explains this frustration as follows:

"We were always explaining two purposes for this indicator: prevent bad vaccine from being used, and prevent good vaccine from being thrown away. But good vaccine being thrown away was by far the bigger issue in those early days; when vaccines were cheap this might be considered a completely acceptable risk but as newer, more expensive vaccines started to come on-stream this became much less acceptable. These studies were done from 1982 to 1984 and then this toxicology issue came up. I felt like it was back to the drawing board. They (Allied) said that although the risk was really really tiny, the toxicology concern was there, because it was potentially teratogenic. In other words, the risk you are talking about is not like an immediate poison, it's the risk of a woman in early stage pregnancy having the possibility of a damaged fetus. Of course, this was a completely unacceptable risk. It was really hard to take it in, but looking at the dividend on the other side, it is huge benefit against this tiny tiny risk. I think it was really disheartening that it took another 10 years basically."

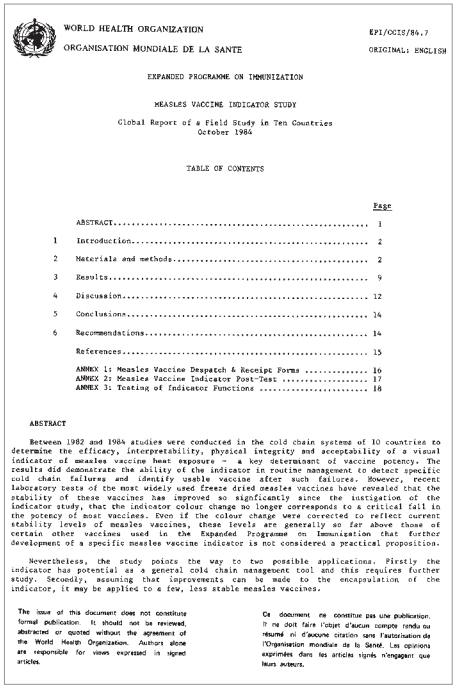
"What we found when we were engaged with commercial development, part of that was to commission some toxicological tests in order to get them (PATH) permits to manufacture the key chemicals." says Steve Fields of Allied, *"We did the toxicological tests and safety studies, and it turned out that there were some toxicity issues."* Allied conducted a series of 12 studies. These studies and the review of a consultant toxicologist, concluded that the solid PTS chemical in the quantity deposited on the label has insignificant oral toxicity and low potential for mutagenicity in humans. And in the view of potential danger of the active chemical to the eyes and skin, the present encapsulation of the indicator was inadequate. The current printing paper was unable to provide such protection.

The WHO report presented the following conclusions:

1. *Example cited in this report demonstrate the ability of the indicator in routine management to detect cold chain failures and to identify usable vaccine following such failures. In all countries, health workers found the indicator to be a useful tool for this purpose.*
2. *However, the laboratory assays which were conducted during the field trials demonstrated a lower correspondence between the change in indicator color and the minimum acceptable virus inactivity than earlier laboratory findings. Current laboratory tests on the stability of measles vaccine reveal that such im-*

provements have been achieved by the major vaccine manufacturers that it would be no longer acceptable to dispose of individual vials of vaccine bearing indicators which have changed color to black.

3. *Although the indicator should not be attached to individual vials of most measles vaccines, it remains a valid general indication of failure in the cold chain. The color change can be used as a basis for handling instructions relating to all EPI vaccines with the exception of oral poliomyelitis vaccine. The indicator has the advantages over the currently used "cold chain monitor" in that it records all exposure temperatures, and it is less expensive.*



WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

EPI/OCIS/84.7
ORIGINAL: ENGLISH

EXPANDED PROGRAMME ON IMMUNIZATION

MEASLES VACCINE INDICATOR STUDY

Global Report of a Field Study in Ten Countries
October 1984

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ABSTRACT

Between 1982 and 1984 studies were conducted in the cold chain systems of 10 countries to determine the efficacy, interpretability, physical integrity and acceptability of a visual indicator of measles vaccine heat exposure - a key determinant of vaccine potency. The results did demonstrate the ability of the indicator in routine management to detect specific cold chain failures and identify usable vaccine after such failures. However, recent laboratory tests of the most widely used freeze dried measles vaccines have revealed that the stability of these vaccines has improved so significantly since the instigation of the indicator study, that the indicator colour change no longer corresponds to a critical fall in the potency of most vaccines. Even if the colour change were corrected to reflect current stability levels of measles vaccines, these levels are generally so far above those of certain other vaccines used in the Expanded Programme on Immunization that further development of a specific measles vaccine indicator is not considered a practical proposition.

Nevertheless, the study points the way to two possible applications. Firstly the indicator has potential as a general cold chain management tool and this requires further study. Secondly, assuming that improvements can be made to the encapsulation of the indicator, it may be applied to a few, less stable measles vaccines.

Between 1986 and 1987, PATH improved the PTS manufacturing process and developed a new format for use on vaccine secondary cartons. Introductory field trials on the measles VVM and carton indicator were conducted until 1989 in Indonesia, Kenya, Sierra Leone, Thailand and Zambia.

PTS technology was considered as not promising for its application onto other vaccines. Constraints of PTS technology included its reaction rate being too slow for use on the most heat labile vaccine OPV, dermal toxicity issues, and printing difficulties.

Bringing VVM to life

Ted Prusik joined Allied Corporation in 1981. At that time, PATH and WHO had already started to work together with Allied and had licensed its PTS technology which was suitable only for measles and had some other issues. Part of Prusik's job at Allied was to determine which compounds they could potentially commercialize within the company. Prusik explains these early days:

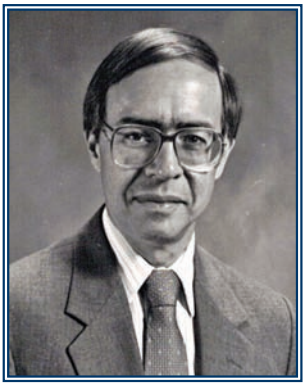
"We resynthesized all of the compounds to see how they worked, how suitable and how flexible they were. It was Tony Preziosi, who was the chemist in the lab and he was a synthesis genius, I mean he could make ten different compounds in a day and help to characterize them very quickly. He was doing some research to find compounds that were

going to be used for inventory management, and as he was synthesizing these, he stumbled upon the compounds that are now used for the VVM. In the memory bank these were unique, because we had a whole family of compounds that had different reactivities, and if you co-crystalize the monomers, you change the reactivity. This is what we finally settled on to in order to cover the range of exposures from days at refrigerated temperatures to years at room temperature. That gave us the technology that is still with us today, a technology that is difficult to mimic with other kinds of chemistry; the monomers just work and they work well.

"I was the one who took the technology and tried to run with it as best we could from the technology point of view on the chemistry side. But that's not a lone journey, you run a team, it's the whole team that does all the development work."

It was Prusik's team that brought today's VVM to practical fruition. There was also Fred Grabiner at Allied Chemical, working with Prusik, but responsible for developing the barcode scanning system, algorithms for mathematical modeling, kinetic fitting of monomer, correlation of color response to product degradation, and quality control (QC) programmes for product release.

"The first thing I was involved at Allied was to read these color changing chemicals with barcodes. Then the issue came whether we can use this to monitor the shelf life of something that doesn't have exactly the same activation energy, the same change with temperature. Allied contacted some academicians and got the answer that you cannot do that. But you did not need an exact solution, that we did the examples to show that we were pretty good in such measurement. This started with food products."



Fred Grabiner in 1993

They made seminal advances. Prusik continues:

"We brought the VVM to life. We were part of the Corporate Technology division within Allied Signal which the Allied Chemical Corporation had become by that time. The decision was made to disband Corporate Technology and focus on the research-based operating companies. All the research groups that were part of the corporate R&D at that time had to find a new home within the company or Allied would try to sell them. However, the management at Allied Signal realized that the Corporate Technology team wanted the chance of taking the technology and trying to develop it and they agreed to this. It was the first time they had agreed to letting a research group take a technology and basically spin it off, and they just took shares in the resulting new company although it already had venture capital funding. So, we took the technology, got the licenses for all of the patents and know how, helped ourselves to some of the furniture from the lab (we still have it in the lab) and started on our journey."

This was the birth of LifeLines Technologies Inc., in August 1987. Stephen C. Fields, Thaddeus Prusik, Frederick P. Grabiner, Peter D. Van Houten, Anthony Preziosi, James R. Jacobson, Lucretia H. Burt, and Peter A. Caputo were all involved in its creation.

"For the last five years of my time at Allied Signal, I was the leader of LifeLines." says Steve Fields, *"I had taken over the research project from Ray Baughman. Ted Prusik was a recent recruit by the R&D department, and he and I joined forces, he was the technical leadership and I, the business."* Fields was also a scientist, having a degree in chemistry, but never worked actively in the field. He was on the business side of the science. When they had the breakaway company, LifeLines, the press release about the story of LifeLines, got the attention of Udayan Gupta from the *Wall Street Journal*, who made a story on Fields.

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WHO'S NEWS

The Perils of a Corporate Entrepreneur

By Udayan Gupta
Staff Reporter of The Wall Street Journal

In 1976, fresh out of the University of Connecticut with his MBA, Stephen Fields thought he would be spending his entire career at Allied-Signal Inc.

By 1982, it looked as if his big opportunity had arrived. Allied's hard-charging chief executive officer, Edward Hennessy, asked Mr. Fields to start a separate operation within the company to find a market for a chemical product that Allied scientists had developed—and that no one knew exactly what to do with. "Corporate entrepreneurship" was a buzzword of the day, and Allied was on the bandwagon.

But last week, after nurturing the orphan product for five years, Mr. Fields decided to adopt it himself. Frustrated by what he called years of "despair and uncertainty," he quit and, with six partners from Allied, formed a company to market the product, which had evolved into a system that monitors the freshness of food.

"It was in an unfamiliar area," Mr. Fields says of the giant company's view of his five-year stint as an in-house entrepreneur, "and the lack of strategic fit with Allied's business haunted us."

Abandoning the Concept

Mr. Field's experience is an example of a marketable idea lost in the labyrinths of a large, changing company, and an illustration of the perils of being a corporate entrepreneur. Five years after it was in vogue, corporate entrepreneurship has been largely abandoned by Allied and many other companies.

Such ventures "were an attempt to commercialize some of the R&D projects which had the potential to become significant new businesses," says Mark Radtke of Venture Economics Inc., a Wellesley Hills, Mass., consulting concern. But if a new venture didn't naturally fit with a company's existing businesses, it typically ended up in trouble.

"You had to struggle for scarce resources with ongoing units, which usually had more clout," Mr. Radtke says.

While at Allied, Mr. Fields and his team took the initial product, a polymer Allied researchers came up with over a decade ago, and built it into an inventory-management system—called Lifelines—that food conglomerates such as General Foods and Del Monte began using to maintain product quality and reduce product-liability risks.

At first, Mr. Fields reveled in his niche, developing a marketable product under Allied's umbrella without, as he said several years ago, "answering to bankers and . . . worrying about cash flow and meeting a payroll."

Wondering about the Future

But as time went on, the 35-year old financial analyst began wondering about his future. After its $5 billion 1985 merger with Signal Cos., Allied began pouring massive amounts of money and effort into restructuring, and showed little interest in maintaining small-scale entrepreneurial ventures. "I realized I would have to move on," Mr. Fields says.

So he did, with Allied's blessing. Now, he says, "I feel more secure on my own than I ever felt as part of Allied's corporate venture group."

In the early 1980s, most big companies trying to commercialize such in-house technologies were trying to match Minnesota Mining & Manufacturing Corp.'s success, says J. Tait Elder. Mr. Elder managed 3M's new products group—the familiar yellow self-stick Post-it Note Pad is one example—and later, Allied's. Allied itself is estimated to have spent almost $20 million a year on its new-ventures unit, which at its peak consisted of six projects.

In fact, Lifelines had a long life at Allied. Other such Allied ventures were either absorbed or dismantled earlier.

'Low Profile'

"What is surprising is that it survived so long within Allied," Mr. Radtke says. Mr. Fields says it survived because it kept a "low profile" and scavenged for additional resources. It persuaded two Allied research units to continue their support even though it had run out of research funds.

Last year, when the heat was really on, Mr. Fields cut his team from 12 to eight, even though he says the project needed more staff, not less.

Finally, as Allied threatened to close Lifelines as part of the company restructuring, Mr. Fields began scrambling for capital to take the project private.

"We were fighting a moving 30-day deadline," he recalls. "My wife was totally behind what we did as long as we didn't lose our house." He eventually did refinance his home for the money to clinch the deal.

An early plus to use capital from individual investors fell through after almost six months of negotiations. Mr. Fields then knocked on the doors of East Coast venture capitalists, who finally came up with backing.

Mr. Fields says four East Coast venture capital firms have pledged $1.2 million—in addition to the $100,000 he and his partners put together—to buy the project from Allied and run it as an independent company, to be based in Morris Plains, N.J., and called Lifelines Technology Inc.

Allied will keep a stake in the company—it spent an estimated $10 million to keep the project going—but Lifelines' managers and investors will hold over 70% of the stock.

Mr. Fields says it wasn't difficult persuading venture capitalists that Lifelines could succeed.

"We are starting out with a developed, proprietary product based on more than a decade of research," he says.

Still, "there is a corporate stigma that we had to overcome," he explains. "Many venture capitalists didn't believe that we could do without the security that corporations provide. We convinced them that we've been risking everything—our careers and our reputations—for the last five years."

* * *

NAME: Stephen C. Fields

AGE: 35

POSITION: President, Lifelines Technology Inc.

CAREER PATH: A University of Connecticut MBA who joined Allied in 1976, he rose to be a corporate manager but left to develop an Allied venture on his own.

CHALLENGE: To succeed at running a business his former bosses didn't want.

Prusik explains that they were active mainly in the food business, making indicators that were very quick-reacting for refrigerated food products, but they also had the technology to cope with room temperature stability and certainly within the range of the vaccines that were being used. But, at that time vaccines were not their focus.

LifeLines communicated with PATH, and they were identified as a potential developer of the VVM using their core diacetylene polymer technology. In 1989, LifeLines received a purchase order from PATH for $25,000 to develop VVM for OPV and make 10,000 samples to be used in the field. Prusik recounts this development journey:

"$25,000 was not a lot of money to develop a technology from the start, and right about that time we got our first big order from the Monoprix supermarket chain in France for use on their refrigerated food products. We put a lot of work in to get the technology to meet the requirements for VVM for OPV, but after more than a year of diligent effort we were unable to satisfy the exact needs of WHO. So, our Board of Directors said

Ted Prusik and Ümit Kartoğlu in Temptime Corp., New Jersey, 2012

'OK, that's it, we've spent enough time and effort on this and we need to abandon the programme. We have spent way too much, and, in any case, the probability that the indicator will be accepted by the big institutions is rather small.' So, we had to let PATH know that we were bringing the research to a halt. Michael Free and Gordon Perkin came to Temptime trying to encourage us and begging us to carry on, because we were close, so very close although we weren't there yet. Michael even got down on his knees and pleaded with to continue the research efforts. But I distinctly remember, we could not make any commitment, because the board had instructed us to stop.

"I remember driving home that night and crying on the way home. But it turned out not to be the finish. What we effectively ended up doing was sort of doing the research under the radar so to speak. It just so happened that at the time we were doing the work for Monoprix, we were faced with a similar kind of situation where we couldn't get the activity just right. It was coincidental that we were able to get the VVM formulation for OPV and the formulation for one of the Monoprix food products, for meat monitoring actually, pretty much together. So, the same solution worked for both and this was really the birth of VVM for OPV."

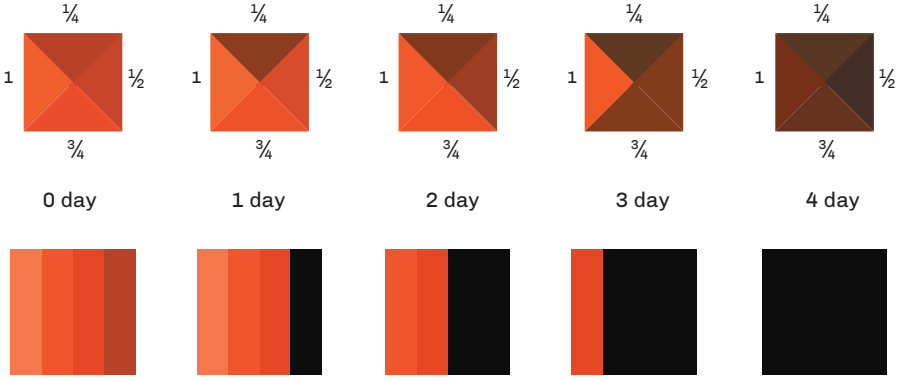
Michael Free also expresses his feelings on teaming up with LifeLines and how he got onto his knees to beg them to continue when LifeLines faced the problem:

"They (LifeLines) weren't having much success with the food industry in the early days. They were looking for other applications and they were quite amenable to looking at vaccines as an application for the technology. We started working with them in the early days, applying what we had learned from the first technology. It started moving, the concept started to evolve... Now we had a new technology, we knew what our objectives are, and we had a target product profile. We totally dropped the other technology (PTS), since it was clear that it was simply not going to go anywhere. And here was something that had much more potential and much broader application and was much more promising.

"The big challenge was really to sustain the commitment of this small break-away company and build the case that this application had commercial potential, that there would be return on investment somewhere down the line. They had started doing some early development, early studies, but it was taking a long time, and the Board started to get very concerned and skeptical. They really felt they were going down a big hole, and that there was no chance of a real return on investment. It was a crisis point when they seemed ready to abandon the application of their technology to vaccines. I went over there personally to speak to them, literally begging them to continue."

The square in a circle

The PTS technology was simple, visually changing from red to black, the indicator was in a circle shape. Compared to this, the VVM from LifeLines was more sophisticated. It was a tint of mauve in color and which got progressively darker by exposure to heat over time. Therefore, it needed a reference for comparison purposes. When we look at the early models of such indicators from Allied Chemical, we can tell how smart was the design of VVM by LifeLines. Here are some examples from Allied Chemical on the use of PTS in early crude device demonstrations for a vaccine product expiring in 4 days at 37°C.



Use of PTS in early crude device demonstrations for a vaccine product expiring in 4 days at 37°C

The early crude device demonstrations using PTS technology were proposed in two different shapes, both square, but one divided into four sections using two diagonals and one divided into four sections using three vertical lines. Of course, geometrically, you have additional options, such as drawing three lines horizontally, or drawing one vertical and one horizontal line intersecting at the middle part of the square. Or you can cut the square by a horizontal line or a vertical line,

then cut each half into two equal triangles, and you can do this in four different ways. Using the colors of PTS technology, I reproduce all these images for comparison purposes.

However, from a graphical point of view the first two, that were also used by Allied Chemicals, are generally considered the best designs.

Here is another design used by Allied, this time for the Epoxyguard™ product life monitor, developed by Ted Prusik (1982).

In this design, the active surface that is the circle in the centre needs a reference for comparability purposes. Here, the reference is shown as six different hues indicating the percent life remaining (at 95, 80, 60, 40, 20% and fully expired).

The PTS PATH Marker on the other hand was simply a circle, changing color from red to black. No reference color was needed.

PTS PATH Marker changing color from red to black

In June 1989, PATH recruited Debbie Kristensen as a technical officer, VVM being the first project assigned to her to lead. From 1989 on, Kristensen became a critical figure in VVM development and implementation. "*My entire career at PATH evolved from this project as it led me into the field of immunization*" says Kristensen, *"and it is unbelievable to me that we are still working on new VVM technologies thirty years later!"*

When it came to the mauve color of today's VVM, the design was more complicated. Working on this indicator design was one of the first tasks Kristensen was involved with. Together with LifeLines, PATH looked at different configurations and color ranges. PATH conducted inhouse and field trials, showing different

colors and shapes to people. Tsu explains this process as follows:

Yellow color, different shapes of VVM (LifeLines)

"We were doing in-house and field trials, to show people different colors: 'can you tell the difference between this one and this one?' or 'how about this one and this one?' And then also trying to figure out how to get the reference point. Of course, we did not need any reference on the red/black marker since it was very clear whether it was red or black. However, with the mauve transition being so narrow in range, we needed a good reference mark. And the question is how do you explain which is the reference color and which is the live chemical? This is how we arrived at a combination of square and the circle. We could have put in circle in circle, but a square in a circle was easier to explain to people."

"That's a pretty smart design decision." I told Tsu. *"Yes,"* she replied, *"but getting to simple is complicated."* She continued: *"I remember being at a meeting with USAID, and I recall a really wise statement by somebody from USAID who said that simple technologies are some of the hardest and most sophisticated things to develop, and it takes a lot more thought to produce something 'simple' for people to use. It is not an easy process. It certainly was our experience with this project that getting to the final design took a lot of time, trial and error. But finally, it all came together and at that point we needed to do some more field studies."*

New VVM was branded "HEATmarker®" by LifeLines.

Developing a capability to print VVMs directly onto vaccine labels

During 1990–1992, the new HEATmarker® VVMs were taken to eight countries for design field trials (Bangladesh, Bolivia, Cameroon, Indonesia, Kenya, Sierra Leone, Thailand, and the United States). In addition to these studies, a detailed study was conducted in Zimbabwe with the MOH analyzing the impact of VVMs on measles vaccine discard rates due to heat exposure. During this time period WHO and PATH intensified their efforts by visiting UN vaccine suppliers to discuss the feasibility of integrating VVM labels into their products.

HEATmarker® prototypes were subsequently sent to ten UN OPV suppliers to obtain further feedback following a meeting in 1990 between Connaught Laboratories, Evans Biologicals, Interexport, Pasteur Merieux, Scloavo, SmithKline Beecham, Swiss Serum, Human Institute, Institute of Immunology, and MAIMEX. On

15 October 1991, PAHO approached the PATH with a memorandum signed by Peter Carrasco, requesting samples for PAHO evaluation:

"Re your letter dated 8 October file code P04.24.05, we request that you provide us with heatmarkers for all vaccines. If you could provide us 100 heatmarkers for our internal use and evaluation we would appreciate it. Also, mock-ups of color progression would be high valuable as well as a latest training material. As you know PAHO/EPI has a vaccine Revolving Fund therefore we need to take a decision on the introduction of this technology before September 1992. Pls ship markers with dry ice. Regards."

As for the manufacturers, incorporating VVM onto their labels presented a huge hurdle. They were resisting because it was going to disrupt their established processes. Prusik explains that they started to receive feedback such as 'we won't be able to do it,' and he continues *"so the battle had begun with pushback from the manufacturers. Of course, we can understand this reaction since we are manufacturers ourselves and we don't like to do things unless we have to do them or need to do them to improve, so there was some strong opposition."*

With high mountains to be climbed, smart solutions needed to be found!

In 1993, LifeLines developed a capability to print VVMs directly onto vial labels. Prusik continues: *"One of the initial pushbacks was that we were making just VVM dots at that time for the prototypes. These were fine for the field trials, but the VVM for OPV is a full label that wraps around the vial. So, the VVM was incorporated directly into the label so the manufacturer didn't have to buy any new equipment. All they had to do was use a standard reel of OPV labels that had all the VVM and printed text on it and apply them in the normal way."*

This helped to overcome the vaccine manufacturer resistance to purchase labeling equipment for a separate VVM label.

During this period, UNICEF organized a consultation meeting with the vaccine industry to explain their intention of including VVMs onto OPV labels. *"In the first Copenhagen meeting, the vaccine manufacturers who participated in the meeting were not enthusiastic at all; they all resisted."* says Steve Fields, *"We met again after some time and their position was the same. I listened to their objections to find a solution to their concerns. I said 'well, let me summarize what I am hearing - all the objections have to do with having to deal with another label. So, the objective is to incorporate the VVM in the prime label. If we do this, we will become your prime label supplier, and you will be able to dispense the label and apply it with your existing label applicator. You will not need to have another machinery.' This put an end to their objection. John Gilmartin (UNICEF SD) said I think we made a decision here."* Fields explains that this was only a plan, and in order to execute it LifeLines would need about a million dollars. But in the end this sizeable funding requirement was resolved with the help of PATH and the equipment manufacturer.

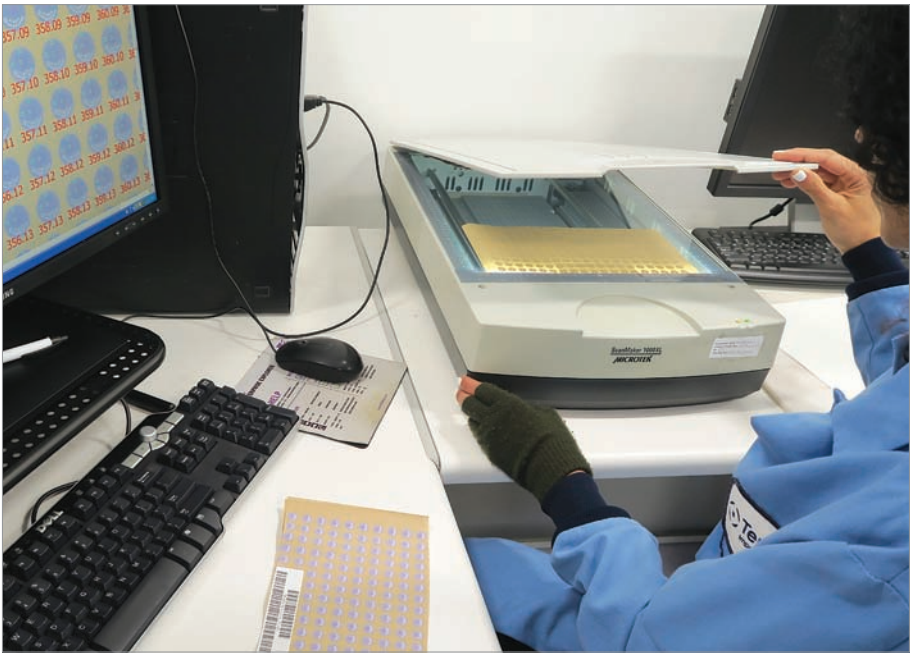
This persuasive declaration of intent from Fields, indicating that the VVM would be integrated directly with the vial was to be a decisive factor in overcoming the resistance to VVM adoption amongst the vaccine manufacturing community.

The challenge of measurement

"Once we had managed to produce the visual indicator for OPV, we needed some kind of instrument to measure them in order to manufacture them and to be able to demonstrate their effectiveness" says Fred Grabiner, *"I found this device, a densitometer, that had an interface that could speak back and forth to a computer so that we could automate the readings. We needed to read a spot about 2 mm, and the X-Rite 404 could read as small as 1.7 mm area.*

"To show that every batch was in specification required a lot of measurements with individual densitometers. We had to find a way to measure more than one indicator at a time. I thought we could do this with a page scanner. When I discussed this with X-Rite they said it wasn't possible because the color space is different. I got

X-Rite 404 spectrodensitometer



Page (flatbed) scanner in action

a page scanner, and worked out a mathematical technique where although it was not universal - we had to calibrate it for every type of indicator and sometimes for individual batches, we could get very close with the page scanner so we can make the measurements. In fact, we started to get equal measurements with our page scanner compared to individual measurements with the spectrodensitometer."

The immunization global community gets together: The TechNet consultation

In the late 1970s, Mogens Munck, who was working for UNICEF in India at the time, proposed the formation of a consultation body as a forum to bring a field perspective to many of the activities in the realm of training and technology. It took many years to formally establish this global forum. The first TechNet Consultation, held in Nicosia, Cyprus from 12-16 March 1990, was attended by 32 participants made up of staff members from WHO and UNICEF Regional and country offices, CDC/Atlanta and non-governmental organizations and consultants.

The TechNet Cyprus Consultation also discussed the VVMs. From this meeting onwards, VVM was always on the agenda and TechNet played a critical role in increasing the demand for vaccines with VVMs as well as guiding and monitoring the progress.

In Nicosia, VVMs were discussed in a breakout group of 13 members: Nassim Ahmed (UNICEF, Malawi), Allan Bass (Consultant, UK), David Basset (CDC, USA), Anthony Battersby (Consultant, UK), Ismatullah Chaudray (WHO, Pakistan), Robert Davis (UNICEF, USA), Thierry Durant (MSF, France), Michael Free (PATH, USA), Rodney Hatfield (UNICEF, Indonesia), Gordon Larsen (Consultant, UK), Margaret Ledoux (Consultant, Belgium), Garry Presthus (WHO, India) and Naresh Srivastava (WHO, India).

The TechNet Cyprus Consultation reported the following on VVM:

Vaccine vial indicators

There was a brief overview of the history of vaccine vial indicator development. The preliminary field trial results have shown that early measles vaccine vial indicator was relatively easy to use and supervisors found that it gave them more confidence in vaccine quality and helped improve stock management. However, there were compliance problems and weaknesses because the slow, initial color change did not allow for an early warning of cold chain breaks and did not serve vaccine monitoring needs for oral polio vaccine.

Improvements have been made since then and the latest generation of vaccine vial indicator now available can be programmed to be suitable for any vaccine and can be used to record any breaks in the cold chain.

The present WHO specifications for vaccine vial indicators can be met by PATH with this new generation indicator. Also, since the vaccine vial indicators can be programmed, other specifications can be met as well. However, the specifications need to be finalized if utilization is to go forward, as the manufacturers cannot keep making modifications each time the specifications change.

Cost guidelines for vaccine vial indicators stipulate that the cost should not exceed 10% of the cost of a 10-dose vial of polio vaccine. It is not clear at this stage whether the current technology will meet this target.

Discussions on vaccine vial indicators

There is potential for confusion on the part of health workers if there is going to be a combined use of vaccine cold chain monitors and vaccine vial indicator in routine vaccine distribution. There needs to be a clear distinction made between the two.

The vaccine cold chain monitors or temperature threshold indicators, which have a short life above the storage range of temperatures, are used for the purpose of monitoring a system. It was suggested that development efforts be concentrated on the vaccine vial indicators which are used for showing if a particular vaccine vial is usable. Once such indicators are established and workers understand their use, alternative ways of monitoring the cold chain routinely can be reconsidered.

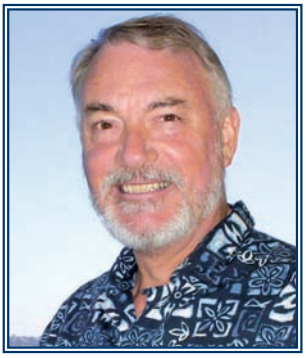
The choice of color of the vaccine vial indicators is open. Although green/yellow has been chosen for oral polio vaccine on the basis of readability in low light, it may be necessary to choose other colors for other vaccines in order to avoid confusion.

Since the vaccine vial indicator can be programmed within wide limits, it was suggested that the indicator be designed to also change color on the expiry date of the vaccine thereby providing a backup to the date written on the vial.

From the Report of 1990 TechNet Consultation, WHO/EPI/LHIS/90.2, pp. 25-26

The yellow indicator came from UK-based Albert Browne Limited. Though it was in response to WHO's call for the development of VVM, the Albert Browne technology changed from yellow to dark blue instantly. Unlike the LifeLines technology it was unable to show the cumulative effect of heat by time.

Peter Evans, former Chief of Vaccine, Supply and Quality at WHO headquarters, dealing with the industry side of the VVMs, says that at the time he champi-

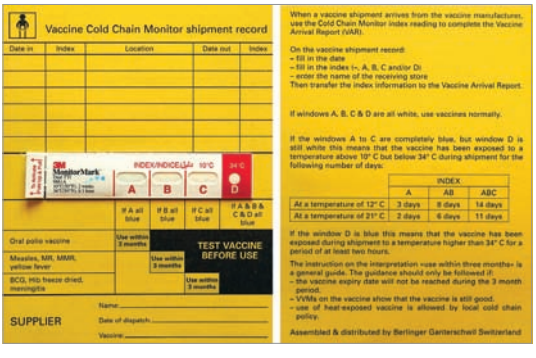


Peter Evans

oned the Albert Browne technology rather than the LifeLines solution. *"Early on, we had three different competitors for vaccine purposes and the Albert Browne solution went from a pale yellow to a dark blue. The advantage of the Albert Browne product was that it was cheap, it was very easy from the manufacturers' perspective, and the reading was absolutely clear. It went from yellow to dark blue almost instantaneously. You had the indicator staying visually dormant for several months and then suddenly it would change, with health worker having no question about it. The VVM from LifeLines was more sophisticated. With it you can do imaging control, you can tell how far towards expiry it has advanced, whether you need to rush and so on. But the Browne indicator was cheap and simple."* Evans goes on to explain that the subsequent consultations with TechNet made it very clear that the progressive, mauve colored, LifeLines indicators would be the final choice. It should also be noted that the Browne technology failed to meet the precise WHO specifications.

Meanwhile, a type of vaccine cold chain monitor widely known as "CCM", a 3M technology marketed by Swiss company Berlinger and Co. AG, was being used with shipments. A solid wax in a blue color was concealed in the indicator to be activated by folding up and pulling the marked edge of the strip. This wax material melted at temperatures over 10°C and progressively wicked onto an absorbent paper over an indication strip consisting of three coloration panels, windows A, B and C. The D window on the far right of the strip was a threshold indicator with the wax melting at temperatures above 34°C.

The CCM indicator served its purpose for several years as a transit indicator, but its accuracy was only ±1.5°C. Today, the CCM indicator is used only with dry ice shipments since the batteries of electronic shipping indicators do not function at such extreme low temperatures. (For further discussions on how to decide which indicator to use and why, please see "The role of TechNet" chapter on page 105).



Vaccine cold chain monitor cards, Berlinger & Co AG.

While all these developments were taking place, John Lloyd, one of the original champions of VVM as a secondary package indicator, was worried.

"The development and initial field testing of VVMs was driven and organized by PATH because at that time the concept still being pursued by WHO was

a secondary packaging indicator to help monitor cold chain and to build the cold chain." explains Lloyd. *"On the other hand, the more radical concept of PATH at that time, led by Vivien Tsu, was to transform the paradigm of the vaccine supply chain, using the VVM to reduce dependency on refrigeration and the cold chain. I was worried at that point that VVMs on vials of vaccine might have the effect of convincing health workers that the vaccine concerned was actually much more stable than they believed and that this would lead to people being disrespectful of vaccine handling. I confess that as a leader of the cold chain activity in WHO, I favored the philosophy of maintaining the cold chain."*

VVMs goes into global vaccine tender for OPV

In 1990, VVMs were a subject of discussion at a Technology Introduction Panel (TIP) meeting of UNICEF in New York. A year later, during the second TIP meeting at UNICEF, WHO staff asked UNICEF to include VVMs for OPV in the 1992-1994 vaccine supply global tender. As a result, UNICEF included a clause in the tender announcement for inclusion of VVMs to be incorporated to OPV labels prior to 1994.

This is also the period where laboratory evaluations of the LifeLines HEATmarker took place. In 1991, PATH under as part of its HealthTech programme conducted a series of studies on HEATmarker to evaluate product durability, water resistance, integrity of adhesives, effect of light exposure, and response rates. These independent laboratory tests by Strasburger and Siegel (USA) were completed in 1992.

UNICEF also included a request for VVM for measles vaccine and OPV in its next tender for 1994-1995. However, only a few manufacturers tendered for this work. Nonetheless, WHO, UNICEF, and OPV manufacturers met up in 1994 and agreed to include VVMs on all OPV beginning in January 1996. In 1995, WHO released their final specifications for VVMs for all OPVs and by 1996, all five OPV suppliers to UNICEF (SmithKline Beecham, Biocine, Pasteur Merieux Connaught, Chiron Behring, and PT Bio Farma) were supplying VVMs on their products.

At the time of VVMs being incorporated into all OPVs (1996), I was working for UNICEF as a health officer for the Central Asian Republics and Kazakhstan Area Office. I remember the very first shipment reaching Almaty, Kazakhstan at three o'clock in the morning. I was at the airport to see this magical tool that would change vaccine logistics for good.

Other technologies emerging as potential VVM solutions

WHO and PATH worked diligently to encourage other companies to develop competitive VVM products, and they both provided technical assistance to emerging companies. Firstly, it was Albert Browne Limited who introduced their competitive VVM technology in 1991. Within three years, 3M (USA) and Rexam/Bowater (UK) had emerged as potential VVM suppliers and in 1996 CCL Label (USA) and Sensitech (USA) surfaced as potential suppliers. However, in the same year, Rexam/Bowater withdrew from further VVM development due to an inability to make a viable product. 3M also discontinued work on VVMs in 1998 due to their failure to produce a product at a competitive price (their product was three times the price of the HEATmarker®). 1998 was also the year in which CCL Label submitted VVM prototypes to a WHO independent laboratory for evaluation, but these failed to meet the required specifications.

In summary, there have been no other companies that have succeeded in bringing to market a product that can meet the performance requirements of WHO. In addition, none of the competing solutions have been able to successfully compete with HEATmarker on the critical matter of price. It is these considerations that have led to LifeLines being the sole supplier of VVMs.

Do we need a more thermostable OPV?

It was at this time, just as potential VVM manufacturers were gradually giving up the struggle, that Julie Milstien from WHO got involved with the VVM project. *"When I was involved we had really two challenges"* says Milstien, *"One was to convince UNICEF that this was going to be a good thing. And the second one was to make sure that the specifications were reasonable. Polio was the first start to go forward with UNICEF.*

Julie Milstien hiking at Chandragiri, Nepal, 2013

"Around that time, we were working with the Children's Vaccine Initiative: which started, I think, in 1991, and the idea of the initiative, was to get a thermostable liquid vaccine that was given orally that would be against all the diseases of childhood. And so, my part of it was to work on a thermostable polio vaccine. And so, we were working very, very hard on trying to get a thermostable polio vaccine and we actually got a thermostable polio vaccine, or a polio vaccine that was stabilized with deuterium oxide. At that point, I guess, UNICEF had just agreed that we could go forward with VVMs on polio vaccine and so, at that point, EPI decided, well, we really didn't need a more thermostable polio vaccine, because we had VVMs, and if we could use VVMs we really would

not need more stable vaccines. And so, the project died and it was very painful and we lost credibility with the manufacturers that were working on it.

"But, anyway, that's the way it went. Our challenge then was to develop the VVMs so that we would know what would be the temperature ranges and that whole work on specifications was way beyond my capabilities – at that time John Lloyd was bringing that forward – but one of the things that we decided to do was then to do a couple of experiments to show that the stability of vaccines actually matched what was happening with the VVMs."

VVM heroes

At the beginning of this chapter, I said that it is difficult to point to one single individual who is synonymous, personally, with the birth of VVM. We have seen

John Allegra

Ray Baughman

Gordhanbhai Patel

Anthony Preziosi

Thaddeus Prusik

Fred Grabiner

Stephen Fields

John Lloyd

Michael Free

Gordon Perkin

Debbie Kristensen

Vivien Tsu

how the healthy development of the new baby is the result of a concerted effort involving many midwives, in many places over many years. What is clear is that the initial thinking behind the use of chemical indicators for the temperature monitoring of vaccine vials came from John Allegra and Ray Baughman, two young visionaries with a simple idea that went on to change the world of vaccine management in the field.

So, as a conclusion of this brief history of VVM development, I would like to salute all these heroes who played a part in bringing VVM technology into the world, some imagining it, some developing it and others making it all happen.

Scaling up

Covering the early research and development cost of VVMs to meet the business and technical requirements was not an easy job for LifeLines. And more importantly, much more funding would be needed to get the VVM to scale, especially for a small break-away company in New Jersey. Ted Prusik explains those painful years:

"Here we are, a company that losing money and in order to make VVMs we needed to raise 1.5 million dollars for a machine that is capable of doing it. Of course, when you have been losing money for 13 years, no bank wants to talk to you. In fact, hardly anyone wants to talk to you! However, PATH came to the rescue, giving us $250,000 as a loan for a down

Ted Prusik in early 1980s with his children

payment although we were still left with finding another $1,250,000. Eventually the equipment manufacturer believed in what we were doing, and said OK, we'll build you the press, because it is not a common machine and it is specially designed to make the VVMs, but they said, you have to promise that you don't tell anybody that we financed it, because we are not a bank, we are a machine manufacturer. So, we kept that secret for quite a long time. So, between PATH and the machine manufacturer we were able to purchase the equipment, but although it still took a year and a half from then to get the first VVM commercially used due to pushback by the vaccine manufacturers. How could you rely on a small company in New Jersey that has no history of supplying the pharma world and entrust them with being able to provide OPV vaccine. That was a tough mountain to climb, although I didn't think any mountain was unclimbable in those days. We did our best to make a quality product and satisfy the needs of a growing market, and we still do."

Donors step in to support VVM implementation

It was to be USAID that provided the long-term support to PATH, through a 5-year renewal of the project, something which was quite uncommon even in those days. *"USAID really provided the backbone of long-term support, albeit in small tranches of money, a few hundred thousand dollars annually for many years."* says Debbie Kristensen, *"Without that backbone of financial support, along with others who pitched in along the way, there is no way VVMs would have gone forward. That was one of the reasons for its success. In today's grant-distributing world you don't see that kind of long-term support. Although USAID did not intend to support it for that long, they continued to be committed. We had a five-year project, and these days you are lucky to get two or three-year projects. So, every time our project got renewed, it continued on with USAID support."*

In a bid to accelerate the implementation, the Department of International Development (DFID) of the United Kingdom purchased 17.75 million VVMs for all four OPV manufacturers in India and funded and managed activities that resulted in a successful integration of VVM labelling onto those OPV vials being produced in India for government purchase and for national VVM training material development.

In 1998, the Japan International Cooperation System (JICS) and Japan International Cooperation Agency (JICA) adopted policies to include VVMs in all vaccine donations.

WHO as an organization that was, setting the technical specifications, as well as providing policy support, and UNICEF, as a buyer of public sector vaccines were two critical champions in bringing VVM implementation to scale. This was despite both organizations having major issues in the beginning. The main con-

cern of WHO was the price that a VVM would add to the vaccines. UNICEF was more concerned with the sole-supplier issue despite being aware of PATH's significant efforts into finding other companies to enter the VVM market and that none of these companies had succeeded in meeting the requirements either technically or financially.

Vaccine manufacturers themselves had no incentive to move forward. Although UNICEF was an important buyer, compared to the commercial market, it was paying much less for the same product. Basically, the industry did not want to make a new investment decision only on a request from UNICEF, and the manufacturers started to come up with all sorts of reasons why they couldn't incorporate VVM onto their products. For the industry, the priority was simply one of avoiding anything that might introduce disruption in the production process.

Inspiration of the lipstick

There were some early adopters. Pasteur-Merieux was the first manufacturer to incorporate VVM onto their OPV. Chiron was quite exceptional in its early adoption. *"That [Pasteur-Merieux adopting the VVM] was really a turning point, and the next thing is a call from Chiron saying we understand that WHO wants VVM on all the polio vaccine – can you clarify that this is the case because we are about the purchase the labelling machine."* says Michel Zaffran (WHO). Chiron had a quite special vial, different than all other OPV vials, and for them, it was a problem to use the label. They had to put a dot on the cap. But in order to put a dot on the cap, Chiron had to redesign the cap to make it bigger to accommodate the VVMs.

Redesigned Chiron OPV cap allowing VVMs to be attached

There were different approaches WHO could take for persuading VVM adoption by vaccine manufacturers. One way was to obligate them and say if they did not do it, they would fail to prequalify and therefore not be considered a supplier. But WHO chose to take a different route, working with manufacturers to help them overcome problems and concerns in order to support them in adopting VVMs successfully. WHO was constructive in guiding every player towards a successful implementation. It was to prove a critical strategy in bringing the new technology to market.

Dario Cresci joined Chiron Vaccines in 1996 as secondary manufacturing site head, polio being one of the company's main products. This how he reacted to the VVM concept: *"The more I learned about the concept, the more I found it to be a very*

Dario Cresci

good solution – very easy to understand, simple and straightforward" says Cresci. *"We looked at different and additional ways of extending our product portfolio so more products could have VVM on them. Since I was a believer of the idea, it was easy for us to work with VVM, and we really enjoyed what we did."*

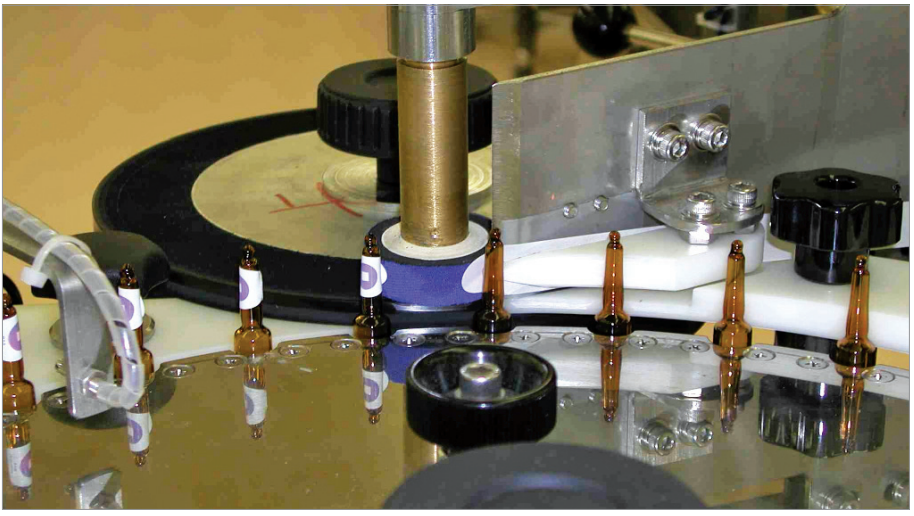
Since the VVM had to be applied on the top of the flip off or on the neck of the ampoule, the application of VVMs for freeze dried vaccines brought a new challenge to vaccine manufacturers. Vaccine manufacturers had to purchase new top labelling machines and the major concern was the speed. The need to apply VVMs was slowing down the production speed. And they did not like it. Cresci at Chiron changed the game for top labelling.

"This was a typical case of serendipity. WHO wanted to extend the usage of VVM, and one of the requirements for freeze-dried vaccines was that VVM would have to be applied on top of the vial cap. The reasons behind this were legitimate, but we were caught unprepared. Luckily, I had very committed staff who were extremely creative and innovative. So, I launched the challenge to my people and said, 'Who's going to be the one to make it happen?'

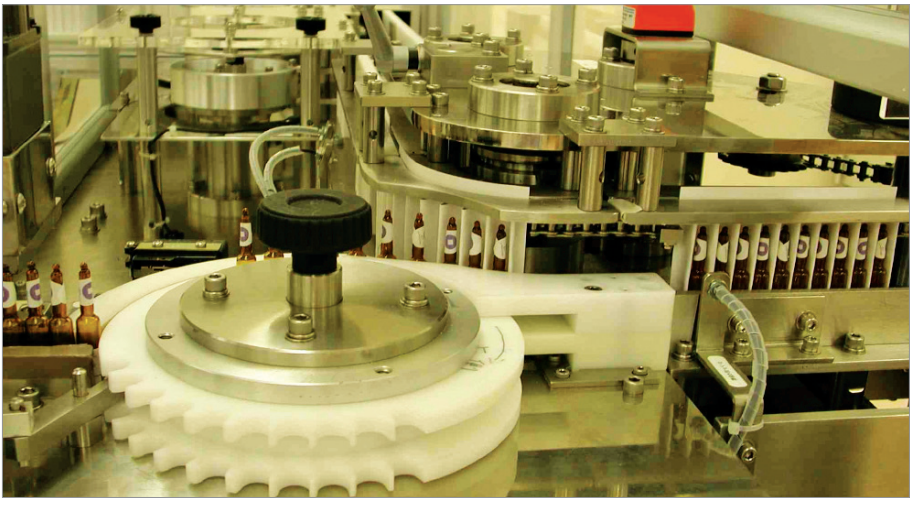
Top label on a lipstick

"Here is the story. One evening, I was looking at my wife as she was putting on lipstick. When she placed the cap of the lipstick onto the dressing table, the label on the cap, one giving the code number and color information of the lipstick caught my attention. My eyes were fixed on the label. I was actually seeing the VVM on the cap! That was the inspiration and from this point we developed the whole idea of modifying the vial in order to accept the VVM. I even personally contacted the company that was applying the label to the lipstick. To my surprise, when I talked to them, they said, yes, it is possible, no problem, we can apply fifty labels in a minute. Fifty labels! This came as a jolt. I said 'my machines are working at 400 labels per minute.' So, we had to do something, because the senior management would never accept any slowing down of production speed. So, we teamed up bringing our different skills together – our expertise in high-speed labelling, or at least higher than what the lipstick company had, and their technical capability of applying a round label on top of the very small cap of a lipstick. And at the end of the day, we came out with a superior labelling machine design that could work at the same speed as our labelling machines, which meant no reduction in lead times, no idle time in the lines, and, very importantly, a new range of unique VVM-enabled products."

However, the attachment of VVM dot around the neck of an ampoule proved more of a challenge than a vial cap because of its shape. The neck of the Japan BCG ampoule was not a smooth conic shape, making it even a more difficult application. In addition, applying a degree of pressure for good adhesion to the neck was resulting in cracking of the ampoule. Nonetheless, as was the case with Chiron for the top labelling application, Japan BCG did not give up. Their engineers put their heads together and came up with a custom-made design solution that utilized, a new machine that used a softer press to very gently pressurize the neck of their BCG ampoules for a full adhesion of VVM dot labels.



Applying VVMs on the neck of BCG ampoules, Japan BCG



Soft press in action for a better adhesion of VVM, Japan BCG

Independent validation of VVMs and field studies

In 1995, WHO released the very first specifications for OPV VVM. The specifications were revised in 1997, but still applied only to OPV.

The first meeting of the Strategic Advisory Group of Experts (SAGE) to the Children's Vaccine Initiative (CVI) and the Global Programme for Vaccines and Immunization (GPV) of WHO was held in Geneva from 12 to 14 June 1996. SAGE recommendations were published in the Weekly Epidemiological Record on 30 August 1996, including its endorsement of VVM introduction.

WEEKLY EPIDEMIOLOGICAL RECORD, No. 35, 30 AUGUST 1996 • RELEVÉ ÉPIDÉMIOLOGIQUE HEBDOMADAIRE, Nº 35, 30 AOÛT 1996

Vaccine vial monitors

Vaccine Vial Monitors (VVMs), currently used on OPV supplied through UNICEF, are time-temperature sensitive labels. They provide an indication of the accumulated heat to which an individual vial has been exposed. Like the other time-temperature indicators already in use (cold chain monitor cards), VVMs do not indicate the actual potency of the vaccine inside the vial. They do warn the user when exposure to heat has occurred beyond an acceptable level and the vaccine is likely to have been damaged.

The SAGE notes with great interest the introduction of VVMs on OPV and acknowledges the major step forward that this represents for the logistics of immunization programmes.

- GPV should continue its efforts to ensure the introduction of VVMs on all oral polio vaccines.
- GPV should help countries monitor the impact of VVMs on vaccine wastage, vaccine handling, and on the logistics of immunization and the cold chain. These data should be reported to the SAGE for review.
- WHO should work with UNICEF, vaccine producers, and VVM manufacturers in order to introduce VVMs on other EPI vaccines, as appropriate.

Pastilles de contrôle du vaccin

Les pastilles de contrôle du vaccin (PCV) actuellement utilisées pour le VPO fourni par l'UNICEF sont des étiquettes thermosensibles apposées sur les flacons. Elles donnent une indication de la chaleur accumulée à laquelle un flacon a été soumis. Comme les autres indicateurs temps-température (fiches de contrôle de la chaîne du froid), les PCV ne concernent pas l'activité effective du vaccin à l'intérieur du flacon. Elles ne font que prévenir l'usager lorsque l'exposition à la chaleur a dépassé un niveau acceptable et que le vaccin risque d'avoir été endommagé.

Le Groupe note avec grand intérêt l'introduction des PCV sur les flacons de VPO et considère qu'il s'agit là d'une étape décisive en matière de logistique des programmes de vaccination.

- Le GPV devrait poursuivre ses efforts pour faire en sorte que des PCV soient apposées sur tous les flacons de VPO.
- Le GPV devrait aider les pays à surveiller l'impact de ces indicateurs sur le gaspillage de vaccin, la manipulation des vaccins et sur la logistique de la vaccination et de la chaîne du froid. Ces données devraient être communiquées au Groupe pour examen.
- L'OMS devrait collaborer avec l'UNICEF, les producteurs de vaccin et les fabricants de PCV de façon à pouvoir utiliser ce type d'indicateurs sur d'autres flacons de vaccins du PEV, le cas échéant.

Starting with the PTS technology, a series of own- and third-party independent validation studies have been conducted on VVMs. The below table summarizes these tests.

Year	Laboratory	Description
1980	Connaught Laboratories (now Sanofi Aventis), Canada	Testing of the early PTS prototypes.
1987-1991	PATH under HealthTech	Numerous physical tests on PTS and HEATmarker prototypes: durability, water resistance, integrity of adhesives, effect of light exposure, response rates.
1992	Strasburger and Siegel (US)	Independent laboratory evaluation of HEATmarker, supported by WHO.
1998-1999	Consumers' Association Research and Testing Centre* (UK)	Second validation of OPV VVMs conducted under WHO contract.

1999	National Institute for Biological Standards and Control (UK)	Validation study commissioned by WHO to correlate OPV stability with VVM response. Good correlation between vaccine potency and VVM status was shown for vaccines produced by all four OPV suppliers to UN agencies.
1999-2001	Precision Measurements and Instruments Corporation (US)	Tested the conformity of HEATmarker VVM7, VVM14 and VVM30 to WHO specifications under contract from WHO.
2001-2003	Consumers' Association Research and Testing Centre (UK)	Completed an additional real time validation test of the HEATmarker VVM7 at 8°C under WHO contract.

* Now, the ITS research and testing Centre.

VVM nomenclature

VVMs were categorized based on vaccine stability and indicated by letters of ABCD.

VVM reaction rates by category of heat stability

Category (Vaccines)	No. days to end point at +37°C	No. days to end point at +25°C	No. days to end point at +8°C
A: HIGH STABILITY	30	193	More than 18 months
B: MEDIUM STABILITY	14	90	More than 18 months
C: MODERATE STABILITY	7	45	More than 18 months
D: LEAST STABLE	2	NA*	140

** VVM (Arrhenius) reaction rates tedermined at two temperature points*

Following its introduction, WHO realized that this nomenclature creates confusion with the international vaccine shipment packaging configurations of ABC. Following a consultation with the vaccine manufacturers, in 2002, WHO has changed the VVM nomenclature from ABCD to 2, 7, 14, and 30, using the number of days to endpoint at 37°C for different stability categories.

Category (Vaccines)	No. days to end point at +37°C	No. days to end point at +25°C	No. days to end point at +8°C
VVM30: HIGH STABILITY	30	193	More than 18 months
VVM14: MEDIUM STABILITY	14	90	More than 18 months
VVM7: MODERATE STABILITY	7	45	More than 18 months
VVM2: LEAST STABLE	2	NA*	140

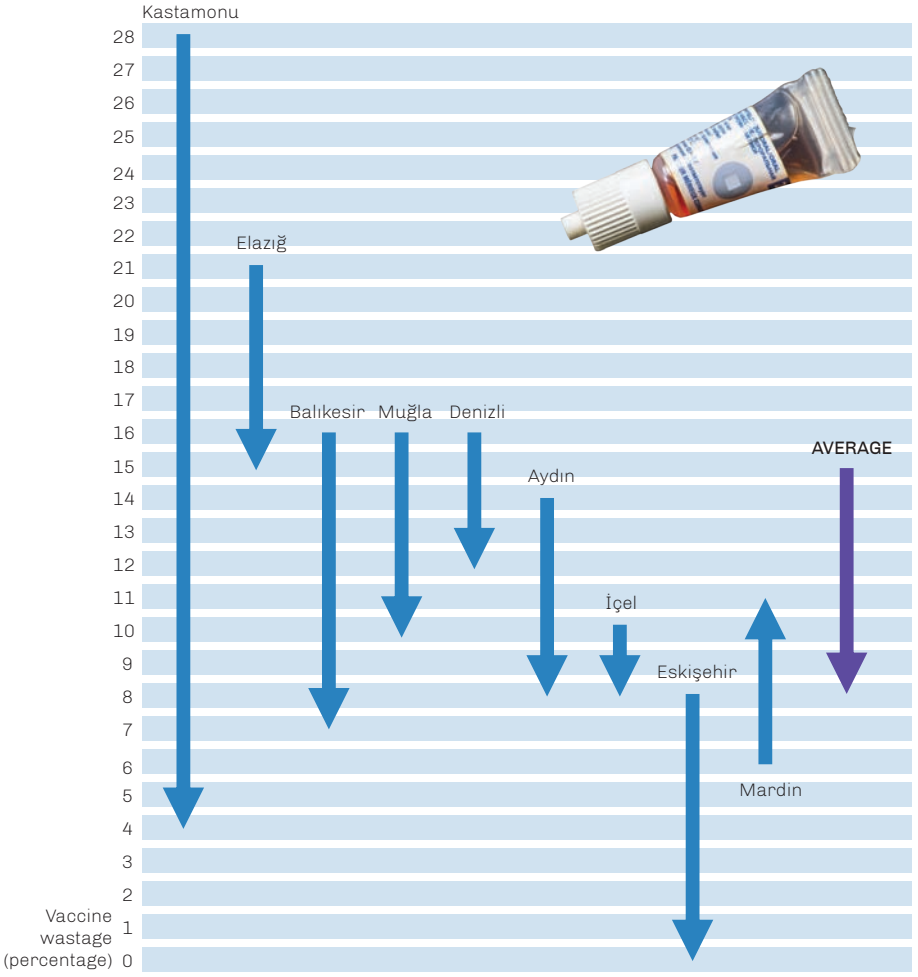
** VVM (Arrhenius) reaction rates tedermined at two temperature points*

Coming in a steady-stream, in-depth VVM field studies were starting to produce compelling results, bringing more encouragement to the public sector.

VVM impact study during 1997 NIDs in Turkey

Oya Z. Afsar and Birhan Altay

The purpose of this study was to test the use of VVMs by the health personnel in the field and to monitor the change in vaccine wastage rates with the introduction of VVMs and an open-vial policy, as recommended by WHO. The study was conducted in selected health centers in 12 provinces during the two rounds of national immunization days (NIDs) in 1997. Contrary to the common practice in Turkey, OPV vials carrying VVMs were not discarded at the end of the day, but continued



Vaccine wastage rates in two rounds during NIDs by provinces, Turkey

to be used in subsequent sessions. In addition, selected empty vials kept in the cold chain were monitored for a period to detect the time of reaching the end-point. Wastage rates were compared with the rates in the first round of NIDs, in which the open-vial policy had not been implemented and where all opened and unopened vials taken to outreach sessions had been discarded at the end of the day.

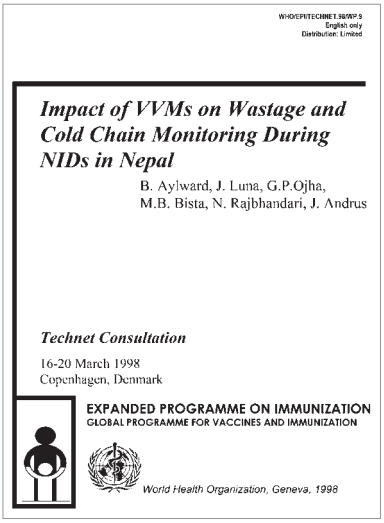
The total number of discarded unopened vials in 12 provinces was 3,860 in the first round while it dropped to 900 in the second round. The differences according to the provinces were statistically significant ($t=4.17$, $p<0.05$) and wastage due to heat exposure was found to decline 77%. The mean wastage rate, resulting from the unused portion of opened vials, was 15.0%±2.3% in the first round and decreased to 8.3%±1.5% in the second round. This difference was also significant ($t=2.59$, $p<0.05$), indicating a 45% reduction in the wastage rate. 14.1% of the opened vials were used in the next day. None of the vials reached to the end-point before they were finished. This may be due to the fact that all vials were finished in one or two days, considering the implementation strategy of NIDs. Among the empty vials monitored within the cold chain, the number of vials reaching the end-point reached a peak in the third and fourth days after the opening. These vials were used in the southern provinces, where the temperatures varied between 25°C-30°C at that time of the year. Although no objective data was compiled regarding the acceptability of VVM by the health personnel, the impression was that it had been easily recognized and interpreted by the staff in the field.

The study concluded that VVM is a valuable logistics management tool particularly for the grassroot level, leading to considerable savings in the national budget while preserving the safety and efficiency of the vaccines.

Impact of VVMs on wastage and cold chain monitoring during NIDs, Nepal

B. Aylward, J. Luna, G.P.Ojha, M.B. Bista, N. Rajbhandari, J. Andrus

A study in Nepal, conducted during the NIDs (6 December 1996 and 17 January 1997) demonstrated the capacity of VVMs both to substantially reduce the wastage of OPV vials which have been returned from outreach immunization sites and to facilitate the monitoring of the cold chain in the field. During the first NIDs in Nepal it was possible to document the VVM status of nearly 19,000 vials of OPV that were returned from the field in vaccine carriers after anywhere between one and six days outside the cold store. Of the approximately 6,000 vials that had been outside of the cold chain for more than three days, only 14 had a VVM reading which suggested that the vaccine should not be used due to excessive heat exposure. Among the other 13,000 vials that had been returned, evaluation of the VVMs demonstrated that seven were probably heat damaged, although these vi-



als had been returned in a vaccine carrier that still contained ice or frozen ice packs.

At the time of supervisory visits to nearly 500 NID immunization posts, the VVMs on virtually all of the OPV vials that were in use indicated satisfactory cold chain conditions. Of the eight vials that were reported to have been heat compromised, further investigation suggested a systematic error in reading the VVM by one supervisor. However, even omitting the results of that supervisor, 50 of the 8,000 vials that were found in the vaccine carriers at the time of supervision were shown to be heat damaged. This clearly indicated that in those situations where one had to question the integrity of the cold chain, VVMs provided the capacity to selectively discard from the cold box or vaccine carrier only those vials which were potentially heat-damaged vials.

It is important to recognize the utility of these findings in the setting in which this study was conducted. The study was planned within six months of the widespread introduction of VVMs. As a result, there was limited information available on both their impact and how that impact might be evaluated under field conditions. Especially challenging was the need to design very simple evaluation mechanisms which would in no way complicate the planning and implementation of the first NIDs in Nepal, yet still collect useful data. Finally, although it was recognized that novel cold chain strategies would be needed to immunize all of Nepal's children on a single day, there remained substantial concerns that the viability of the vaccine would undoubtedly be compromised. Because of such concerns, it was particularly important to ensure that this study could provide data demonstrating that in future years the VVMs would make it feasible to further stretch the cold chain, even taking the vaccine beyond the cold chain where necessary during the NIDs.

While these results were encouraging, it is important to recognize the limitations of this study, both with respect to how representative they were and to what extent they could be generalized. Firstly, by nature of the design of this study as a 'convenience' sampling, the results may not be representative of the vaccine storage and handling conditions in all NID posts in Nepal. Secondly, results collected under the climatic conditions of Nepal in December and January are not directly applicable to sub-Saharan Africa in spring or summer. Even in the hotter districts of the Terai, the temperatures seldom reached higher than 25°C during these

NIDs. Third, this study was conducted during a national immunization day, during which the transport, storage and handling of vaccines are substantially different from routine immunization services. The opportunity to realize substantial savings by reducing vaccine wastage during an NIDs is actually limited since vaccine use on these occasions is usually very efficient with less than 15% overall wastage compared with up to 80% during routine immunization sessions. Finally, there is the possibility that problems with the design and implementation of the study may have compromised the results. For example, there was substantial evidence that supervisory error was responsible for many of the reports of heat damaged vials. It was impossible, however, to evaluate whether there were systematic errors in the other direction, such that the number of damaged vials was significantly underestimated.

Despite the problems and limitations noted above, the study demonstrated the capacity of VVMs to provide an effective tool for monitoring and evaluating the integrity of the cold chain. Furthermore, it established a basis for being substantially more aggressive in the flexibility and stretching of the cold chain during supplementary immunization activities for polio eradication in the future. And importantly, this study aided the development of the instruments needed for conducting similar studies.

VVM impact study, Kingdom of Bhutan, July 1997-November 1998
PATH (funded by WHO)

The Kingdom of Bhutan began using VVMs on vials of OPV in 1997. This Bhutan study demonstrated how the use of VVMs can minimize unnecessary wastage of vaccine, especially when combined with policies to retain opened multi-dose vials of liquid vaccine for more than one day.

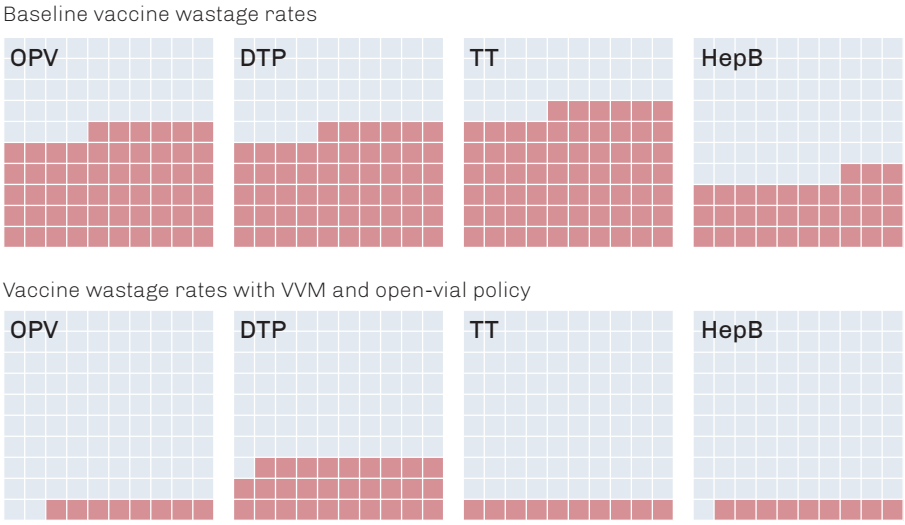
The impact of VVMs and new vaccine- handling practices were studied in eleven districts. Health workers in all districts were trained to read VVMs and collect data accounting for the utilization/wastage of doses of all EPI vaccines during the study period. Three districts adopted the open-vial policy for all liquid vaccines, three districts adopted the open-vial policy for OPV only, and five districts collected baseline vaccine wastage data. From July 1997 through February 1998, the five baseline districts also experimented with the transport of vaccines without ice packs for outreach and the use of VVMs on OPV vials to monitor the heat exposure of other vaccines with which they were transported.

VVMs were used to identify and discard 255 doses of heat-damaged OPV during the study. The heat exposures occurred during long (1- to 3-day) outreach trips and during a kerosene shortage in one district that resulted in an inability to prop-

erly refrigerate vaccines. Health worker understanding of the purpose and interpretation of VVMs was very high as evidenced by interviews and the results of a Knowledge, Attitudes, and Practices survey that was conducted between May and August 1998.

The implementation of open-vial policies resulted in dramatic decreases in the wastage of liquid vaccines. Compared with the baseline districts, wastage decreased by 48.8% for OPV, 27.1% for DPT, 55.7% for TT, and 23.8% for hepatitis B vaccine. Adoption of these policies nationwide could result in annual savings of $17,760 in the cost of vaccine alone.

Vaccine wastage rates before and after implementation of VVM and open-vial policy (brick color markings correspond to wastage)



OPV (VVM and open-vial policy) and DTP, TT and HepB (open-vial policy)

Many important lessons were learned from Bhutan regarding vaccine handling practices and the introduction of VVMs and open-vial policy:

- The use of VVMs on OPV vials as proxies for the heat exposure of other vaccines was discovered to be an inadvisable practice early on in the study due to the strong likelihood that any given vial of vaccine will have been exposed to conditions different from the OPV vial(s) with which it is transported.

- The transport of vaccine without ice during outreach could be highly useful for Bhutan during polio NIDs, but leaves health workers without ice for keeping reconstituted measles and BCG vaccines cool during routine outreach trips.
- When introducing open-vial policies for liquid antigens, attention must be given to setting simple rules for time limits for keeping the open vials. Ideally, the time limits will be linked to the re-supply of vaccine and will not require health workers to document the date on which each vial is opened.
- The introduction of open-vial policies for liquid antigens should include training to reinforce the need to discard freeze-dried measles, BCG, and Hib vaccines within six hours after reconstitution. This was successfully accomplished in Bhutan.

The correlation

In 1997, WHO commissioned a study to test the correlation of VVM reaction with the OPV potency. The study was conducted by National Institute of Biological Standardization and Control (NIBSC) in the United Kingdom. The results were presented by David Wood (NIBSC) at the 1988 TechNet Copenhagen Consultation.

Despite testing by manufacturers, concerns were still sometimes raised that VVMs might not accurately reflect the status of the OPV to which they are attached. This was the main drive for WHO to document the correlation of VVM reaction with the OPV potency. Here we need to underline the fact that although OPV potency was used to correlate VVM reaction at different temperatures, WHO never indicated VVM as a potency indicator since the potency of a vaccine is affected by various factors, temperature abuse being just one of them. Here the consideration centered around how temperature abuses would affect the potency of OPV when all other factors are controlled and how well VVM would reflect this.

Upon receipt of the OPV, five vials were randomly selected for each time and temperature point and all samples were stored at -70°C storage until testing. Samples of vaccine with VVM attached were placed in sealed plastic bags inside an airtight container and submerged in a water bath maintained at 37°C. Incubation periods included 24, 72, and 96 hours. As soon as vaccines were removed from the water bath, VVMs were visually inspected and given a score based on their hues. Then vaccines were moved back to -70°C storage until the test for vaccine potency was carried out. Potency tests were conducted by assaying the total poliovirus

content of each vial in Hep2C cells in microtitre plates, using the standard methodology described in the WHO manual.[4]

The study showed that there was good correlation between vaccine potency and VVM color change for vaccines produced by all four manufacturers that provide OPV to UN procurement agencies. The conclusions of the NIBSC correlation study included:

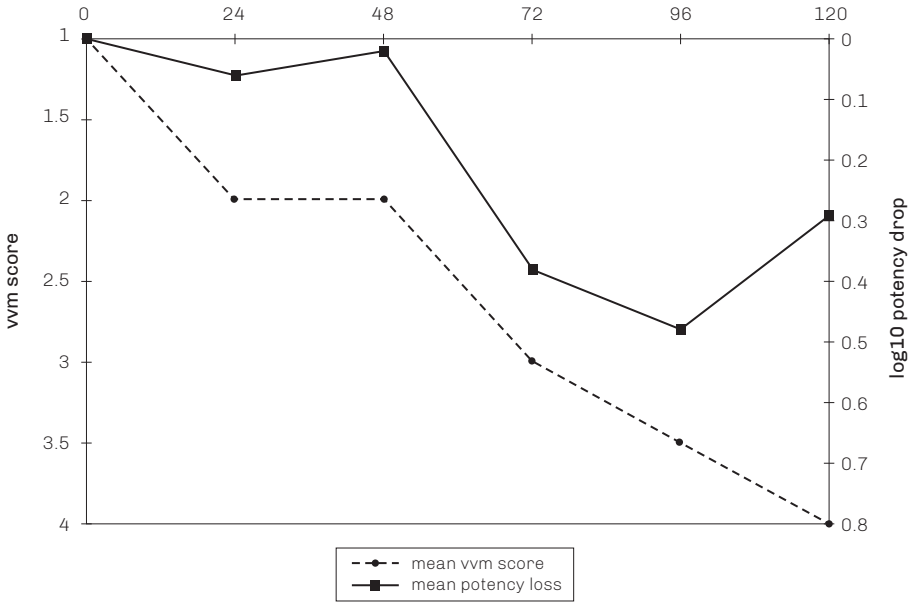
1. Simple visual inspection of VVMs against the standard scale that measures change in color is a realistic test for widespread application.
2. Assay of total virus content, using the standard WHO methodology, is simple, effective, and suitable for widespread application.
3. The test can identify two problems, that is, 1) VVMs reaching the discard-point significantly before vaccines lose their potency; and 2) the reverse, vaccines losing their potency significantly before VVMs reach the discard-point. When VVMs expire too quickly relative to the thermal stability of the vaccine, vaccine will be discarded while still potent, adding to the problem of vaccine wastage. When they expire too slowly, there is a risk that sub-potent vaccine will be administered.
4. The rate of vaccine potency loss differs among manufacturers. The correlation study showed that manufacturers have not taken the advantage of the flexibility in WHO specifications. All have used the minimum VVM standard, and as a result, some vaccines have still been high in titres when the VVMs have reached their discard points.

However, we should note here that additional investigations were carried out to find out why one of the VVM had expired too quickly relative to the thermal stability of the vaccine. Subsequently, it was found out that the vaccine manufacturer of this particular product had used VVM specifications that did not meet WHO specifications.[5] Following the study, the manufacturer had to change to a WHO-compliant VVM.

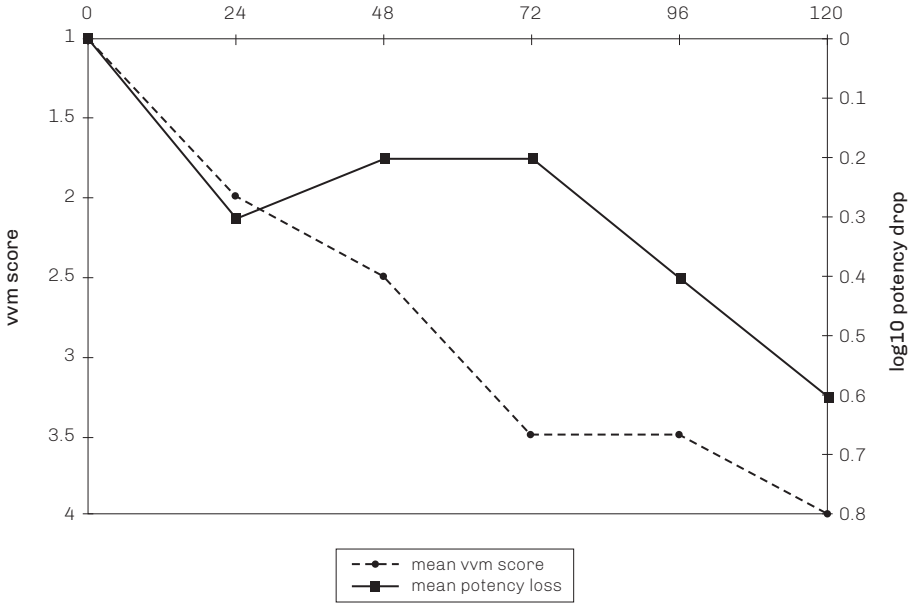
4 WHO. (1997) *Manual of Laboratory Methods for testing of Vaccines used in the WHO Expanded Programme on Immunization.* WHO/VSQ/97.04

5 In the following years, WHO and LifeLines made an agreement that LifeLines would only print VVMs for vaccine manufacturers of WHO prequalified vaccines in a type that is approved by WHO. As a result, all VVM2s for OPV, for example, would be meeting the same WHO specification.

Comparison of drop in potency for OPV and VVM at 35°C (Manufacturer B)



Comparison of drop in potency for OPV and VVM at 37°C (Manufacturer D)



Advocating the use of VVMs on all vaccines

Following the release of the country studies, at the TechNet 1988 Consultation in Copenhagen, WHO, UNICEF, PATH and USAID met to discuss the introduction of VVMs on all EPI vaccines. In 1999, WHO and UNICEF issued a joint statement on the use of VVM on every vaccine of this type. This "Quality of the cold chain" joint statement was the first public call for all agencies purchasing vaccines to include VVMs as one of the minimum requirements to meet WHO specifications. This historical joint statement was signed by Bjorn Melgaard, Director of Global Programme for Vaccines and Immunization at WHO, Veronica Li-Frankenstein, Director of UNICEF Supply Division and David Alnick, Chief of Health Section at UNICEF Programme Division.

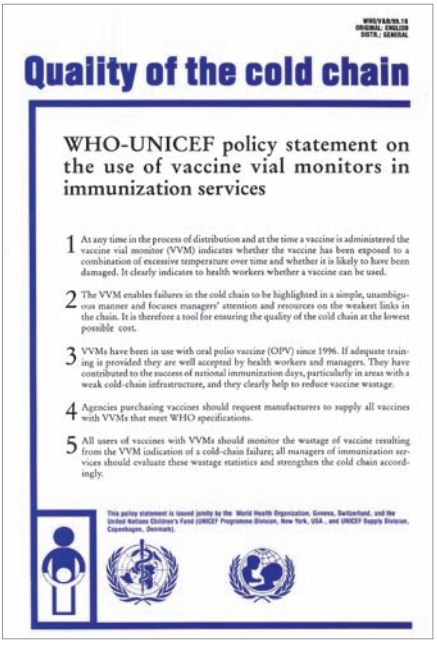
The call included a 5-point statement, followed by background information and its cost implications. The joint statement contained the following paragraph regarding the cost savings from the introduction of VVMs:

"Despite the extensive operational benefits of VVMs, their use does not increase system costs. Indeed, there is a net saving to immunization programmes when VVMs are used. For example, when the results of a study in 12 provinces of Turkey were extrapolated nationally, the countrywide savings from wastage reduction during national immunization days for polio eradication amounted to about $71,500 per year. Again, when a study of eight districts in Bhutan was extrapolated to the national consumption of polio vaccine for routine immunization the annual saving was about $6,770.

"Such savings in the cost of immunization arise from reductions in the wastage of vaccine that is rejected due to cold-chain failures, in the wastage of partly-used vials of vaccine taken to the field, and in the cost of cold-chain equipment where the climate is temperate.

"If similar reductions can be achieved in typical rates of wastage when VVMs are used with all the liquid vaccines figuring in routine immunization programmes the gross savings due to the introduction of VVMs could reach $4.8 million annually.

"Consequently, when vaccine wastage is included in the system cost of using VVMs it can be expected that there will be no increase in vaccine costs to country programmes and that there could be significant global savings."



WHO/V&B/99.18
ORIGINAL: ENGLISH
DISTR.: GENERAL

Quality of the cold chain

WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services

1 At any time in the process of distribution and at the time a vaccine is administered the vaccine vial monitor (VVM) indicates whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It clearly indicates to health workers whether a vaccine can be used.

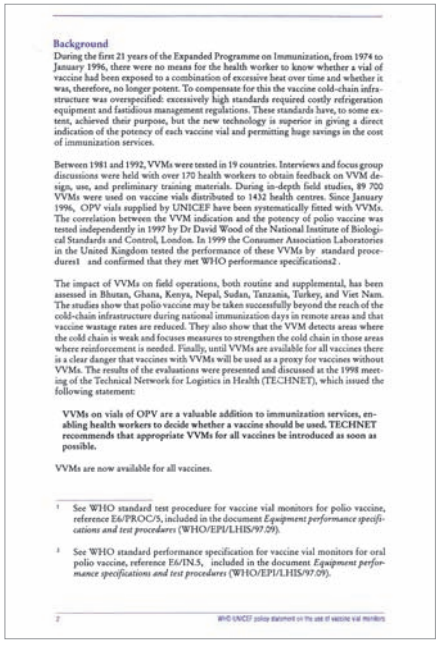
2 The VVM enables failures in the cold chain to be highlighted in a simple, unambiguous manner and focuses managers' attention and resources on the weakest links in the chain. It is therefore a tool for ensuring the quality of the cold chain at the lowest possible cost.

3 VVMs have been in use with oral polio vaccine (OPV) since 1996. If adequate training is provided they are well accepted by health workers and managers. They have contributed to the success of national immunization days, particularly in areas with a weak cold-chain infrastructure, and they clearly help to reduce vaccine wastage.

4 Agencies purchasing vaccines should request manufacturers to supply all vaccines with VVMs that meet WHO specifications.

5 All users of vaccines with VVMs should monitor the wastage of vaccine resulting from the VVM indication of a cold-chain failure; all managers of immunization services should evaluate these wastage statistics and strengthen the cold chain accordingly.

This policy statement is issued jointly by the World Health Organization, Geneva, Switzerland, and the United Nations Children's Fund (UNICEF Programme Division, New York, USA , and UNICEF Supply Division, Copenhagen, Denmark).



Background

During the first 21 years of the Expanded Programme on Immunization, from 1974 to January 1996, there were no means for the health worker to know whether a vial of vaccine had been exposed to a combination of excessive heat over time and whether it was, therefore, no longer potent. To compensate for this the vaccine cold-chain infrastructure was overspecified: excessively high standards required costly refrigeration equipment and fastidious management regulations. These standards have, to some extent, achieved their purpose, but the new technology is superior in giving a direct indication of the potency of each vaccine vial and permitting huge savings in the cost of immunization services.

Between 1981 and 1992, VVMs were tested in 19 countries. Interviews and focus group discussions were held with over 170 health workers to obtain feedback on VVM design, use, and preliminary training materials. During in-depth field studies, 89 700 VVMs were used on vaccine vials distributed to 1432 health centres. Since January 1996, OPV vials supplied by UNICEF have been systematically fitted with VVMs. The correlation between the VVM indication and the potency of polio vaccine was tested independently in 1997 by Dr David Wood of the National Institute of Biological Standards and Control, London. In 1999 the Consumer Association Laboratories in the United Kingdom tested the performance of these VVMs by standard procedures1 and confirmed that they met WHO performance specifications2.

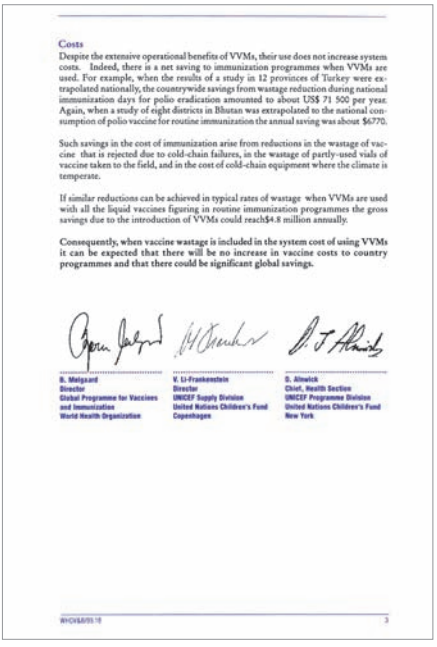
The impact of VVMs on field operations, both routine and supplemental, has been assessed in Bhutan, Ghana, Kenya, Nepal, Sudan, Tanzania, Turkey, and Viet Nam. The studies show that polio vaccine may be taken successfully beyond the reach of the cold-chain infrastructure during national immunization days in remote areas and that vaccine wastage rates are reduced. They also show that the VVM detects areas where the cold chain is weak and focuses measures to strengthen the cold chain in those areas where reinforcement is needed. Finally, until VVMs are available for all vaccines there is a clear danger that vaccines with VVMs will be used as a proxy for vaccines without VVMs. The results of the evaluations were presented and discussed at the 1998 meeting of the Technical Network for Logistics in Health (TECHNET), which issued the following statement:

VVMs on vials of OPV are a valuable addition to immunization services, enabling health workers to decide whether a vaccine should be used. TECHNET recommends that appropriate VVMs for all vaccines be introduced as soon as possible.

VVMs are now available for all vaccines.

1 See WHO standard test procedure for vaccine vial monitors for polio vaccine, reference E6/PROC/5, included in the document *Equipment performance specifications and test procedures* (WHO/EPI/LHIS/97.09).

2 See WHO standard performance specification for vaccine vial monitors for oral polio vaccine, reference E6/IN.5, included in the document *Equipment performance specifications and test procedures* (WHO/EPI/LHIS/97.09).



Costs

Despite the extensive operational benefits of VVMs, their use does not increase system costs. Indeed, there is a net saving to immunization programmes when VVMs are used. For example, when the results of a study in 12 provinces of Turkey were extrapolated nationally, the countrywide savings from wastage reduction during national immunization days for polio eradication amounted to about US$ 71 500 per year. Again, when a study of eight districts in Bhutan was extrapolated to the national consumption of polio vaccine for routine immunization the annual saving was about $6770.

Such savings in the cost of immunization arise from reductions in the wastage of vaccine that is rejected due to cold-chain failures, in the wastage of partly-used vials of vaccine taken to the field, and in the cost of cold-chain equipment where the climate is temperate.

If similar reductions can be achieved in typical rates of wastage when VVMs are used with all the liquid vaccines figuring in routine immunization programmes the gross savings due to the introduction of VVMs could reach$4.8 million annually.

Consequently, when vaccine wastage is included in the system cost of using VVMs it can be expected that there will be no increase in vaccine costs to country programmes and that there could be significant global savings.

B. Melgaard	V. Li-Frankenstein	D. Alnwick
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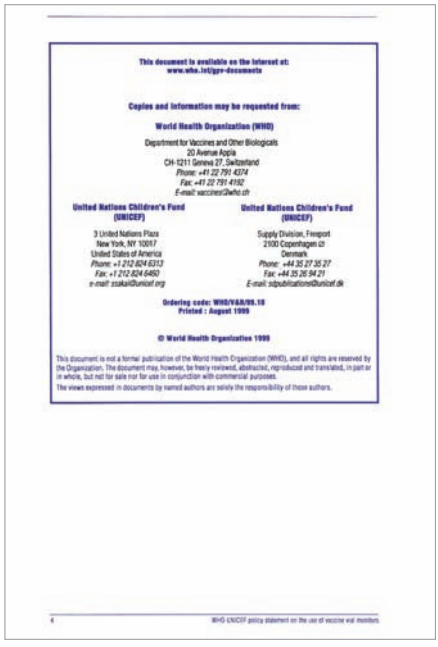

This document is available on the Internet at:
www.who.int/gpv-documents

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As a result, in a pre-tender meeting in Copenhagen, UNICEF announced that VVMs would be included on all vaccines in their year 2000 tender.

World Bank leader James Wolfensohn

Gavi includes VVMs among the minimum requirements for vaccines

Global immunization rates were barely five percent by the time WHO launched the Expanded Program on Immunization in 1974. With the help of the Universal Infant Immunization Campaign, WHO and UNICEF brought the coverage of six vaccines included in the EPI (tuberculosis, diphtheria, tetanus, pertussis, measles and polio) to a remarkable rate of 80% by 1990. But, with donors having other priorities, countries started to face challenges in sustaining immunization programmes. Furthermore, vaccine manufacturers had no incentive to invest in providing vaccines to the world's poorest and needed regions.

In March 1998, the World Bank leader James Wolfensohn convened a summit bringing together WHO, UNICEF, academics, ministers of health, international agencies and the pharmaceutical sector to address the challenges about the future of immunization efforts. Bill and Melinda Gates added to the momentum by hosting a dinner at home to allow leading scientists to discuss the possibilities for action to overcome the obstacles preventing millions of children from receiving essential vaccines.

Bill and Melinda Gates pushed their guests to propose "pioneering solutions". The answer to the challenge was found during a second summit held in Bellagio, Italy where major players in global immunization (key UN agencies, pharmaceutical leaders, representatives of bilateral aid agencies and major foundations) agreed to collaborate as part of a new partnership. This is how the Global Alliance for Vaccines and Immunization (Gavi, the Vaccine Alliance) was born. In November 1999, the Gates Foundation announced its first contribution of $750 million over five years, as the seed money for the launch of Gavi. Two months later, in January 2000, the launch of Gavi was formalized at the World Economic Forum in Davos, Switzerland.

In the same year, UNICEF included VVMs among the 'minimum requirements for vaccines procured by UNICEF' in its invitation to bid for 2001-2003.

First GAVI Alliance logotype when it was announced

Gavi followed this course by including the VVMs among the minimum requirements for vaccines in its request for proposals (RFP) for under-used vaccines, related products and contributions.

Gavi's move towards VVMs added another central power to UNICEF's position for scaling up the VVMs onto all other vaccines.

The end of "no ice, no vaccination"

Local health workers carry in a cooler with vaccines into a health center in Monga, a town in a remote region of northern Democratic Republic of the Congo (DRC)

For immunization campaigns the maintenance of a traditional cold chain was highly reliant on refrigerators and freezers for the storage of vaccines and on insulated cold-boxes and carriers for their transport. The presence of ice was a prerequisite at all times during transportation and at the vaccination site for the continuation of the work of the teams. Challenges were numerous. Many populations had limited access due to difficult terrain. In addition, the cold life of the equipment in relation to the distances to be travelled was not always favorable to workers in the field. All these cold boxes and vaccine carriers loaded with icepacks had to be carried manually and they were heavy. But at the end of the day, with a traditional cold chain, "no ice" literally meant "no vaccination".

The VVM changed this "no ice, no vaccination" dogma. The added cold chain flexibility that was built around the availability of VVM on OPV vials allowed teams to go further in time as well as further geographically. They did not have to carry bulky equipment anymore and the dependency on ice replenishment was reduced. With the flexible cold chain, the number of icepacks needed was also fewer, making the freezing of these icepacks a faster process that required less equipment compared to the traditional cold chain. In a conventional cold chain, products that exited the cold chain for whatever reason, were not allowed to get back in. They had to be discarded. However, with the help of VVM, countries started to abandon the policy of discarding OPV vials at the end of the session or in any cold chain failure, and such practices resulted in serious reductions in cost. And most importantly, health workers and store managers started to decide which vials to use first on the basis of VVM status.

In the manual *"Making use of vaccine vial monitors: Flexible vaccine management for polio"*, published in 2000,[6] WHO explained this approach as follows:

6 WHO. (2014) *Making the use of vaccine vial monitors: Flexible vaccine management for polio.* WHO/V&B/00.14

"The fast chain is a cold chain strategy that seeks to increase the effectiveness of campaigns by a reduction of the dependence on cold chain equipment through pro-active management and short supply lines. The number of refrigerators and freezers required for intermediate storage is kept to a strict minimum through the intense use of cold boxes as secondary distribution points after vaccines leave the central/regional stores. Although the fast chain was already applied before vaccine vials had VVMs, the combination of both increases even further the possibilities for a flexible cold chain during NIDs.

"The elements described above reduce dependence on refrigerating and freezing systems at peripheral level. The fast chain, in combination with the VVM, has the following advantages:

- *difficult to access populations can be reached without installing additional equipment at peripheral level;*
- *installation of a specific NIDs cold chain with its excessive need of ice and probable incompatibility with the routine programme requirements, can be prevented;*
- *the cold chain can be cheaper, although this may be offset by the increased need for freezing equipment at central level."*

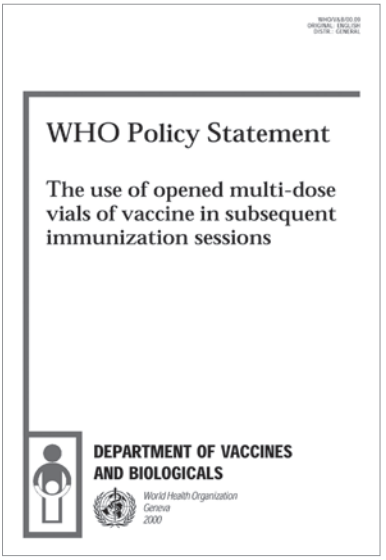
In the manual, WHO also highlighted the fact that, as a result of successful field tests, teams in the front-line that are confronted with melting icepacks, can continue vaccination until they have finished the work, or VVM has reached its discard-point, whichever comes first.

VVM facilitates a new policy introduction by WHO

In 1995, WHO introduced a new policy statement on the use of opened vials in subsequent immunization sessions.[7] At the time of the policy statement, the prevailing practice was to discard all vials of opened vaccines at the end of the session, regardless of the type of vaccine or the number of doses remaining in the vial. The new policy had the potential to reduce vaccine wastage rates up to 30%, with a possibility of commensurate annual savings worldwide of $40 million in vaccine costs. VVMs were considered to be a powerful means of simplifying the introduction of the new policy and associated training tasks. Because of this WHO left it to Member States to decide whether to delay the introduction of this new policy until such time as vials were being supplied fitted with VVM.

7 WHO. (1995) *WHO policy statement: The use of opened vials of vaccine in subsequent immunization sessions.* WHO/EPI/LHIS/95.01

The new policy stated that open vials of OPV, DTP, TT, DT and HepB vaccines could be used in subsequent immunization sessions until a new shipment of vaccines arrives, provided that the expiry date had not passed, that the vaccines had been stored under appropriate conditions (0-8°C),[8] and those opened vials of vaccine which have been taken out of the health centre for immunization activities (e.g. outreach, NIDs) were discarded at the end of the day.



Although the policy statement mentioned the use of VVMs (at the time of the issuance of this policy statement, even OPV did not include VVMs), it was a long way from making the utmost advantage of having VVMs.

In 2000, WHO revised the policy. In this revision, VVMs were factored in. The revised policy stated that multi-dose vials of OPV, DTP, TT, DT and HepB, and liquid formulations of Hib vaccines from which one or more doses of vaccine have been removed during

VVM facilitates better access to hard-to-reach areas

8 The range of cold chain was initially defined as 0-8°C. With the increased risk of inadvertent freezing of vaccines, the lower point has been pulled up to 2°C.

an immunization session may be used in subsequent sessions for up to four weeks, provided that the expiry period has not passed, vaccines are stored under appropriate conditions, vaccine vial septum has not been submerged in water, aseptic technique has been used to withdraw all doses, and the VVM (if attached) has not reached the discard-point. The rationale for the 28-day limit was based on the assumption that, at the furthermost peripheries, stock is replenished once a month. The 28-day limit is not indicative of the maximum performance of the preservative.

The revised policy did not change the recommended procedures for handling vaccines that must be reconstituted (BCG, measles, yellow fever, and freeze-dried formulations of Hib vaccines). Once these vaccines are reconstituted, the recommendation given was to discard all opened vials at the end of the immunization session or at the end of six hours, whichever came first.

The policy was recently revised again in 2014.[9] For details, please refer to "VVM induced vaccine management policies" chapter on page 201.

Aerodynamic loss of lift

Despite the decision of both UNICEF and Gavi to include VVMs as part of their tender requirements and donors like JICA/JICS adopting a policy to include VVMs in all donations, the response from vaccine manufacturers remained remarkably poor. In 2001, only three UNICEF suppliers, Japan BCG, Pasteur Dakar, and Chiron fully complied with the VVM attachment for vaccines other than OPV.

Spanish Patrulla Aguila performing at aerodynamic stall

It was like an aircraft stall, the aerodynamic loss of lift that occurs when an airfoil wing exceeds its critical angle of attack. When it happens, the lift is decreased. That is exactly what was happening with the expansion of VVMs into other vaccines. Vaccine manufacturers were coming back with many reasons why they could not do it. And, there was one other reality: the structural fragility of the vaccine

9 WHO (2014). *WHO Policy Statement: Multi-dose vial policy (MDVP). Handling of multi-dose vials after opening.* Revision 2014. WHO/IVB/14.07

market. For example, there was a period when only two manufacturers were providing measles vaccine to UNICEF, one vaccine with VVM and the other without. It was simply not possible for UNICEF to meet the demand with the VVM vaccine only and the second manufacturer knew this. UNICEF had no other choice than to procure the non-VVM product.

These circumstances were all in the manufacturer's favor in terms of delaying the implementation of VVM on vaccines other than OPV.

When an aeroplane stalls, it must be recovered, otherwise the stall will quickly develop into a dangerous spin. Likewise, with VVMs. If they did not get accepted onto all vaccines, all the painstaking gains could have been totally lost.

When I joined WHO headquarters in February 2001, as the responsible officer for the VVM implementation, my immediate priority was to recover the stall. I started to work on a technical consultation meeting on VVM to address all the issues raised by vaccine suppliers they claimed that were limiting their ability to provide VVMs on all vaccines. I had long sessions in planning every detail of the meeting with my supervisor Julie Milstien at WHO and my friend and colleague, VVM champion Debbie Kristensen at PATH. The whole meeting was planned and carefully debated in advance - everything from the opening remarks and the nitty-gritty of all possible concerns to the final consensus that we were hoping to achieve.

VVM FOR ALL

BCG, OPV, HepB, DTP, DTP-HepB, DT, Td, TT, Hib, YF, Measles, MR, MMR

The consequential "VVM FOR ALL" initiative resulted in a historical technical consultation in 2002 that changed the course of VVM expansion onto vaccines other than OPV.

Recovering the stall

On the 27th March 2002, a meeting took place at the Geneva Headquarters of WHO to review the implementation of the VVM programme. At this session were 71 representatives from all UN vaccine suppliers, time-temperature indicator technology companies, UNICEF and WHO Regional Offices, Member States and other key partners. The meeting served as a forum to review progress to date and discuss the remaining technical and logistical concerns regarding VVM implementation.

In designing the meeting, WHO, with the help of UNICEF, solicited input from the UN vaccine suppliers on the issues that were limiting their ability to provide VVMs on all vaccines. Their unease ranged from regulatory/legal concerns to validation and logistics/operations matters. WHO responded to all these questions on 28 August 2001. In fact, in addition to having regular contact with vaccine manufacturers, WHO, in conjunction with UNICEF, had already began visiting vaccine manufacturers on a one-on-one basis to discuss their VVM implementation issues in detail.

A total of 18 questions and answers were put together and shared with all participants of the technical consultation on 21 March 2002. At this point, I feel I must mention that the early claims by vaccine manufacturers that they were not

involved in the process of introducing new VVMs for other vaccines were simply not accurate. The response from WHO to these allegations can be seen in the WHO circular below which also summarizes some of the activities that preceded this technical review.

1. Vaccine manufacturers were not involved in the process of introducing new VVMs for other vaccines

The historical information on the introduction of new VVMs for other vaccines is as follows, and this explains how vaccine manufacturers were involved in the process as well as the reasons for selecting only four categories of VVMs rather than individual product specific designs.

- In March 1998, the TechNet consultation in Copenhagen resulted in a recommendation for development and deployment of VVMs for all EPI vaccines as soon as possible. The recommendation was based on the positive field response received since the 1996 introduction of VVMs on OPV. In addition to the benefits offered by VVMs at the point of use, VVMs have facilitated highly successful outreach efforts in places where OPV was safely delivered to populations that were previously considered unreachable by the traditional cold chain.
- On 5 June 1998, WHO sent a letter to vaccine manufacturers with proposed specifications for VVMs. In this letter, WHO stressed the urgency of seeking vaccine manufacturers' opinions on whether any of the time-temperature curves proposed for VVMs for vaccines – other than OPV- in the attached paper by Arthur Galazka were too conservative, relative to the actual stability of their own vaccines.
- On 15 June 1998, a technical meeting was held in WHO Headquarters with the participation of representatives from WHO, UNICEF, PATH, USAID and VVM manufacturers. In this meeting, participants recommended using one specification document with a table outlining the different VVM reaction rates for all VVMs. Meeting participants also recommended initial development of as few VVM types as possible. It was agreed that customized products can be pursued after introduction to take full advantage of the stability of individual

vaccines. It was also agreed that besides the "least stable" VVM for OPV, three additional categories of VVMs be introduced for moderately, medium and highly stable vaccines. VVM reaction times were defined based on WHO minimum stability requirements for vaccines falling in these categories. The selected curves represent a compromise between the need to maximize the useful life of vaccine at the lowest temperature and the need to ensure that vaccines that have been exposed to high temperatures sufficient to begin the degradation process are not used. The following table was agreed upon:

Table 1. VVM reaction rates by category of heat stability

Category (Vaccines)	No. days to end point at +37°C	No. days to end point at +25°C	No. days to end point at +8°C
A: HIGH STABILITY	30	193	More than 18 months
B: MEDIUM STABILITY	14	90	More than 18 months
C: MODERATE STABILITY	7	45	More than 18 months
D: LEAST STABLE	2	NA*	140

** VVM (Arrhenius) reaction rates tedermined at two temperature points*

- On 29 October 1998, a meeting was held in Geneva at the WHO Headquarters with participation of representatives from WHO, UNICEF, vaccine manufacturers, PATH and VVM manufacturers. In between the June and October meetings, WHO conducted a series of visits to many vaccine manufacturers to discuss the specifications and implementation issues. Final verification of the acceptability of the VVM specifications was required from the vaccine manufacturers before VVM laboratory qualification testing could begin. In the same meeting, a 3M representative indicated that after four years of development work, 3M had abandoned their technology for VVMs as they could not provide this technology to compete with current prices offered by Lifelines Technology, Inc.
- On 19 August 1999, WHO sent a copy of the "Specifications for Vaccine Vial Monitors" to all vaccine manufacturers. No objection was raised by vaccine manufacturers regarding the stability of vaccines relative to VVM reaction rates.
- WHO made revisions in the VVM specifications (E6/IN5) and test procedures (E6/PROC5) to reflect recent developments such as changing the VVM nomenclature from ABCD to VVM2, VVM7, VVM14 and VVM30 and to include all four VVM types in testing procedures. On 11 March 2002, both documents were circulated to all UN prequalified vaccine manufacturers as well as to UNICEF, PATH and LifeLines for feedback.

The purpose of the meeting was to provide an open forum for vaccine manufacturers in which all previous technical questions and responses about VVM implementation were to be put on the table and discussed.

Objectives of the meeting were to:

1. Highlight the value of VVMs based on experience to date,
2. Summarize the constraints identified by the vaccine manufacturers,
3. Review the response to these constraints, and
4. Agree on action points for full implementation of VVMs on all vaccines.

The meeting represented an opportunity for vaccine manufacturers to express any remaining technical questions. Questions were accumulated during the beginning of the meeting, grouped by topic, and responded to at the end of the sitting.

The gathering also presented an opportunity for the dissemination of information on VVM availability and the growing trend in VVM uptake.

Table. Where are they? VVM implementation by vaccine type, 27 March 2002

Vaccine	Countries receiving vaccines with VVMs
OPV	All countries receiving OPV from UNICEF and/or using UNICEF procurement services for OPV purchase
BCG	Bangladesh, Cambodia, East Timor, Jordan, Nepal, North Korea, Myanmar, Pakistan, Philippines, Syria
Yellow fever	Angola, Benin, Burkina Faso, Central African Republic, Chad, Gambia, Kenya, Mali, Pakistan
Measles	Albania, Burundi, Congo, Croatia, Cuba, Ghana, India, Jordan, Kenya, Lebanon, Macedonia, Morocco, Nigeria, Pakistan, Rwanda, Sierra Leone, Syria, Tanzania, Uganda, Vietnam, Zaire
MMR	Colombia, Cuba, Syria, Yugoslavia
HepB	Albania, Azerbaijan, Bangladesh, Benin, Cambodia, Cape Verde, Fiji, Gabon, Kyrgyzstan, Lebanon, Moldova, Mongolia, Morocco, Pakistan, Russia, Spain, Turkmenistan, Uzbekistan, Yemen, Yugoslavia, Zambia
TT	Burkina Faso, Indonesia, Uganda

Source: Compiled data from WHO, vaccine manufacturers and LifeLines

VVM availability since 1996 was showing an upwards trend, mainly due to polio NIDs and the fact that four manufacturers had already adopted VVMs on non-OPV vaccines. By the time of the meeting, over 500 million VVM units had been used since its introduction in 1996.

Questions, questions...

Dr. Mercy Ehel Ahun, the immunization programme manager in Ghana gave a presentation on the programme perspectives of VVMs. Dr. Ahun said that VVMs were essential to make an informed choice about whether or not to use a particular vial of vaccine, that could potentially have been compromised as a result of access problems, again cold-chain equipment and shortages of paraffin, gas, and electric power. She further explained that the VVM was the only tool that was available at all times (during distribution and storage as well as when the vaccine is administered) to indicate whether the vaccine had been exposed to a combination of excessive heat over time and the likelihood of having it been damaged.

"The field has a need for VVMs to help monitor vaccines effectively and to deliver vaccine not deactivated by heat. Today, the best contribution vaccine manufacturers can make would be to provide VVMs on all vaccines to make a difference in the life of a child."

There was a general consensus that VVMs could play an extremely valuable role in improving the quality of immunization efforts throughout the world.

A remote village in Kalimantan island, Indonesia, that could only be reached by river

In the next session that was held, I gave a presentation on the questions and concerns raised by the vaccine manufacturers and reminded all participants that WHO had responded to all these questions before the meeting (circular of 21 March 2002). I summarized the questions in categories:

VVM full label application to TT vaccine, BioFarma, Indonesia

Validation issues

1. The shelf life of the VVM is less than the shelf life of the vaccine
2. Will WHO conduct correlation studies for VVMs and vaccine potency for all vaccines?
3. Can the VVM consistently reflect the true stability of each vaccine?
4. What data exist to show how the VVM is validated?
5. Is there some typical specification for VVM adhesion?
6. Chemical temperature indicators produce a high percentage of false readings

Logistical issues

1. Concerns about introducing a different labeling system for a portion of their production
2. How to maintain the logistics of import and inventory control?
3. Different multi-lingual, multi-production and multi-packed quantities
4. Additional capital expenditures to implement VVMs
5. Does the current GMP requirement prohibit pre-printed labels or require an on-line printer with a blank roll?

Regulatory issues

1. Does VVM attachment to the vaccine vial need to be approved by the national regulatory authority?
2. Who is legally and financially responsible when a vial or shipment is rejected because the status of the VVMs indicates excessive heat exposure?
3. Does the manufacturer's obligation cease at the time that the shipment is accepted in country?

Programmatic issues

1. What is the benefit of having a VVM on a vaccine that is very heat stable, such as hepatitis B?

2. Is the VVM color change clear, and does it convey the information to the field worker in a form that is easy to understand?

Commercial issues

1. LifeLines is the sole supplier of VVMs, there is no other competitor
2. Why doesn't the LifeLines warranty mirror the minimum shelf life required of the vaccine suppliers (18 months from the date of shipment from the vaccine supplier)?
3. Why does LifeLines have a +/-10% tolerance on the quantity of VVMs delivered?
4. Why does a minimum VVM order quantity have to be set?

In the case of commercial issues, vaccine manufacturers were encouraged to approach the VVM manufacturer, Lifelines, directly since many of the issues had already been addressed by the company.

In addition to the above list, industry representatives were asked whether they had any additional statements and/or questions.

Walter Vandersmissen from GSK took the floor and made the following remarks on behalf of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA):

- *"The vaccine industry does not need further convincing that VVMs serve a purpose.*
- *Each issue has more or less importance to individual companies.*
- *Concern is due to the disconnect between what VVM was conceived as and what it seems to have become in the effort to address regulatory issues. Originally there was a correlation between VVM response and potency. The industry wants such a correlation. Therefore, we are making a plea to find a VVM that can do this. There is also a need for public/private partnership. WHO should ask for proposals for a "more perfect" VVM indicating the remaining potency of the vaccine.*
- *Also, there is a regulatory question. WHO has inquired and stated that regulatory approvals are not needed. We find this surprising, but will be happily surprised if it is true. There is a need*

to clarify if regulatory authorities in Western countries will demand certain things. We also need validation standards to validate VVM performance. The regulatory authorities in this case may be tolerant, but that is not the norm.

- *The VVM informs of exposure to heat and manufacturers are responsible for product potency. But there are circumstances where the current VVM will not reflect the condition of the vaccine. The VVM does not register freezing for instance. Also, there is a tolerance with shelf life and expiry. The vaccine might be OK and the VVM not OK. Also, are we sufficiently certain that brief exposures to high heat will not be shown by the VVMs, yet might harm the vaccine? There is also a liability issue. Manufacturers can take responsibility for a vaccine only on the provision that it has been correctly stored, and they need a liability disclaimer that says that the VVM is something provided at a customer's specific request.*
- *LifeLines is a sole supplier. They have a significant responsibility when supply VVMs. Also, it is important to realize that the standards we have set today do not prevent something better from evolving. Some manufacturers are already content with the regulatory/liability issues, but others may not be.*
- *VVM development was carried out without the due rigor of the pharmaceutical world, e.g. GMP conditions. Manufacturers have been advised by LifeLines, however, that progress with GMP has been made.*
- *We are also puzzled that if LifeLines is so indispensable and VVMs are so desirable, then why doesn't PAHO also want VVMs? Therefore, we make a plea for standardization in this mass market as much as possible.*
- *Also, implementation means time and cost for investment by vaccine manufacturers in terms of equipment and management. We are not necessarily opposed to this, but we need to execute in the most efficient manner possible. Some companies are more ready than others (e.g., those who already have VVMs on polio vaccine), and there are disparities between companies due to the number of "late joiners".*

It was a significant statement that Vandersmissen made in his opening statement when he said that the vaccine industry did not need any further convincing that VVMs serve a purpose. His second highly supportive statement was that although implementation meant time and investment by vaccine manufacturers, they were not opposed to this, only that they wanted the VVM introduction to be carried out with a controlled and methodical approach. However, some of his comments were forceful and pushing the limits of what VVMs were designed for. An example of this was when he insisted that WHO should be seeking proposals for the development of a dip-stick indicator, something which he referred to as a "more perfect" VVM that would indicate the remaining potency of the vaccine.

This request seemed to be at odds with the reality of supply chain temperature monitoring at that time. If the industry was so much concerned with what was happening to their products in the field, the existing temperature monitoring devices were not going to be particularly helpful in giving an answer, simply because there were no linkages between any of the devices that were in use at different levels of storage and distribution supply chain. In this respect, VVM was the only tool that was available throughout the supply chain, from the manufacture until the point of use. This is why I liked to call VVM the "smart expiry date".

Other participants raised the following points:

- *With the new specifications, the lower endpoint is now 5°C. Would like to know more about the reasons why 5°C replaced the 8°C specifications in the document.*
- *Has a technique to measure the potency prior to use been explored?*
- *Three machines for labeling are mentioned in the meeting folder. We need to put VVMs on the neck of ampoules. Japan BCG used a machine developed in Japan to do this. Is the piggyback machine used for ampoules or just for vials? The ampoule neck is very high and it is hard to imagine technically adhering a VVM to a neck of an ampoule without breaking it.*
- *If the VVM manufacturer has a supply problem and the vaccine manufacturer cannot receive VVMs, who is responsible?*
- *Does the VVM show the freeze cycle in OPV?*
- *Regarding the new test procedures, testing should be performed within 10-15 days following the receipt of sample VVMs. If VVMs are to be kept at -20°C in a freezer, then why cannot testing be performed at any time?*

Some of these questions (e.g., why the lower end-point is now 5°C) were already answered in the Q&A document that was circulated to all participants a week prior to the meeting. Furthermore, the same file was in their folders right in front of them. Nonetheless, the request for a dip-stick potency indicator was again brought up by another participant.

I explained that all the issues will be discussed in coming sessions dedicated to validation, logistics, regulatory and programmatic matters.

Regulatory and legal issues

When VVMs were implemented with the OPV, WHO paid reassessment visits to manufacturers and various regulatory authorities, provided a VVM information pack, and kept an open dialogue on the VVM issue. Regulatory authorities had been aware of VVMs since 1996 but although the need for regulatory oversight

had not come up as an issue with OPV VVMs, there was now some concerns being raised by manufacturers. As a result, WHO decided to accelerate their interchange with regulatory authorities including those dealing with the larger suppliers of vaccine to the UN system. The reaction from regulatory authorities can be summarized as follows:

Regulatory considerations on VVM implementation on all vaccines: Responses from National Regulatory Authorities (NRA)

Region	NRA position
Asia	**India:** Notification to regulatory authorities needed and some attention required during routine GMP inspections as for any other item related to packaging and shipping and transport.
	Indonesia: Notification to regulatory authorities needed and some attention required during routine GMP inspections as for any other item related to packaging and shipping and transport.
Europe	**Belgium:** No regulatory approval required for vaccines that are exported, but would be subject to checking during GMP inspections and would like to be notified of VVM implementation.
	France: No regulatory approval required for vaccines that are exported, but would be subject to checking during GMP inspections and would like to be notified of VVM implementation.
	EMEA: Awaiting response
America	**USA:** If the vaccine is not licensed for U.S. distribution, the exportation must comply with the regulatory requirements described in Sections 801 and 802 of the Food, Drug and Cosmetic Act (21 CFR 381 and 382) which refer to export provisions. If specific vaccine as labeled is licensed for distribution in the US, manufacturers need a supplement to their license application. The exact situation of vaccine for UN market needs further clarification with USFDA. USFDA advises U.S. manufacturers implementing VVMs to contact the agency directly.

Dr. Otavio de Oliva, Regional Advisor for AMRO (PAHO), commented on PAHO's position on VVM implementation to the effect that they had not accepted VVMs at that point, because they were available only for OPV and polio had already been eradicated in the Americas. Nevertheless, they were revisiting this position, and before they took a decision, country level regulatory issues (country where VVM produced, country where vaccine produced, and the receiving country) needed to be checked. Dr. de Oliva also mentioned that PAHO would investigate the positions of the regulatory authorities in the Americas. He explained that PAHO's delay was due to their wish that all vaccines should have VVMs.

"All technical information with regard to the use and interpretation of the VVM must be provided to countries. Also, countries must agree to the added expenditure. PAHO is also considering training needs. All these questions must be answered, at which point PAHO will probably accept vaccine with VVMs."

Dr. de Oliva was challenged with a question as to which countries were interested in VVMs but he said this information was not available. Then the uptake listing that I had mentioned at the beginning of the meeting came up that showed Colombia and Cuba receiving MMR vaccine with VVMs. Dr. de Oliva said he was not aware of this. He consistently referred to "acceptance" by regulatory authorities, and not to the demand from the countries in the region. It was never clear whether any EPI programme in the region was actually consulted.

Several participants brought up the issue of the responsibilities of vaccine manufacturers vs. that of LifeLines. Their concern was centered on what would happen if a shipment was rejected based on the VVM readings. The industry did not want to take any responsibility in this regard. In reality, international shipments are accepted/rejected based on the contractual terms that have been agreed between the two parties. In this case such contracts already contained a clear definition of the criteria for acceptance at the time of delivery and the vaccine industry did not have any problem with this. VVMs were not designed as shipping indicators, and although they were required to be checked upon arrival, their inclusion did not dictate whether to accept or reject the shipment so it was difficult to understand what was the issue with VVMs. In any case, the concern was totally theoretical, because, in reality, the likelihood of a VVM going bad in an international shipment is extremely slim, unless there are problems with the shipping itself, an event which would be picked up by the dedicated temperature monitoring devices in place for that purpose. It was difficult not to think this was another delaying tactic.

Public liability considerations were discussed separately with similar 'what if' scenarios considered. Situations such as what might happen if a faulty VVM managed to get into the field. The answer to this is that the chances of a non-functioning VVM getting into the field is extremely low from the risk point of view since there are at least five redundant controls in place:

- Validation by the VVM manufacturer is done first with the monomer dye, then during the printing and finally before release at 37°C.
- Vaccine manufacturers additionally validate VVMs using the same validation procedure, testing the VVMs at 37°C.
- On arrival of VVMs to vaccine manufacturer, spectrodensitometer readings are executed and this is cross checked with the release certificate values coming from LifeLines.

- Vaccine manufacturers also run random testing at 37°C from the VVMs they use
- Vaccine manufacturers conduct GMP audits of LifeLines

Although this defective VVM issue was totally theoretical, the following two possibilities were explained:

- the VVM could reach end-point earlier, and the vaccine would be disposed of resulting in some wastage, but there would be no increase in risk or liability.
- the VVM could fail to reach the end-point in time, with the potential risk of using a heat exposed vaccine. This is the only scenario where a potential liability exists. However, this scenario exists with or without VVMs. It should be noted that in six years of experience and over 10 billion doses of vaccine (corresponding to more than 500 million VVMs used), there have been no documented failures of a faulty batch of VVMs reaching the field.

During the discussions, one industry representative mentioned that he could envisage a number of potential complaints and liability situations amongst them the fact that vaccines get repackaged in some countries and different shades of VVMs are imaginable. *"We won't be able to address all these possibilities"*, he groaned.

We were getting closer to what we wanted the industry representatives to unleash. I explained that the example given was more of a potential wastage, than a liability issue. *"The VVM is a tool that reduces rather than increases liability. The risk of exposure to unacceptable temperatures exists no matter what."*

Another industry spokesperson admitted that they all accepted that there is some liability involved. *"It is a fact of life,"* he said *"however, we would like vaccine manufacturers to clarify any reasons why they believe that VVMs could make the situation worse, bearing in mind that the risk of temperature excursions is always there, with or without VVMs."*

"The reality is that it doesn't make the situation any worse" said Vandersmissen, who represented vaccine manufacturers from industrialized countries, *"In fact it makes it literally visible. Before the VVM, there was no way of telling if vaccine had been heat abused. Now it can be traced. The positive is that non-viable vaccine will be discarded, but the flip-side of that is that people will want compensation for it."*

At this point I interjected: *"Isn't there the risk anyway? Isn't VVM a tool to reduce the use of unacceptable quality vaccines?"*

"Yes, it will reduce the risk," said Vandersmissen, bringing the discussion to an end, *"but it won't take it away."*

Health worker in Kaou health centre (Niger) tells he trusts VVM

The participants all agreed that liability issues exist with or without the VVM, and that an inclusion of VVM did not add any additional liability. On the contrary, it served to reduce the liability of vaccine manufacturers.

Validation issues

Next up, the process of adding VVMs to products was reviewed, highlighting the points where the VVMs are validated and other quality control tests are conducted. All the steps and procedures involved in VVM application starting from the request by the vaccine manufacturer to VVM attachment to individual vials were explained.

Panacea Biotech raised the question of conformity issues between VVM batches that they had received with different starting optical densities between batches. Ted Prusik explained that the issue raised here is not the optical density issue, rather it is about consistency between the batches. *"We all have a common mission to provide high quality vaccine to the point of use to prevent vaccine preventable diseases"* said Prusik, *"LifeLines wants to work openly and transparently with the vaccine manufacturers. LifeLines prides itself on its demonstrated progress in quality over the last several years and in its continuing quality improvement initiatives. This commitment is emphasized in our current Quality Policy of 12 February 2002. The evolution of our Quality Management System began with management's decision in September 1999 to become ISO 9001:1994 registered. This commitment resulted in the successful registration of our company by SGS International Certification Services, Inc. in March*

2001 (Certificate Number: US2001/2459). A surveillance audit was completed by SGS in September 2001, with registration being maintained. The quality system currently registered is compliant with the FDA quality system requirement (QSR) under 21 CFR 820. Such a commitment is consistent with the rationale provided relating cGMP to ISO standards under 21 CFR 210/211 during its proposal phase (May 1996). The Company has demonstrated its increasing commitment to improving the quality system by now taking two key steps:

- *First, to become ISO9001:2000 registered in May 2002, Lifelines will be committing to specific performance metrics that are required by the new revision and generally consistent with the position of the FDA regarding process control and cGMP.*
- *Second, the system will be further refined to enhance cGMP compliance by June 2002."*

Ümit Kartoğlu with Jean-Paul Martin, Zermatt, Switzerland, April 2019

LifeLines becomes a quality driven organization

Jean-Paul Martin, President and CEO of LifeLines was the instigator of LifeLines becoming a quality driven organization. *"When I discovered what LifeLines was doing with VVMs, I fell in love with the product. When I first came to Lifelines I was thrilled at the VVM prospect and naively believed that it probably could be developed quite quickly and that the associated problems would be relatively easy to address. But I must say this was a mistake, it took much longer than we thought. At the time, the company was losing a lot of money although there was a high level of respect for quality. It was a challenge to reach this high-quality standard with VVMs and the initial yields were low. But the Lifelines team were fantastic. We had to become ISO9001 certified, which took us two and a half years, and this stimulated a step-by-step improvement of every aspect of the process."*

The most recent ISO 9001 and ISO 13485 quality certificates of Temptime

Prusik summarized: *"The Company has developed a transparent 'open door' policy and is delighted to cooperate with any vaccine manufacturer in the examination and improvement of its quality system, and also to organize any visit to the facilities to provide information and training on all aspects of VVM function, use and implementation. GSK and Aventis Pasteur recently audited LifeLines, with few comments."*

Dr. Prusik further explained the VVM manufacturing process and polymer color reaction and how LifeLines prepares each batch for release. *"LifeLines monitors storage conditions in storage freezers and water baths with thermocouple monitors. Due to the inherent variability of densitometers, based on practice the allowable variability was increased slightly in the specifications. LifeLines uses computer interfaces with their densitometers and flatbed scanners to reduce release times."*

At this point, the entire debate moved into a more free-form, provocative mode with the aim of challenging VVM, even for the things it had not been designed for:

"VVMs do not record freezing temperatures."

"This is correct. However, it should be noted that VVMs are indicators of heat exposure, not freezing. It is unfair to expect the VVM to do more than what it is designed for."

Vaccine manufacturers started to demand new VVM reaction tests even for data they did not have for their own products. In this regard, three major comments/questions came up:

- *"In real life the product will not be at consistent temperature and temperature spikes may occur. Therefore, Merck wants to see the range of performance. Besides, we should be looking at multiple lots and use a standard sample size."*
- *"We [Wyeth] also want to see the cumulative effect of up and down temperatures rather than static ones."*
- *"Have there ever been any tests done with probes inside and on the vial together?"*

Dr. Nora Dellapiane (WHO), underlining the concerns raised regarding the peaks in temperature and the desire for studies in variable conditions, stated that vaccines for licensing never go through such field tests, and asked whether any vaccine manufacturer have such data for their products.

The answer was a resounding "No" and Vandersmissen averred that they do not need to collect such data.

It seems that vaccine manufacturers were demanding studies on VVM for risk scenarios that they had never seriously contemplated for their own products!

Prusik explained that the difference between the label level and internal vial temperature is minimal. He further elaborated: *"Before considering any new test, LifeLines suggests that we ask two questions: 1) Is there a real interest for public health in doing these extra studies? 2) Is there an interest to ask more of the VVM than you ask*

of your vaccine? The major manufacturers who have been using the VVMs for years, seem comfortable with the VVM which gives reliable protection against the possibility of vaccinating children with vaccines that could have been heat inactivated."

There was no reaction but silence from the participants to Prusik's questions and comments.

The session ended with an agreement that all validation and conformity studies should follow the standard test procedures (E6/PROC/5 dated 25 March 2002) and product specifications (E6/IN5 dated 25 March 2002). It was also agreed that, some manufacturers may need additional testing to meet internal or national regulatory authority requirements. LifeLines offered to work with individual vaccine manufacturers to study any additional testing that could be of specific interest to their vaccines.

Logistics issues

Next on the agenda were Japan BCG and Chiron who each delivered practical presentations on how they overcame their VVM label application problems. Japan BCG had solved the formidable problem of how to successfully label the fragile neck of an ampoule while Chiron had uncovered the secrets of top labelling. These presentations served as an example to all others who were still struggling with such applications.

Sole-source supplier issue

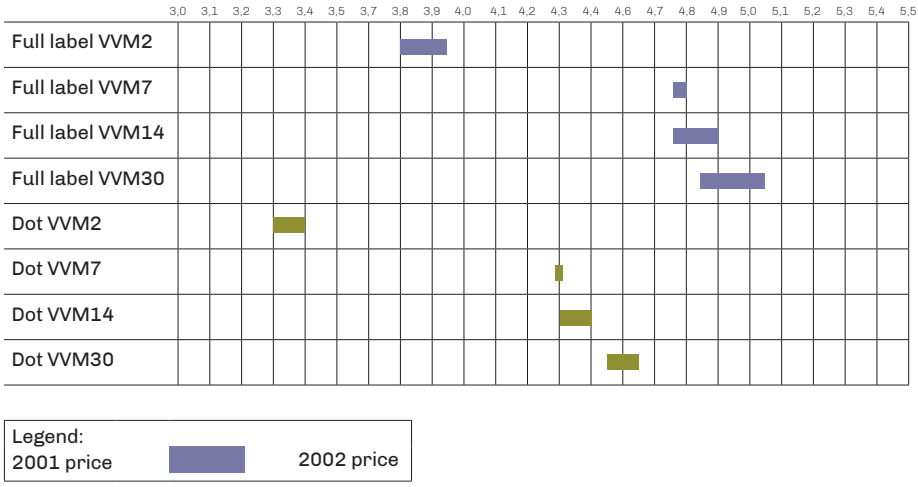
It was during the final 'any other business' session that questions around the reliance on a sole-source supplier was raised by several manufacturers. Their claim was that vaccine prices were decreasing and there were no competitors for LifeLines. In reality, the vaccine prices were not decreasing, *"We have lost vaccine producers and prices are increasing"* said Steve Jarret (UNICEF SD), *"There is tremendous concern about the exit of manufacturers from basic vaccines and shortages of supply. We have to listen to manufacturer's concerns and do not want to place undue constraints on them. UNICEF plans to visit not yet pre-qualified manufacturers to discuss commercial issues with regard to these traditional vaccines."*

The process of VVM development had started back in 1989 during which time PATH had worked with several different potential VVM manufacturers (3M, LifeLines Technology, Bowater/Rexam, Albert Browne, CCL Label, and Sensitech). But apart from LifeLines, none of these companies had succeeded in developing a VVM that could meet WHO specifications or be produced at an affordable price. The reality is that in today's world we often deal with single sources of supply,

vaccines themselves being a good example. Indeed, some of the delegates at the Geneva meeting enjoyed sole supplier status for some of the new combination vaccines.

The question of being a sole-source supplier and that of taking monopolistic advantage are two different issues. Ever since its involvement with VVMs, LifeLines Technology always kept its VVM prices as low as possible with any price uplifts never more than fractions of cents and always below the original target price. In order to illustrate this, a comparison of standard full label and dot VVM unit prices for 1 million units in U.S. cents by 2001 and 2002 was displayed.

VVM price comparison for 1 million units in U.S. cents, 2001 and 2002



The joke that did the rounds during the meeting's winding-up coffee break was that since 3M had developed a technically viable VVM at three times the price of the HEATmarker product it only needed LifeLines to triple the price of their product for 3M to stay in the market and compete. Ergo, competition at a stroke...!

Vaksin Hepatitis B rekombinan
Hepatitis B Vaccine recombinant
0.5 ml
Bayi/Neonate
Prefill Injection device
1 dosis (0.5 ml) mengandung/1 dose (0.5 ml) contains :
HBsAg.....10 mcg
Al+++.....0.25 mg
Thimerosal.....0.01 %w/v
Injeksi Intramuskular/Intramuscular Injection
Harus dengan resep dokter/On medical prescription only
Kocok sebelum dipakai/Shake well before use
Keterangan selanjutnya lihat brosur/For further information see brochure
Simpan pada suhu/Store at 2-8°C
No. Reg. GKL 9602605453A1
PT. BIO FARMA
Bandung-Indonesia
365046
APR 08

Five senses

Following the 2002 Technical Review of VVM Implementation meeting, it took until 2007, the 10th year anniversary of VVM implementation, before the majority of prequalified vaccine products, nearly 80%, were displaying a VVM.

In 2002, for a measles campaign, Vietnam received measles vaccine from two separate sources, with the vaccine vials from one bearing VVMs, and vaccines from the other without. It was clear that the non-compliant manufacturer was aware that there were no other manufacturers in a position to meet the demand – so they simply omitted to comply with the VVM requirement. Faced with this situation, the authorities in Vietnam managed to channel the vaccine fitted with VVM to the remoter and more distant locations and circulated the vaccines without VVM mainly in cities. Hard-to-reach communes with very weak or no cold chain were highly reliant on the VVMs which protected against unwelcome temperature damage and reduced the number of supply trips, wastage and, ultimately, the cost.

In 2002, WHO released two critical publications on VVM implementation, both prepared by a team at PATH, led by Debbie Kristensen. The first of these publications was a practical guide on how to adopt global vaccine management poli-

cies for national use.[10] The guideline highlighted that national programmes were missing out on opportunities to improve vaccine management and to save resources by not considering the adoption of relevant global policies. The focus was on the development of new global policies for improving the administration of safe and effective vaccines, policies that were subsequently adopted and issued by WHO, UNICEF and UNFPA in recent years:

- the WHO-UNICEF policy statement on the use of vaccine vial monitors (VVMs) in immunization services (WHO/V&B/99.18);
- the WHO policy statement on the use of opened multi-dose vials of vaccine in subsequent immunization sessions (WHO/V&B/00.09);
- the WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services (WHO/V&B/99.25).

The guideline used the adoption of VVMs as a case study and means to improve the efficiency and effectiveness of vaccination programmes, simplify vaccine handling and reduce vaccine wastage, as well as to improve the availability, quality and safety of immunization efforts. In order to gain the benefits, national immunization services and their partners were called upon to prepare national policies, write procedures and, most importantly, implement and monitor them.

The publication went on to take readers through all the steps involved in the adoption of these protocols starting with the translation of global policy into local language and its subsequent distribution. While taking readers through this process, examples were given from each of the abovementioned three global policies, including the VVM.

Case study 7:
National VVM policy example (fictitious)

Policy title/(number):	Use of vaccine vial monitors (VVMs)/(7385)
Topic:	Vaccine selection and discard, vaccine vial monitors
Date policy takes effect:	30 June 1999
This policy replaces policy:	7001 of December 1982
Responsible Office:	National immunization service
Responsible Officers:	National logistics officer (implementation) National vaccine procurement officer

10 World Health Organization. (2002). *Adopting global vaccine management policies for national use,* World Health Organization, Geneva, WHO/V&B/02.32

Authorizing legislation (if necessary): Vaccine regulation 171-00, vaccine procurement 284-00, and destruction of state property (vaccine) 333-221

Policy statement: National health staff should use VVMs present on the vaccine vial or container to help select or discard vaccines. Vaccine with a VVM indicating excessive heat exposure should be discarded. The quantities of vaccine discarded should be noted on the stock inventory form, and the reason for discarding should be noted. This information should be reported centrally, and wastage rates by cause should be reported annually.

Reason for the policy: The purpose of this policy is to:

- reduce the quantity of usable vaccine that is discarded when storage or transport temperatures exceed 8°C;
- prevent heat-damaged vaccine from being administered;
- facilitate vaccination in areas without refrigerators or freezers;
- identify problems in cold chain management;
- achieve realistic wastage rates to aid in projecting the quantities of vaccine needed in the future;
- decrease the costs of immunization services.

Impacted persons: Vaccine procurement officers, MCH and EPI nursing staff, NID vaccinators, logisticians, drivers, EPI managers and incinerator supervisors.

Impacted procedures: 701 vaccine procurement procedures, 342 vaccine donation, 281 vaccine use and reporting, 990 vaccine shipping and storing, 043 calculating vaccine wastage rates, and 088 procedures for cold chain failures.

Forms and reference documents: Vaccine specifications for tender form, vaccine inventory and discards form, NID reporting form, VVM training poster, and VVM training sticker.

Major conditions or restrictions: Vaccines must meet national and WHO quality standards in addition to having VVMs. If no qualified vaccine is available with VVMs, the head of the national regulatory agency may approve purchase of vaccine without VVMs. The private sector will be encouraged to use vaccine with VVMs.

Donated vaccine is required to meet the WHO regulatory criteria and is required to have VVMs.

The second publication from Kristensen's team at PATH was a rewrite of the previously published *"Vaccine vial monitor and open vial policy – questions and answers (WHO/EPI/LHIS/96.01)"*, under a new title: *Getting started with vaccine vial monitors (WHO/V&B/02.35)*. It was a local language version of this document that was used in workshops in Vietnam for training health workers on the use of VVM with measles vaccine for field-testing purposes.

The question and answer style of the book made it easy to read. The contents consisted of 37 questions organized under six headings from 'how a VVM works' to 'the impact on programme operations.'

Getting started with vaccine vial monitors also included two KAP survey questionnaires on the impact of VVMs.

Acceleration

In 2002, one more UNICEF supplier, LG Chemical fully complied with the VVM attachment relating to vaccines other than OPV.

In 2003, WHO held a regional meeting with vaccine manufacturers in New Delhi, India in an attempt to accelerate the expansion of VVM beyond OPV. In the same year, PATH, under Carib Nelson's leadership, assisted the Indonesia Minis-

Debbie Kristensen, Ted Prusik, Darin Zehrung, and Carib Nelson in a global health conference, Washington D.C., USA, 2007

try of Health in conducting a cold chain study into the removal of icepacks to prevent freezing and reinforce usefulness of VVM in the prevention of vaccine freezing. A series of meetings were organized in Jakarta, Indonesia, for this important change in local vaccine distribution policy, and I was part of the working group representing the WHO.

An important milestone was reached when the Supply Division at UNICEF issued a new tender for 2004-2006 in which the inclusion of VVMs was one of the minimum standards for all vaccine purchases. From this time forward, UNICEF always included VVMs as one of their mandatory requirements for vaccine purchases.

UNICEF requests vaccines with VVM

4.2.9. VACCINE VIAL MONITORS (VVM)

Vaccine vials should be fitted with Vaccine Vial Monitors (VVMs). VVMs should comply with WHO PQS Performance Specification (WHO/PQS/E06/IN05.1) and in the PQS independent type-testing protocol (WHO/PQS/E06/IN05.VP.1). (Annex C).

4.2.11. VVM and UNIT PRICING

UNICEF requests vaccines with VVM. Unit pricing is to include the price of VVM, however the manufacturers shall also provide the price addition, if any, that inclusion of the VVM represents. If a manufacturer has not implemented VVM but has a plan to do so, unit pricing shall be offered without VVM with a price adder which is to be included in the unit price when VVM becomes implemented.

From the Request for Proposal, UNICEF, RFP-DAN-2012-501387

In its meeting in Dakar, Senegal in November 2002, the board of directors at Gavi resolved that all vaccines purchased by the Vaccine Fund had to include VVMs after 2003. The decision by Gavi as another important purchasing body represented a significant stimulus to the VVM project.

In its first meeting of 2003, the Gavi Board recommended immediate intensive action by appropriate Gavi partners to accelerate the implementation of VVMs, as fast as consistent with maintaining vaccine quality. And in its July 2003 issue of *Gavi Immunization Focus*, the organization published an article on VVM implementation in which they opined that the long waiting for VVMs might be finally over.

In 2003, I was busy with development of the Effective Vaccine Store Management (EVSM) initiative. Along with the initiative, I was also developing a learn-

ing programme for country managers, a 5-day course based on experiential learning principles. This was the creative period in which much-loved comic-strip characters, Wrong Ahmed and Correct Ayesha, surfaced in the training material much to the delight of the participants who benefitted from a more fun and, at the same time, a more memorable learning experience.

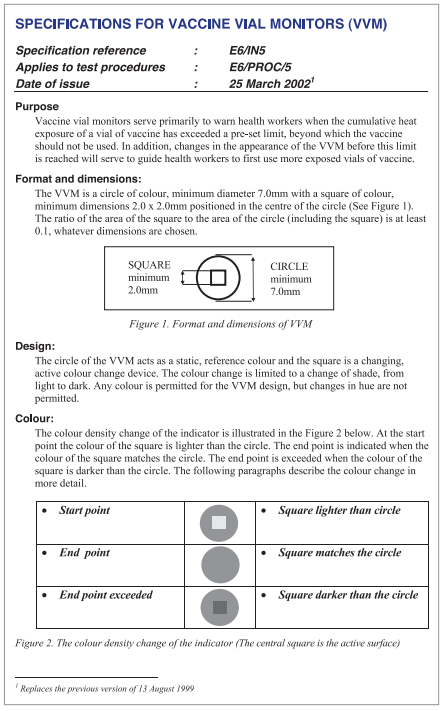
In January 2004, the Serum Institute of India became fully compliant with integrating VVM onto all its products.

In the 2004 TechNet consultation that was held in Antalya, Turkey, the study findings on the use of cold-water packs to prevent freeze damage and accelerate VVM implementation were presented. In the same year, WHO changed the VVM nomenclature from ABCD to VVM 2, 7, 14 and 30.

Dr Suresh Jadhav, Executive Director of Serum Institute of India Ltd., with 20 dose TT vaccine vial with VVM

In 2006, WHO's *Performance, Quality, Safety* (PQS) project, issued a revised product specifications and verification protocol for VVM. Revised version *WHO/PQS/E06/IN05.1* replaced the old 25 March 2002 version. A new format was also

brought to the document. The revised version was released on 30 November 2006 following a consultation with the vaccine industry.



SPECIFICATIONS FOR VACCINE VIAL MONITORS (VVM)

Specification reference	:	*E6/IN5*
Applies to test procedures	:	*E6/PROC/5*
Date of issue	:	*25 March 2002*[1]

Purpose

Vaccine vial monitors serve primarily to warn health workers when the cumulative heat exposure of a vial of vaccine has exceeded a pre-set limit, beyond which the vaccine should not be used. In addition, changes in the appearance of the VVM before this limit is reached will serve to guide health workers to first use more exposed vials of vaccine.

Format and dimensions:

The VVM is a circle of colour, minimum diameter 7.0mm with a square of colour, minimum dimensions 2.0 x 2.0mm positioned in the centre of the circle (See Figure 1). The ratio of the area of the square to the area of the circle (including the square) is at least 0.1, whatever dimensions are chosen.

Figure 1. Format and dimensions of VVM

Design:

The circle of the VVM acts as a static, reference colour and the square is a changing, active colour change device. The colour change is limited to a change of shade, from light to dark. Any colour is permitted for the VVM design, but changes in hue are not permitted.

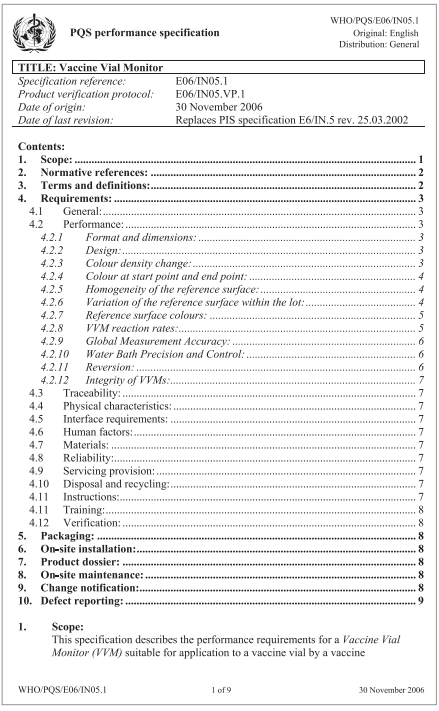
Colour:

The colour density change of the indicator is illustrated in the Figure 2 below. At the start point the colour of the square is lighter than the circle. The end point is indicated when the colour of the square matches the circle. The end point is exceeded when the colour of the square is darker than the circle. The following paragraphs describe the colour change in more detail.

• *Start point*		• *Square lighter than circle*
• *End point*		• *Square matches the circle*
• *End point exceeded*		• *Square darker than the circle*

Figure 2. The colour density change of the indicator (The central square is the active surface)

[1] *Replaces the previous version of 13 August 1999*



PQS performance specification

WHO/PQS/E06/IN05.1
Original: English
Distribution: General

TITLE: Vaccine Vial Monitor

Specification reference:	E06/IN05.1
Product verification protocol:	E06/IN05.VP.1
Date of origin:	30 November 2006
Date of last revision:	Replaces PIS specification E6/IN.5 rev. 25.03.2002

Contents:

1. Scope:

This specification describes the performance requirements for a *Vaccine Vial Monitor (VVM)* suitable for application to a vaccine vial by a vaccine

WHO/PQS/E06/IN05.1 1 of 9 30 November 2006

2002 and 2006 versions of the VVM PQS performance specification

The celebration: year 10

Vaccine vial monitors were introduced in 1996 followed by 10 years of successful implementation. By the time of the 10th year anniversary, all vaccines with just a couple of exceptions, were being supplied with VVMs through UN procurement agencies. Preceding the introduction were 20 long years of development work. So, in order to mark the 10th anniversary and in recognition of all the hard effort and commitment from many individuals, organizations, institutions and manufacturers, I decided to plan a celebration event that would take place in Geneva on 3 May 2007.

Preparations took many months, working closely with all partners, countries, organizations, institutions and manufacturers. Coinciding with the event, WHO and UNICEF announced a new policy statement focusing on the future of VVM, urging member states to include VVMs in all tender documents as well as encour-

aging donors to adopt a policy for the inclusion of VVMs in all vaccine donations. The policy statement further recommended all Member States to consider the adoption of policies permitting the use of vaccines beyond the cold chain where warranted for routine immunization activities or on a limited basis or under special circumstances, such as:

- national immunization days
- hard-to-reach geographical areas
- immunizations provided in the home – including hepatitis B vaccine birth dose
- cool seasons
- storage and transportation of freeze-sensitive vaccines (DTP, DT, TT, Td, hepatitis B and Hib vaccines) where the risk of freezing is greater than the risk of heat exposure.

WHO/IVB/07.04
ORIGINAL: ENGLISH

WHO-UNICEF policy statement on the implementation of vaccine vial monitors:

The role of vaccine vial monitors in improving access to immunization

World Health Organization (WHO) and United Nations Children's Fund (UNICEF),

Marking the 10 years of successful implementation of vaccine vial monitors (VVMs);

Referring to the WHO-UNICEF policy statement on the use of vaccine vial monitors in immunization services (WHO/V/SB/96.18), Making use of vaccine vial monitors (WHO/V/SB/00.14), Getting started with vaccine vial monitors (WHO/V/SB/02.30), WHO-UNICEF joint statement on effective vaccine store management (WHO/IVB/03.14), and Monitoring vaccine wastage at country level (WHO/IVB/02.18/Rev.1);

Emphasizing the Global Immunization Vision and Strategy aiming to protect more people against more diseases by expanding the reach of immunization to every eligible person, including those in age groups beyond infancy, within a context in which immunization is high on every health agenda;

Determined to reach every mother and child for vaccination against vaccine preventable diseases;

Noting the challenges in immunization service delivery especially in areas with weak or no cold chain infrastructure;

Acknowledging with appreciation the dedication of health workers throughout the world to overcome challenges in reaching all mothers and children with life saving vaccines;

Recognizing the cooperation of vaccine manufacturers in applying vaccine vial monitors on WHO prequalified vaccine products;

Acknowledging that the VVM is the only tool among all time and temperature indicators that is available at all times – in the process of storage, distribution and at the time the vaccine is administered – indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged;

Further noting that since its introduction in 1996 with oral polio vaccine, the VVM has contributed to the success of national immunization days as well as to overcoming access problems in areas with weak or no cold-chain infrastructure and reduction of vaccine wastage;

Appreciating the evidence produced by many field studies on the positive impact of the VVM on field operations, both routine and supplemental;

Recognizing that the benefits of VVM in overcoming the cold chain challenges and reaching the hard-to-reach populations will not be realized if they are not available;

Noting the use of VVMs to support policies for storage and administration of vaccines outside the cold chain to reach infants in rural and remote areas, such as for the hepatitis B vaccine birth dose for newborns;

Stressing the need that health workers require a consistent supply of vaccine with VVMs in order to be able to rely upon them as a tool;

CALLS UPON all self-procuring Member States to include the VVM among the minimum requirements for vaccine purchase agreements;

URGES all donor agencies and international non-governmental organizations to adopt a policy that explicitly calls VVM to be included as a minimum standard in every vaccine donation;

RECOMMENDS all Member States to adopt VVM-based vaccine management practices to maximize the benefits of VVM to:

- ensure that vaccines administered have not been damaged by heat;
- reduce vaccine wastage;
- facilitate immunization outreach and increasing access and coverage;
- pinpoint cold chain problems;
- manage vaccine stocks; and
- prevent inadvertent freezing of vaccines.

FURTHER RECOMMENDS all Member States to consider adoption of policies permitting the use of vaccines beyond the cold chain where warranted for routine immunization activities or on a limited basis or under special circumstances, such as:

- national immunization days;
- hard-to-reach geographical areas;
- immunizations provided in the home - including hepatitis B vaccine birth dose;
- cool seasons;
- storage and transportation of freeze-sensitive vaccines (DTP, DT, TT, Td, hepatitis B and Hib vaccines) where the risk of freezing is greater than the risk of heat exposure.

This policy statement is issued jointly by the World Health Organization, Geneva, Switzerland, and the United Nations Children's Fund (UNICEF Programme Division, New York, USA , and UNICEF Supply Division,Copenhagen, Denmark).

World Health Organization unicef

J.M. Okwo-Bele, Director, Immunization, Vaccines and Biologicals, World Health Organization

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Family and Community Health, Department of Immunization, Vaccines and Biologicals
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For the celebration, I teamed up with a well-known cinematographer Ümit Kıvanç and his assistant Gençer Yurttaş from Istanbul, Turkey and embarked on three trips very enjoyable to Vietnam, Indonesia and Niger filming the "Five Senses" video. The VVM device was deemed to offer health workers a visual equivalent

of the "five senses", the sensory information that humans rely on in order to process information from the outside world.

Reaching one remote village on river Song Buoi, Thach Lam Commune, Vietnam

Outreach in Tchin-Tabaraden, Niger

Labeling of TT vaccine with VVM at BioFarma production facilities, Bandung, Indonesia

Ümit Kıvanç and Gençer Yurttaş following the vaccine distribution in Kalimantan island, Indonesia

In the end, the 10th year celebration event was to bring together more than 100 representatives from diplomatic missions, countries, vaccine manufacturers, public sector agencies, donors and individuals. The occasion was chaired by Ms. Daisy Mafubelu, Assistant Director-General, Family and Community Health. Following the opening remarks by Ms. Mafubelu, the "Five Senses" video was shown which focused on how the effective use of VVM helps countries to reach more children.

Five Senses

Handling vaccines requires great care. All vaccines are sensitive to heat and some to freezing. Careful storage and transport conditions are needed to protect vaccines from harmful temperatures. Imagine the challenge of getting vaccines from a manufacturing facility to remote settlements in Vietnam, Indonesia or Niger. The vaccines leave the production site in temperature-controlled trucks, they are flown as cargo to the country's capital for storage, then transported deeper into the country, stored again, and finally delivered to the location where they will be administered. Storage facilities often have sporadic electricity or no electricity at all. Transport might be between islands or on dirt roads across rivers, and swamps.

Health workers carry the vaccine using trucks, motorbikes, boats, canoes, bicycles and in many cases on foot... With all these steps, the journey might take a year with the most challenging leg at the very end where the vaccinator struggles to reach populations dispersed by difficult geography, famine, or war. The vaccine is at constant risk.

It is impossible to visually identify when the vaccine is damaged by heat. Therefore, in the past, strict conservative measures had to be used by immunization programmes that resulted in often unnecessary disposal of loads of vaccines whenever heat exposure was suspected. In the past, heat damaged vaccines could have also gone unnoticed. Health workers at remote locations had to blindly rely on others who handled vaccine before it reached them. If errors

occurred, heat damaged vaccines may have been given to children leaving them unprotected from disease.

A vaccine vial monitor, or VVM, is circular indicator, printed directly on the vaccine vial label or affixed to the top of the vial or ampoule. The inner square of the VVM is made of heat-sensitive material that is initially light in color and becomes darker when exposed to heat over time. By comparing the color of the square to the reference ring, health workers can determine the extent to which the vaccine has been exposed to heat. The vaccine can be used as long as the color of the inner square is lighter than that of the reference ring.

This simple, yet elegant, tool indicates whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It clearly indicates whether a vaccine can be used. This is why health workers today feel very confident. Now they rely on what they see. Now they make informed decisions based on the interpretation of VVM indicators.

VVM ensures that the administered vaccine has not been damaged by heat. It is estimated that over the next ten years VVM will allow health workers to recognize and replace more than 230 million doses of unusable vaccines. VVM reduces wastage, saving annually 5 million USD worth of vaccines. VVM facilitates immunization outreach and increases immunization access and coverage. With VVM, over the next ten years health workers will be able to deliver more than 1.5 billion more doses in remote settings including delivering the

birth dose hepatitis B vaccine to millions of newborns in hard-to-reach areas. VVM pinpoints the cold chain problems and helps to effectively manage vaccine stocks – store keepers and immunization managers now adopt VVM based vaccine management, making decisions with the help of VVM readings.

VVM shapes the future of cold chain today, a future in which dependency on the cold chain is removed. Today, VVM is seen as a catalyst for much-needed changes in strategies of vaccine distribution via the cold chain. VVM allows immunization programmes to exploit the stability of each vaccine to the greatest possible extent, minimize distribution costs, and increase flexibility in the handling of vaccines in the field, thus helping to make operations more effective.

Although developed as a heat-exposure indicator, VVM also contributes significantly to the reduction of vaccine freeing. VVM makes it possible to detect and avoid excessive heat exposure to vaccines when methods are employed to store and transport vaccines without ice and equipment that is a known source of freeze damage. VVM allows health workers to feel confident that a load of

vaccines does not necessarily go bad if the power fails for a night. VVM allows health workers to see the heat stability of vaccines and accept the fact that freezing is a greater danger than a mild heat exposure.

Conceived as a dream in 1979, today the availability of the VVM is the results of immense efforts and dedication to strengthening public health on the part of many organizations, institutions, companies, and individuals. Without VVM, health workers can rely only on the expiry date of a product. But when

you are buying a bread in a bakery, besides seeing how fresh the bread is, you can smell it, you can touch and feel it, listen to the crispy sound it makes, and taste it. VVM expands the horizon of all immunization programmes, VVM is a "five senses" offer to health workers, although they only look at it, with VVM health workers discover things other than a printed expiry date, as if they feel, hear, smell and taste... and they know with confidence which vaccine can be used or not...

VVM expands the horizon of all immunization programmes, wherever the challenge is. It offers a railroad, a bridge, a tunnel, a motorbike, a canoe, a bicycle, and a pair of shoes to reach the unreachable.

Dr. Ümit Kartoğlu

Following showing of the "Five Senses" video, four speakers gave a brief history of VVMs: Debbie Kristensen from PATH focused on the problem definition that prompted VVM development (1979-1989); Ted Prusik from Temptime Corporation talked on the solution, the VVM; Dario Cresci from Novartis brought the industry response in implementing VVMs and how the challenges were handled in applying the monitor onto vials; and Dr. Mercy Ahun from Gavi talked on the benefits in the field. To acknowledge the efforts put into this pioneering tool, WHO distributed certificates of recognition to countries, organizations, agencies, and individuals for their contribution to the development and early implementation of VVMs.

WHO recognized the following countries for their involvement with VVM development for contribution to global public health

Argentina – conducted validation study with early VVM prototypes in early 1980s.

Bangladesh – participated in HEATmarker VVM design study between 1990-1992.

Bhutan – conducted most in-depth study of VVMs ever; assessing multi-dose vial policy and impact of the use of VVMs on multiple vaccines in 1998.

Bolivia – participated in HEATmarker VVM design study between 1990-1992.

Brazil – conducted validation study with early VVM prototypes in early 1980s.

Cameroon - participated in HEATmarker VVM design study between 1990-1992.

Egypt – conducted validation study with early VVM prototypes in early 1980s.

India – imported OPV with VVMs for NIDs and after the experience issued an official request to WHO for assistance in supplying VVMs on locally produced OPV. With funding from DFID, India successfully implemented labelling of all locally produced OPV with VVMs. In 2007, India adopted a policy demanding VVMs on all locally produced vaccines.

Indonesia – conducted introductory trial with early prototype VVMs for measles vaccine in late 1980s. Participated in HEATmarker VVM design study between 1990-1992. Indonesia also demands VVMs on locally produced vaccines.

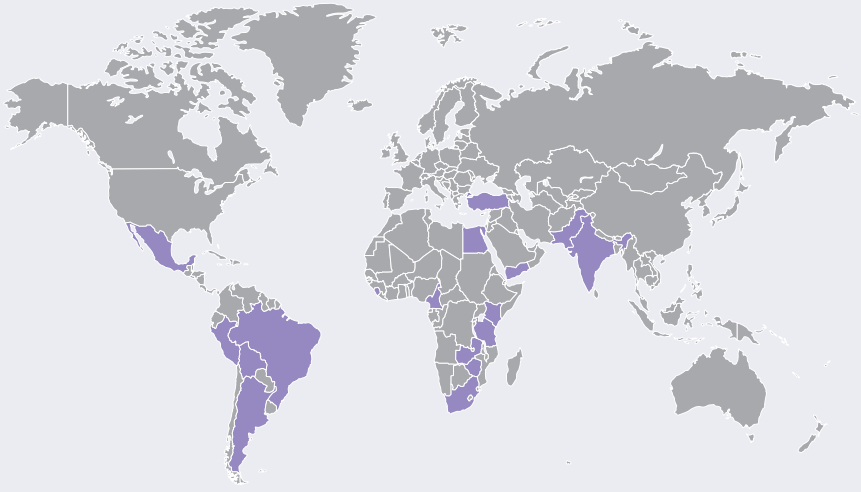
Kenya – conducted validation study with early VVM prototypes in early 1980s. Conducted introductory trial with early prototype VVMs for measles vaccine in late 1980s. Participated in HEATmarker VVM design study between 1990-1992. Conducted impact study of VVMs on OPV in 1997.

Mexico – participated in VVM design study in 1981.

Nepal – conducted validation study with early VVM prototypes in early 1980s. Conducted impact study on VVMs on OPV in 1997.

Pakistan - conducted validation study with early VVM prototypes in early 1980s.

Peru - conducted validation study with early VVM prototypes in early 1980s.



23 countries involved in VVM development and early implementation studies

Philippines –conducted validation study with early VVM prototypes in early 1980s. Participated in VVM design study in 1981.

Sierra Leone - conducted introductory trial with early prototype VVMs for measles vaccine in late 1980s. Participated in HEATmarker VVM design study between 1990-1992.

South Africa – conducted VVM knowledge, attitudes and practices (KAP) study in 2000.

Tanzania – conducted pilot introduction study of VVMs on OPV in 1995. Conducted impact study of VVMs on OPV in 1997.

Thailand - conducted introductory trial with early prototype VVMs for measles vaccine in late 1980s. Participated in HEATmarker VVM design study between 1990-1992.

Turkey – conducted impact study of VVMs on OPV in 1997.

Vietnam - conducted pilot introduction study of VVMs on OPV in 1995. Conducted impact study on use of VVMs on measles vaccine in 2002.

Yemen – conducted validation study with early VVM prototypes in early 1980s.

Zambia - conducted introductory trial with early prototype VVMs for measles vaccine in late 1980s.

Zimbabwe - conducted validation study with early VVM prototypes in early 1980s. Conducted a study on the impact of VVMs on measles vaccine discard rates due to heat exposure in 1992.

Public sector agencies contributed to global public health through their critical involvement in VVM development, implementation and expansion

Basic Support for Institutionalizing Child Survival Project – provided subcontract to PATH to draft a written summary of early field experiences with VVMs.

Canadian Public Health Association – supported an introductory field trial of PTS-based VVMs in Sierra Leone and an impact study of HEATmarker VVMs in Zimbabwe.

Canadian International Development Agency – supported introductory field trial of PTS-based VVMs in Zambia.

Centers for Disease Control and Prevention – provided co-funding to the USAID HealthTech programme (managed by PATH) to advance availability of VVMs for measles vaccine. Activities included demonstration of cost-effective solutions for labelling vial caps and ampoules, and development of VVM training materials.

Department of International Development – funded and managed activities that resulted in successful integration of VVM labelling onto OPV vials produced in India for government purchase and VVM training material development for national use.

Edna McConnell Clark Foundation – provided initial product development feasibility funding to PATH for VVMs using the PTS chemical licensed to PATH by Allied Corporation. Supported design studies of PTS-based VVMs and VCMs in Mexico and the Philippines.

International Development Research Centre of Canada – co-funded above activities with the Edna McConnell Clark Foundation.

Japan International Cooperation Agency – In 1998, adopted a policy to include VVMs in all vaccine donations.

Japan International Cooperation System – adopted a policy to include VVMs in all vaccine donations. The first Grant-Aid project handled by JICS included vaccine supply titled "The project for eradication of poliomyelitis in the United Republic of Tanzania", since then JICS includes VVMs on all tender documents for vaccine purchase.

London School of Hygiene and Tropical Medicine - collaborated with PATH and WHO in search for initial VVM technologies which resulted in selection of PTS format.

OXFAM – supported design studies of PTS-based VVMs and VCMs in Mexico and the Philippines.

Pan American Health Organization – Involved in early dialogue with WHO and PATH regarding VVMs beginning 1985. Provided support for a validation field trial of PTS-based VVMs in Brazil. Provided oversight to PTS and HEATmarker VVM field trials in PAHO countries.

Program for Appropriate Technology in Health – facilitated VVM development and advancement with support from a variety of donors, the largest of which the USAID Technologies for Health (HealthTech) programme. Developed and produced PTA-based VVM and VCM prototypes. Collaborated with a variety of private sector companies, including Allied Corporation, LifeLines Technology, 3M and CCM Label, to advance potential VVM technologies. Collaborated on early design, validation, and introductory field studies of VVM/VCMs. Met with

vaccine suppliers to discuss VVM implementation issues. Provided two equipment loans to LifeLines Technology via the PATH Fund for Technology Transfer. Purchased VVM prototypes from LifeLines for use in field studies. Demonstrated feasibility of cap and ampoule labelling in collaboration with Serum Institute of India, CCL Label, and LifeLines. Assisted WHO with development of VVM training materials.

United Nations Children's Fund - Supply Division involved in early discussions on VVM introduction via the "Technology Introduction Panel" in 1990. Held two meetings (New York 1991 and Copenhagen 1994) to discuss inclusion of VVMs in upcoming vaccine tenders. Developed 1999 policy statement with WHO advocating use of VVMs on all vaccines. Responsible for inclusion of VVMs in tender specifications and negotiations with vaccine suppliers.

United States Agency for International Development – primary supporter of funding to PATH for VVM development, field evaluation, and introduction via the HealthTech programme.

Individuals recognized for their contribution to global public health through their critical involvement in VVM development, implementation and expansion

Mercy Ahun – led pivotal VVM technical session at WHO in 2002.

Nora Dellepiane – provided technical expertise to early VVM development and testing and continues to play a major role in VVM implementation by vaccine producers as part of the WHO prequalification process.

Peter Evans – broached the idea of VVM with vaccine producers during the early years by visiting them one by one (with Michael Free and Debbie Kristensen from PATH) to discuss implementation issues, arrange for shipment prototypes for evaluation, and pave the way forward. He was a UNICEF staff member, seconded to WHO at the time.

Hans Everts – showed the world how to use VVMs to successfully conduct polio outreach in the most difficult parts of the world. Developed a WHO protocol for flexible management of vaccines to turn the lessons learned into tools for others.

Rebecca Fields – Led VVM team during early technical work and field evaluations while at PATH, including production of early prototypes VVMs produced by PATH. Continued to be an advocated for VVMs while at BASICS.

Michael Free – Vice President and Senior Advisor for Technology at PATH. Michael is the leader of the USAID funded HealthTech Project and was the leader of the Project during the entire time it supported VVM work. Michael was the individual who single-handedly convinced LifeLines to continue working on VVMs when their Board of Directors wanted to drop the project.

Arthur Galazka (in memory) – developed the four categories and performance parameters for the VVMs based on his work in characterizing the stability of vaccines.

Fred Grabiner – Developed the complex proprietary algorithms used to analyze and predict the performance characteristics of the VVM color change in response to virtually any time-temperature profile. Also developed the methods and equipment for automated pre-release testing of VVM.

E. G. P. Haran – worked as a consultant under DFID funding and successfully implemented VVM adoption by every OPV producer in India. Also helped with VVM introduction in India.

John Lloyd – Worked at WHO and later at PATH to launch and implement the VVM. Drafted WHO's VVM specifications as well as the WHO/UN policy on VVMs while at WHO. Major champion; largely responsible for inclusion of VVMs on all polio vaccines and the effort to include VVMs on all other UN-purchased vaccines.

Ümit Kartoğlu – has led the VVM effort at WHO during the expansion phase to vaccines beyond polio until the present day. Has been largely responsible for facilitating the increased adoption of VVMs by UN vaccine suppliers by painstakingly addressing issues and removing barriers. Has developed innovative learning materials and methods for VVM introduction. Is a major champion of the use of VVMs to facilitate novel methods to manage vaccine distribution and storage.

Debbie Kristensen – team leader for VVM development and introduction at PATH for 18 years. Has worked on every aspect of the technology from product design to laboratory testing of the adhesive to validating labelling equipment to writing training materials to post-market evaluation of the product in country programmes. Served as the PATH liaison with industry partners. Co-led many meetings with vaccine suppliers in collaboration with WHO to provide background information on the VVM and arranged shipment of samples to them for evaluation. Encouraged new entrants/potential suppliers and assisted them with evaluating their products for compliance with WHO specifications. Assisted WHO with gathering and documenting evidence to respond to vaccine sup-

pliers before and after the pivotal supplier meeting in Geneva. Developed the Bhutan study protocol, conducted the training, singlehandedly ran the study in collaboration with the MOH, conducted KAP surveys, analyzed the data, and wrote the report under contract to WHO.

Steve Landry – USAID Chief Technical Officer for the HealthTech project during much of VVM development and introduction. Advocated for VVM inclusion in Gavi purchases while working in Gavi.

Julie Milstien – provided technical expertise to early VVM development, specifications, and testing. Played a major role in inclusion of VVMs in the WHO prequalification process for vaccines.

Carib Nelson – PATH staff member who has conducted studies utilizing VVMs in multiple countries and led the way for innovative use of VVMs to deliver vaccines in logistically difficult situations – for example delivery of birth dose of hepatitis B vaccine to children in homes or outreach delivery of tetanus toxoid to women. Also, is a leader in efforts to prevent freeze-damage to vaccines by using VVMs to store and transport vaccines at higher, less damaging temperatures.

Gordon Perkin – President of PATH during most of all of PATH's work on VVMs. A major champion of the technology. His advocacy continued during his work at the Gates Foundation.

Ted Prusik – led the research project to improve the chemical reaction of the reagent in the VVM to match the VVM performance with the stability of polio vaccine resulting in the VVM2. His further efforts enabled the extension of VVM properties to match the requirements of the other EPI vaccines.

Patrick Tam – First team leader for the VVM project at PATH. Identified the first technology used by PATH to produce VVM prototypes in-house. Demonstrated the art of the possible.

Vivien Tsu – led the PATH VVM team during early field trail years and coordinated most of the VVM field trials in collaboration with WHO and MOHs. Was directly involved with much of the in-country work as well.

David Wood – developed protocols for testing and validating VVM performance at WHO and managed much of the testing for product qualification.

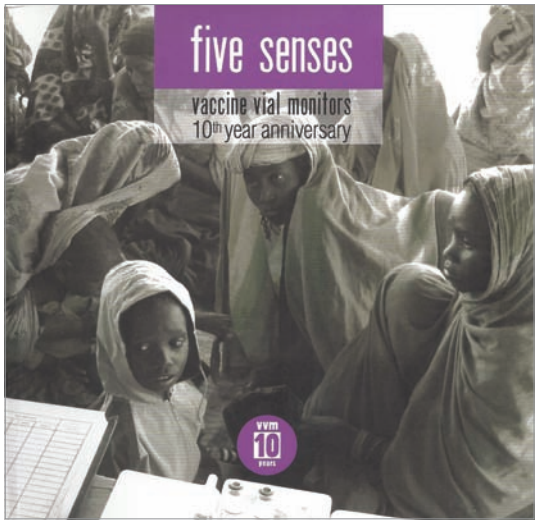
Michel Zaffran – worked at WHO during the early days when the VVM was merely a concept and helped to launch and advance the product. Worked on VVM field trials. Facilitated early VVM meetings with vaccine producers and potential VVM manufacturers.

Vaccine manufacturers recognized for inclusion of VVM on their products

BB-NCIPD Ltd., Bulgaria
Berna Biotech AG, Switzerland
Berna Biotech Korea Corporation, Korea
Bio-manguinhos, Brazil
Center for Genetic Engineering and Biotechnology, Cuba
CSL Limited, Australia
GlaxoSmithKline Biologicals, Belgium
Haffkine Bio Pharmaceutical Corporation Ltd., India de Dakar, Senegal
InterVax, Canada
Japan BCG Laboratory, Japan
LG Life Sciences Ltd., Korea
Merck and Co. Inc., USA
Novartis Vaccines and Diagnostics GmbH & Co, KG, Germany
Novartis Vaccines and Diagnostics S.r.l., Italy
Panacea Biotech Ltd., India
PT BioFarma (Persero), Indonesia
Sanofi Pasteur, France
Serum Institute of India Ltd., India
Shantha Biotechnics Private Ltd., India
Statens Serum Institut, Denmark

The "Five Senses" book, containing interviews I made with John Lloyd, Michel Zaffran, Peter Evans, Julie Milstien and Dario Cresci, as well as the milestones from the VVM history was published in time for the 10th year Anniversary and distributed to all participants. The Five Senses video was also shared with all participants in DVD format.

A photo exhibition by Ümit Kartoğlu, Jean-Marc Giboux, Philippe Blanc and Gençer Yurttaş was opened in the main entrance of the WHO headquarters in Geneva from 3-9 May 2007.



interviews

The powerful role of VVM in immunization services is to communicate their ability to reach hard-to-reach children John Lloyd*

interviews

How far you can push the envelope, how much can you use VVMs to take vaccines out of the cold-chain? Julie Milstien*

In one clinic the drug storeroom key was broken and it took staff six days to obtain a copy. Upon opening the room, they discovered that the gas cylinder was empty: a situation which would normally necessitate discarding all vaccines in stock. In this case, all the vaccines were discarded except those with VVMs showing no heat exposure damage, which were kept and used.

Health worker, Zimbabwe, 1992

"Live" HEATmarker™ VVMs were sent to WHO, Connaught, Evans Biologicals, Human Institute, Institute of Immunobiology, Interexport, MAIMEX, Pasteur Merieux, Sclavo, SmithKline Biologicals, Swiss Serum and PAHO for evaluation.

1992
Independent laboratory evaluation of LifeLines HEATmarker™ VVMs for OPV completed by Strasburger and Siegelt laboratory.

Zimbabwe study completed by PATH and MOH on the impact of VVMs on measles vaccine discard rates due to heat exposure. (1992)

UNICEF included a clause in the 1992–1994 vaccine tender notifying manufacturers that they would request labeling with VVMs prior to 1994.

1993
Albert Browne developed prototype VVMs for evaluation, but indicators had a slow initial color change and did not meet specifications.

interviews

The VVM helps achieve confidence at really remote places Peter Evans*

In-depth VVM impact study completed in Bhutan by WHO.

A meeting on the introduction of VVMs on all EPI vaccines was held at WHO Geneva and attended by WHO, UNICEF, PATH, USAID, LifeLines, and 3M.

PATH, CCL Labeling Equipment, LifeLines and a pharmaceutical company conducted a collaborative cap labeling demonstration project to demonstrate feasibility to vaccine suppliers, WHO, and UNICEF. WHO sent a letter to all WHO pre-qualified vaccine producers requesting feedback on VVM specifications.

1999
CCL Label confirmed interest (in letter to UNICEF) in further VVM development.

Sensitech (US) expresses interest to WHO regarding VVM development.

interviews

How can you feel safe if you do not see the VVM? Dario Cresci*

The 10th year anniversary event was to play an instrumental part in bringing VVM to the fore of the agenda, and facilitated the expansion of VVM onto other vaccines. It was the physical coming together of all the organizations, manufacturers and individuals that had celebrated and collaborated effectively to bring this project forward and improve public health around the world.

interviews

Make better use of the real stability of the vaccine - use the VVMs Michel Zaffran*

The role of TechNet

TechNet21 is a global network of professionals committed to strengthening immunization services by sharing experiences, coordinating activities, and helping to formulate optimal policies. Its members come from every corner of the world.

TechNet was established in 1990 and held its first consultation in Nicosia, Cyprus. Starting with the Cyprus Consultation, VVM was always on the agenda and TechNet played a critical role in increasing the demand for vaccines with VVMs as well as guiding and monitoring the progress.

A second TechNet consultation took place in Casablanca, Morocco, on 18-22 November 1991 and was attended by 55 participants. At this Morocco forum the indicators from Life-Lines and Browne were presented and discussed. Some of the participants expressed their worries that the gradual change towards VVM might encourage careless habits and undermine the cold chain once health workers realized how much heat exposure some vaccine could tolerate.

VACCINES AND VIAL INDICATORS

Individual vaccine vial indicators

Two chemical indicators, HEATmarker and Browne model, were presented. They are both designed to be applied to individual vials of vaccine and to present the end-user with a clear indication of whether the vaccine has been exposed to excessive heat and should not be used. The HEATmarker shows the progression of heat exposure. It has an inner square of color which gradually from white to a light shade of blue which then becomes progressively darker. The user compares the shade of the inner square to a blue outer reference ring. When the color of the inner square is as dark as the outer ring, or darker, the vaccine should not be used. Variations of HEATmarker have been tested in many countries. Preliminary feedback has shown that health workers are able to interpret HEATmarker. Because of its progressive change, HEATmarker can also be used as a management tool for stock control.

The Browne indicator does not show a progressive change. It starts off a bright canary yellow, and, when the vaccine reaches the point at which it cannot be used, it changes quickly to royal blue. With the Browne indicator it is easy to read when the vaccine should not be used but it is not intended for use in stock control.

Field trials have shown that some health workers do not believe vaccine vial indicators. The change in the indicators corresponds to the stability of the vaccine but many health workers have been trained to consider that vaccine is much less stable.

The group expressed uncertainty on how the vial indicators would be used. Some of the group saw the value of HEATmarkers' gradual color change. Others were fearful that the gradual change might encourage sloppy work habits and undermine the cold chain once health workers realized how much heat exposure some vaccine could withstand.

The group were not yet prepared to make a recommendation in favour of one indicator over the other. They did, however, agree on the value of being able to recognize damaged vials, particularly in polio eradication.

Recommendations

Vaccine manufacturers should be encouraged to assess the feasibility of introduction both HEATmarker and the Browne indicator and seek ways to overcome any production problems relating to installation.

In the event that all vaccine manufacturers consider it feasible to introduce both HEATmarker and the Browne indicators at an acceptable cost, a selection of health workers and supervisors who have used both PATHmarker and HEATmarker should be asked which indicator they prefer.

Plan of action (TechNet working programme for 1992-1993)

5.1. If vaccine manufacturers report that Browne indicator is feasible, test it in the field.

5.2. Formulate, discuss and test changes in policy as vial indicators are introduced. Write discussion paper proposing policies for using vaccine beyond the cold chain.

5.3. Prepare guidelines that will allow countries to confirm which vial size to choose for each vaccine.

5.4. Conduct studies on the use of tetanus toxoid beyond the cold chain; one in Kenya (PATH) and one in Bolivia (PAHO); (other studies using hepatitis-B vaccine are anticipated). The protocols for such studies should stipulate that:

- every vaccine vial which is used in the study must bear a temperature threshold indicator;
- the proportion of vaccine which can be given without loss of potency under ambient temperature conditions should be monitored;
- the managerial acceptability of relaxing the cold chain under field conditions will be examined.

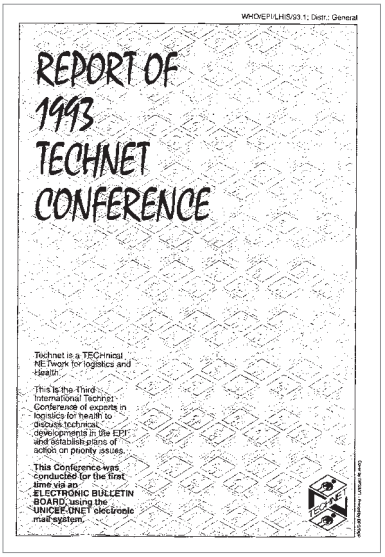
5.5. Study methods and technology to enable vaccine vials to be opened and used on more than a single day.

From the Report of 1991 TechNet Consultation, WHO/EPI/LHIS/92.1, pp. 17-18 and 34

Ultimate signal

The third consultation was conducted for the first time via the UNICEF-UNET electronic bulletin board, and was attended by 32 participants during 29 March – 7 April 1993.

These consultations were already starting to shape the cold chain well before VVMs became a commercial reality on OPV vials. On the basis that the need to cool vaccines is an important constraint to raising immunization coverage rates, that expenditure on cooling equipment can be lowered, and working on the assumption that VVM would be fitted on all vials, participants focused on two related issues: how to speed up the distribution process and how to relax temperature limits. This was a very resolute move for the group compared to the hesitancy shown at the Morocco Consultation the previous year. Of course, the fact that UNICEF had added a clause to its tender documents asking manufacturers to incorporate VVM onto OPV vials was a critical factor in this change of heart. The group believed that the shorter the period of distribution, the higher the storage



temperatures could be tolerated without compromising the stability of those vaccines that were of low thermal stability. They believed that a fast distribution system feeding the outlying areas could be just as safe and less expensive than trying to run a standard cold chain. The group called this approach the "fast chain", and they believed that the development of inexpensive vaccine vial monitors was about to make "out-of-the-cold-chain" distribution a practicable alternative. The group recommended that research into this (with a special focus on polio, neonatal tetanus and measles) should be an operational priority for the EPI.

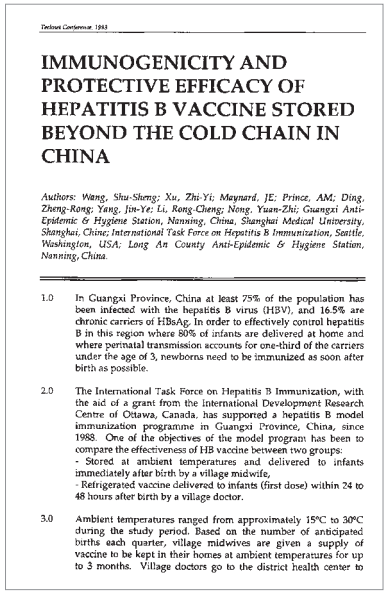
The group agreed that vaccine vial monitors were an essential pre-requisite for any removal of vaccine from the national cold chain system. It was underlined that whatever changes are made to vaccine handling procedures, it was of paramount importance that the health worker was able to check that it is safe for use prior to administering it. With such a move, the hope was that VVMs would start to appear on routine deliveries of OPV during 1994 in accordance with the terms of the new UNICEF vaccine tender.

HepB and TT vaccines were repeatedly identified as potential candidates for removal from the cold chain. Both were very stable vaccines but sensitive to freezing. The risk of freezing temperature excursions to these vaccines in the cold chain was much higher than the risk of mild heat exposure. This change of approach would facilitate reaching children in hard-to-reach areas and as a result increase overall vaccination coverage.

It was also thought that taking OPV beyond the cold chain would be possible. In this thinking, the application of VVMs along with an accelerated three-month distribution period for the vaccine within the cold chain were prerequisites.

In these discussions, VVM was called to be the "ultimate signal" with regard to using or not using a particular vaccine. When discussing what management rules should exist for taking vaccines beyond the cold chain the group did not refer to this as "VVM based vaccine management". They were of the opinion that if the VVM on a vaccine indicated to health workers that the vial could not be safely used, then immediate steps could be put in place to protect the vaccine more effectively in the future. This was agreed as another benefit of VVM: "the pinpointing of cold chain problems" (so they can be fixed).

The importance of field studies prior to any decisions to take vaccines out of the cold chain (OCC) were widely appreciated. The very first field study in taking Hep B vaccine out of the cold chain in Long-An county, Guangxi, China was presented during the third TechNet Consultation. The results (with no VVMs) encouraged the participants enormously. The study was sponsored by the China's EPI. It is worth summarizing the results of this historical study.



Technet Conference, 1988

IMMUNOGENICITY AND PROTECTIVE EFFICACY OF HEPATITIS B VACCINE STORED BEYOND THE COLD CHAIN IN CHINA

Authors: Wang, Shu-Sheng; Xu, Zhi-Yi; Maynard, JE; Prince, AM; Ding, Zheng-Rong; Yang, Jin-Ye; Li, Rong-Cheng; Nong, Yuan-Zhi; Guangxi Anti-Epidemic & Hygiene Station, Nanning, China, Shanghai Medical University, Shanghai, China; International Task Force on Hepatitis B Immunization, Seattle, Washington, USA; Long An County Anti-Epidemic & Hygiene Station, Nanning, China.

1.0 In Guangxi Province, China at least 75% of the population has been infected with the hepatitis B virus (HBV), and 16.5% are chronic carriers of HBsAg. In order to effectively control hepatitis B in this region where 80% of infants are delivered at home and where perinatal transmission accounts for one-third of the carriers under the age of 3, newborns need to be immunized as soon after birth as possible.

2.0 The International Task Force on Hepatitis B Immunization, with the aid of a grant from the International Development Research Centre of Ottawa, Canada, has supported a hepatitis B model immunization programme in Guangxi Province, China, since 1988. One of the objectives of the model program has been to compare the effectiveness of HB vaccine between two groups:
- Stored at ambient temperatures and delivered to infants immediately after birth by a village midwife,
- Refrigerated vaccine delivered to infants (first dose) within 24 to 48 hours after birth by a village doctor.

3.0 Ambient temperatures ranged from approximately 15°C to 30°C during the study period. Based on the number of anticipated births each quarter, village midwives are given a supply of vaccine to be kept in their homes at ambient temperatures for up to 3 months. Village doctors go to the district health center to

"The study used a 10 mg plasma-derived vaccine produced at the Beijing Institute of Serum and Vaccine and reported by the manufacturer to be stable for up to 3 months at 35°C. In the study location, over 80% of births occurred at home, attended by village midwives or doctors. In one group of infants (n = 358), the first dose of vaccine was stored for up to 3 months at ambient temperature (15–30°C) and administered by the birth attendant. In the other group (n = 232), the first dose had been refrigerated and was administered by the village doctor within 72 h of delivery. The second and third doses were given routinely at ages 1–2 and 5–8 months.

"Infants were tested for antibody to HBsAg (anti-HBs) and HBsAg 12 months after the third dose. The prevalence of any anti-HBs was 81.6% in the OCC group and 81.9% in the refrigeration group. Maternal HBsAg rates were 15.4% and 20.7%, respectively. There was no difference between HBsAg rates amongst vaccinated infants in the OCC and refrigeration groups (1.1% vs 2.2%). All HBsAg-positive (HBsAg+) infants were delivered by HBsAg+ mothers. The estimated protective efficacy of vaccination (the percent reduction in HBsAg attributable to vaccination amongst infants exposed to HBV) was similar at 84.5% and 77.8%, respectively in the two groups. This is the only study of HepB vaccine OCC to include this indicator.

"Despite certain limitations (relatively low vaccine immunogenicity and a lack of temperature data), this study concluded that the HepB vaccine stored OCC in semi-tropical conditions for up to 3 months can remain both immunogenic and protective."

The group also thought about how to protect against heat spikes, and came with three innovative solutions: keeping the vials close to the body to limit temperatures to 37°C; using cool water from wells or streams; and evaporative cooling.

The single and most powerful measure

The TechNet Consultation from 31 May to 4 June 1994 in Washington, D.C., made a call for VVMs to be implemented without further delay. The consultation put forward a strong case that VVMs have the potential to make the cold chain more effective, that they permit a more flexible use of vaccine in the field and that they could drastically reduce prevailing levels of vaccine wastage.

The cold chain problem definition by Washington Consultation was short and clear:

"Even where a good cold chain exists, it is not perfect. If a cold chain failure takes place, workers cannot know whether the vaccine is still effective. Where the cold chain does not exist, immunization is not able to take place at all. These factors are not only a major barrier to the global immunization activities which aim to eliminate and eradicate disease."

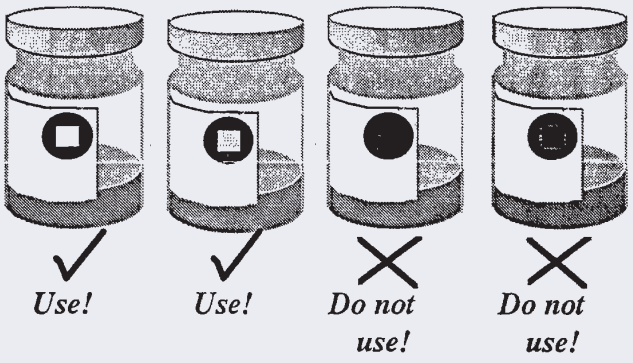
And, the solution was even more clear:

"The single, most powerful measure to remove this barrier, at minimum cost is the implementation of vaccine vial monitors (VVMs)."

This statement was followed by a short explanation and recommendations on VVM:

"The VVM consists of a time and temperature indicator which is calibrated according to heat stability characteristic of each vaccine. It is a disc of color which can be attached or printed directly on the vaccine cap or label. When the potency of the vaccine is at risk, the VVM changes color according to the history of accumulated time and temperature exposure.

Figure: Vaccine Vial Monitor (VVM)



The VVM technology has undergone laboratory tests and field trials in the EPI for over a decade. VVMs are affordable and, although they have been available since 1976, they have not yet been implemented in routine vaccine distribution.

The VVM enables health works to:

- Keep oral polio vaccine up to five days and, thereby, virtually eliminate vaccine wastage
- Make an accurate assessment of the effect of cold chain failures and decide whether or not to use the vaccine involved
- Recognize vaccine stock which has been partially exposed and select to use it before it has to be rejected
- Take vaccine vials "beyond the reach of the cold chain" for limited periods where necessary in getting to difficult areas.

The *Institut Pasteur-Merieux* is the first major UNICEF supplier to offer to attach VVMs to its vaccine. They will supply 20,000 vials of oral polio vaccine with VVM this year (1994).

RECOMMENDATIONS

- **Progressively attach vaccine vial monitors to all vials of vaccine, starting immediately with oral polio vaccine. Provide all countries with the necessary instructional materials in advance.**
- **Continue to discard oral polio vaccine at the end of the session until each vial provided with a vaccine vial indicator. An opened vial of polio may be kept up to 5 days if a vaccine vial monitor is attached."**

From the Report of 1994 TechNet Meeting, WHO/EPI/LHIS/94.3, pp. 17-18

The 1994 TechNet Consultation endorsed the plans of action for regional offices for Africa (and separately for Ethiopia and Tanzania), Americas, Western Pacific (and separately for Papua New Guinea) and GVP/EPI Geneva with specific highlights on the VVM.

PLANS OF ACTION FOR AFR (*continued*)

OBJECTIVE :	**3. Promote the use of the vaccine vial monitor (VVM) to ensure that potent vaccines are administered and reduce wastage. Encourage countries to revise the open-vial policy for vaccine, in accordance with more stable vaccines. Promote the use of Commodity and Logistics Management software (CLM) for inventory control.**
STRATEGY :	• Through annual sub-regional EPI managers meetings. • Writing to Ministries of Health through official channels to obtain their commitment.
YEAR/S :	1994/1995

Activities related to Objective 3	Responsibility of	Time frame	Cost est. /donors	Priority	Indicator
3.1 Motivate EPI national managers during their annual Sub-Regional Meeting. 3.2 Encourage countries to organize staff training on how to handle vials with VVMs and to increase their use in the programme. The training should be combined with sterilization workshop. (in 46 countries)	WHO/UNICEF	1994/1995	WHO/ UNICEF		% of countries using vaccine with VVMs by June 1995.
3.3 Encourage countries to organize refresher training for senior health staff, concerning the policy change (46 countries) *(The training should include the new policy on injection safety, injection materials, vaccines and vaccine vial monitors.)*	WHO/UNICEF	1994/1995	$ 230,000 WHO/ UNICEF		% of countries with revised policy on the use of opened vaccine vials by June 1995.

The plan of action for Americas, presented by Peter Carrasco holds a historical importance.

PLANS OF ACTION FOR AMR -- SUBMITTED BY PETER CARRASCO

OBJECTIVE:	**1. Safe disposal of single-use syringes; safe sterilization.**
STRATEGY :	Document methods of disposal of single-use syringes and routinely make available TST indicators
YEARS :	1994/95

Activities related to Objective 1	Responsibility of	Time frame	Estimated cost	Priority	Indicator
1.1 Introduce use of TST indicator in countries that sterilize their EPI syringes and needles	AMRO/HQ	07/94 -- 12/95	$ 3,000	1	Limited quantities of TST indicators procured, distributed and evaluated in selected countries.
1.2 Document precise methods of disposal of single-use syringes	AMRO/HQ	07/94 -- 07/95	$ 5,000	1	Questionnaire on disposal of syringes prepared, distributed, returned and analysed.
1.3 Field test low workload jet injector in Brazil	GPV/Geneva and PAHO/Brazil	08 - 09/94	$ 5,000	1	Field trial in Brazil conducted and report circulated.

OBJECTIVE:	**2. Assure that opened vials of vaccines are discarded before the vaccine loses potency**
STRATEGY :	Introduce vaccine vial indicators on TT, DPT and DT vaccine.
YEARS :	1994 - 1996

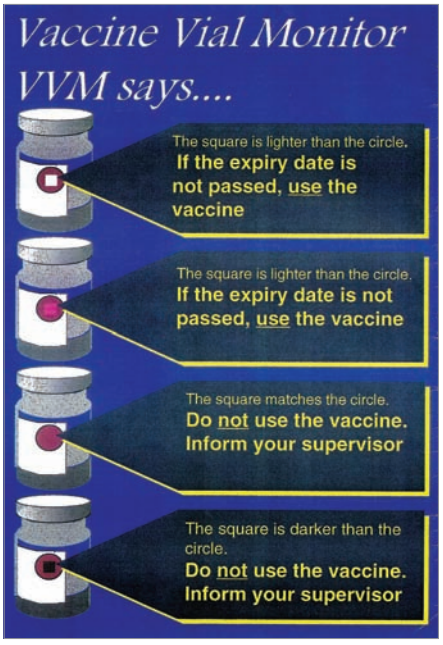
Activities related to Objective 2	Responsibility of	Time frame	Estimated cost	Priority	Indicator
2.1 Circulate samples of vaccine vial monitor with costs and instructions on use to AMRO countries.	AMRO/HQ	07/94 -- 07/96	$ 5,000	2	Instructions and other information circulated to countries and responses analysed.
2.2 Request that 1995 EPI Revolving Fund tenders include vial monitors for EPI vaccines.	AMRO/HQ	06/95 -- 09/95	--	2	1996 EPI vaccines supplied with vaccine vial monitor.
2.3 Survey all countries to determine quantities of vaccine/number of sites where EPI vaccines will be taken out of cold chain.	AMRO/HQ	07/94 -- 12/95	$ 5,000	2	Circulation and analysis of results of questionnaire to investigate where and how much vaccine is likely to be taken out of the cold chain.

In a memorandum addressed to PATH (dated 15 October 1991), signed by Peter Carrasco, requesting VVM samples for internal use and evaluation, it was indicated that they needed to reach a decision on the introduction of VVM before

September 1992. The above copied plan of action for Americas (dated 4 June 1994) is a clear indication that this decision was made in favor of inclusion of VVMs in the PAHO Revolving Fund tenders. As it happens, this pronouncement was to mark the end of PAHO's positive approach to VVM publicly. Soon afterwards, things were to change dramatically, a turn of events that I examine in the "PAHO controversy" chapter on page 275.

Introduction and impact

The next TechNet Consultation was held in Manila, the Philippines, from 12-16 February 1996, and this, in one sense at least, was a celebration of the introduction of VVM. It was Pasteur-Merieux that supplied a pilot batch of 43,800 10-dose OPV vials to Tanzania at the end of 1995. Pasteur-Merieux went on to confirm that VVMs were being introduced into the production line at the end of February 1996.



There were three other OPV manufacturers involved in this celebration. Although SmithKline Beecham was cautious at the start of the project, and, seemingly reluctant to go ahead with VVM, it was actually the first manufacturer to introduce VVM into its production line. Biocine (Sclavo) supplied a pilot batch of 50,000 OPV vials to Vietnam in June 1995, and VVMs were now in their production line. Behring/Hoechst announced its commitment to supply OPV with VVMs in 1997.

At that time, all three OPV suppliers were using the LifeLines VVM. Being aware of the interest of other companies in developing VVM (by that time CCL, Sensitech and 3M) the group warned the community that on the launch of another VVM there needed to be investigations in the field to see whether health workers were confused, and because a detailed comparison between the two labels needed to be made. In the event, of course, since no other manufacturer was able to either meet the WHO requirements or introduce a price-competitive product, this was never to happen.

By this time, the enthusiasm was at the peak for the introduction of VVMs to revolutionize the way vaccines are handled. Since all vaccines other than OPV are relatively stable, the information presented on the number of days for the VVM on a vial of OPV to reach its discard-point was very encouraging for the group.

Constant temperature, day and night	**Time for VVM on a vial of OPV to reach "discard-point"**
Room temperature: 25°C	20 days
In a refrigerator: 25°C	8 days
In a refrigerator: 4°C	250 days

The group suggested that the impact of VVMs on the cold chain should be closely monitored and studies should be conducted to evaluate:

- the most probable behavioral changes in vaccine handling which can be expected to result from the introduction of VVMs;
- the impact on coverage of the use of OPV beyond the cold chain;
- the reduction in quantities of ice needed for NIDs;
- the use of domestic refrigerators in a variety of settings;
- the impact on vaccine wastage rates.

The members of TechNet felt that the introduction of VVMs should be the first step in the progressive adoption of an open-vial policy where programme managers could be reassured that VVMs would serve as a reliable reference for health workers who were using opened vials on more than one day.

The TechNet members agreed that once the introduction of VVMs with OPV was proven to be successful they should be used as soon as possible with other antigens, preferably all other EPI antigens, starting with the measles. This was because VVM technology for measles vaccine was fully developed and ready to use, and also because measles vaccine was being increasingly used in special immunization operations that would benefit from the use of VVM. TechNet also suggest-

ed that VVMs should be attached to measles vials in a way that they would have to be discarded or destroyed when the vial is reconstituted, so the absence of VVM would then serve as a signal to the health worker that the opened vial of measles vaccine should be discarded at the end of the session concerned.

TechNet formulized the priority activities with regards to VVM as follows:

- *"During 1996, TechNet members will help to initiate and supervise studies assessing the impact of introducing VVMs on the efficiency and cost of immunization operations in at least one country of each WHO Region. These studies will adapt routine reporting systems to examine a set of parameters described in a guideline protocol to be circulated by WHO at the end of March 1996 and will be conducted as VVMs become available. WHO/EPI will prepare a summary of the studies and disseminate it to WHO Regional Offices, UNICEF and TechNet members by the end of the year.*
- *WHO will arrange for a retrospective review of VVM field trials conducted before 1995, and the results will be disseminated to WHO Regional Offices, UNICEF and TECHNET members by the end of the year.*
- *To supplement the testing already conducted by VVM manufacturers for the vaccine industry, WHO/VSQ and UNICEF will arrange for immediate independent laboratory testing of samples of VVMs taken from each manufacturer's production line.*
- *Following the introduction of VVMs, changes should be made in the use of VVMs:*
  - *UNICEF should make immediate arrangements to reduce the number of CCMs in international OPV shipments to one per carton.*
  - *WHO will draw the attention of national managers to the danger of distributing CCMs with VVMs beyond national stores, and will reinforce the information in a question and answer format.*
- *VSQ and UNICEF will promote wider use of VVMs by:*
  - *working with local OPV manufacturers to attach VVMs to their vials;*
  - *recommending to UNICEF's international suppliers of OPV that they ship the vaccine with VVMs to all their customers;*
  - *making presentations to expand the use of VVMs to other vaccines, starting with measles freeze-dried vaccine.*
- *The policy on the use of opened vials will be treated as a separate issue from VVMs. TECHNET members will work with national managers in reviewing, improving and disseminating VVM training materials. Members will provide feedback to WHO on progress before the end of 1996."*

The Manila TechNet Consultation also recommended that WHO/GVP and UNICEF introduce a standardized vaccine arrival report (VAR) form and user guide. A draft form was subsequently released for testing and the form included a question as to whether VVMs were attached or not. This was the first official documentation of the presence of VVM on vials (although not yet the status of VVMs on arrival).

Country studies bring confidence

At the Copenhagen, Denmark TechNet Consultation on 16-20 March 1988 the slow update of VVM training plans at the country level was noted despite the ready availability of good training materials. I participated in, while serving as a health officer from UNICEF Area Office for the Central Asian Republics and Kazakhstan.

The TechNet group was happy to see solid grounds for recommending the use of VVM with all other vaccines based on the positive feedback coming from the field.

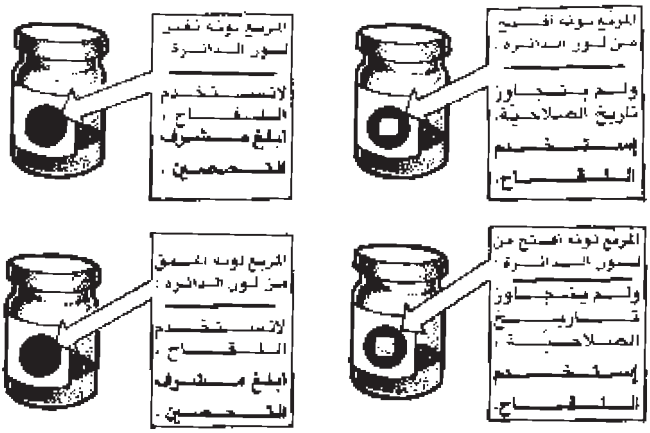
As a consequence of the Manila Consultation, efforts had been made to collect data on the impact of VVMs on the performance and delivery of immunization programmes at country level. VVMs had, in general, been well accepted and understood in country studies.

Study type	Participating countries	Status
Polio NIDs	Nepal, Turkey, Vietnam, Yemen	Completed
	Niger, Sudan	In progress
Routine immunization services	Tanzania, Vietnam	Completed
	Bhutan, Gambia, Ghana, South Africa	In progress
Knowledge, attitude and practice	Mozambique	Completed

The main finding in all the studies was that training in vaccine handling was essential. Unfortunately, a UNICEF survey of 50 countries at the beginning of 1997 suggested that few of them had conducted training at district level, even though the necessary training materials had been widely distributed. Although some countries cited polio NIDs as the reason for their failure to train, but it was noticeable that others, such as Nepal and Yemen, had successfully incorporated training on VVMs into training and planning sessions before NIDs.

In Yemen, innovative pocket flash cards were used to train vaccinators, and, furthermore, VVM instruction was given during national television broadcasts with the aim of achieving public awareness before NIDs.

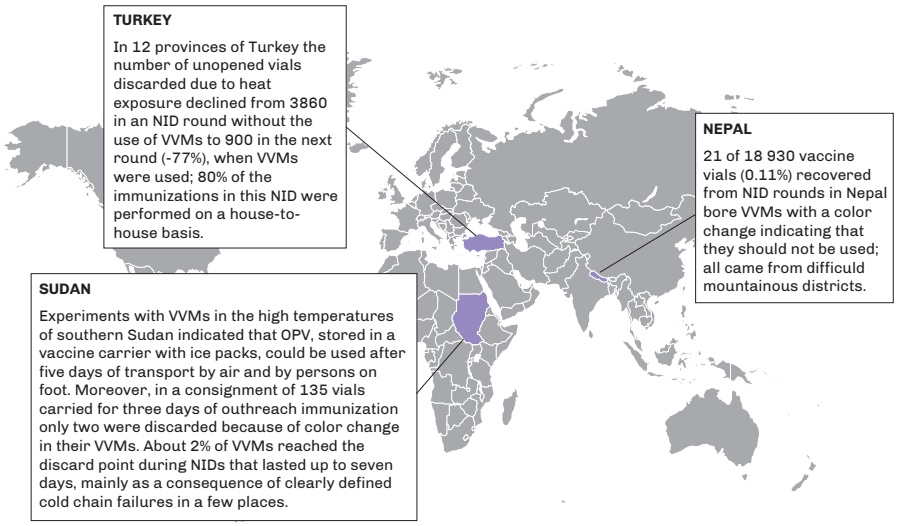
The policy of discarding unopened vaccine vials only at the point where their VVMs indicated this to be desirable resulted in reduced vaccine wastage compared with the levels being experienced under the 'cautious discard' policy that was in place prior to the introduction of VVMs.



VVM flash cards used in Yemen

The use of VVM in conjunction with a wide array of different cooling methods (including wrapping vaccines in wet cloth, putting vaccines in gourds, buckets, clay pots or calabashes with water or ice packs; putting wet rags on vaccine carriers to extend their cold life, cooling melted icepacks in river water, wrapping vaccines in rags and placing them in holes dug along rivers, and allocating icepacks to teams in accordance with the expected duration of their journeys) allowed the teams go confidently to places they would not have been prepared to visit had they needed to rely exclusively on ice.

With respect to the possible influence of VVMs on routine vaccine handling, it was considered to be unlikely that this 'beyond the cold chain' activity would have any noticeable negative effect on vaccine handling in the routine programme. Everybody seemed to realize that relaxing the cold chain was possible in a controlled campaign, as distinct from routine activities, and that this could not have happened without VVMs.



Other highlights from the country studies using VVMs can be summarized as follows:

- Coverage during NIDs can largely exceed the limits set by the cold chain in terms of both geography and time, i.e. teams can go further and can continue immunizing for longer periods.
- Health workers can use their own initiative to solve local cold chain problems if given the necessary tools and basic instructions.
- The VVM provides a message that is simple and easy to understand and gives health workers the confidence to take vaccines beyond the cold chain.
- Training health workers to understand and use VVMs is a simple matter.
- In many cases, cold chains for NIDs would probably not need much more equipment than is required for routine programmes.
- OPV was successfully transported in most study areas of Bhutan without vaccine carriers or ice packs. Because ice packs are still needed to cool reconstituted measles vaccine, however, the benefit to EPI is insignificant.
- In Nepal, only 14 of 6000 vials taken beyond the cold chain for more than three days were discarded because of VVM color change.

Implementation of the open-vial policy with VVMs significantly reduced the vaccine wastage. Interim reports from two districts and one hospital in Bhutan

show reductions in wastage from a few percentage points to over 90% for all EPI vaccines, relative to a 1996 baseline. The mean wastage rate of polio vaccine during NIDs in Turkey declined from 15% in the first round, before implementation of the multidose policy, to 8.3% in the second round following the introduction of this policy. A maximum reduction from 28% to 4% was achieved in one province. In one province of Tanzania the reported wastage of OPV fell from 49% during a four-month period in 1995 to 12% a year later when VVMs were introduced and the multidose vial policy was implemented.

The members of TechNet were in broad agreement that VVM was a reasonable indicator of cold chain integrity. This was fully demonstrated in the Nepal and Turkey studies and in Burkina Faso. The number and location of VVM color changes indicated breaks in the integrity of the cold chain, calling for investigation and improvement in procedures or equipment.

- Of 8,000 vials inspected in vaccine carriers from 460 NID posts in Nepal, 50 whose VVMs showed some color changes were clustered at locations where the cold chain had been compromised.
- An experiment in Turkey involved fitting VVMs to empty vials that were distributed in the cold chain; the VVMs changed color after three to five days in the hot southern provinces and after more than ten days in the cooler central and northern provinces.
- In Burkina Faso, large amounts of OPV that arrived too late for the 1996 NIDs were stored for over a year in a cold room at 4°C. The VVMs had changed color by the time the vaccine was to be used in the 1997 NIDs. The VVMs confirmed that the vaccine had become unusable because of incorrect storage.

The Bhutan study also highlighted the importance of why an OPV VVM could not be used as a proxy for other vaccines that were not fitted with VVM. In this case, the TechNet members suggested that other monitors like CCM should be used until VVMs were available for other vaccines.

The TechNet members were actively discussing VVMs for other vaccines and the question arose as to whether VVMs should be introduced for the other EPI vaccines in a stepwise manner or simultaneously. There was no valid basis for prioritizing, given that VVM maximizes the use of all vaccines in the field irrespective of their heat stability, and without compromising effectiveness. It was therefore decided that the additional vaccines should be tackled together, although some VVMs could be introduced more quickly than others if justified on technical or financial grounds.

Interestingly, the subject of a vial-mounted freeze indicator was brought up for discussion despite the fact that this technology was not yet available. However, the TechNet members agreed that such additional indicators were of a lower priority and their development should be deferred until the current VVM has been introduced on all the remaining vaccines. The feeling was that the implementation of VVMs should not be delayed by the search for these new technologies.[11]

The Copenhagen Consultation resulted in three recommendations on VVMs:

***Recommendation 1**: VVMs on vials of OPV are a valuable addition to immunization services, enabling health workers to decide whether or not the vaccine should be used. TechNet recommends that VVMs be introduced for all vaccines as soon as possible.*

***Recommendation 2**: The utilization of VVMs with OPV should be enhanced to assure vaccine quality at point of use and to improve the management of vaccine delivery.*

***Recommendation 3**: Because VVMs accurately indicate only the heat exposure of the vials they are on, VVMs on OPV vials should not be used as a means of evaluating the heat exposure of any other vaccines. Other monitors (CCM, Stop!Watch™) should be used until VVMs are available for other vaccines.*

Along with these three recommendations, TechNet formulated two major activities in support of VVM implementation:

Priority activity 1: Enhancing utilization of VVMs on OPV

Training

- Every regional EPI managers' meeting should receive country reports on the status of the VVM training effort.
- A *resource packet* of good examples of training materials and how they have been used should be compiled and distributed to each country using VVMs (PATH to compile packet; WHO/EPI to distribute it).
- A minimum package of activities should be completed by every country receiving VVMs, including:
  - a national orientation session (as part of a scheduled meeting if possible) at which central and provincial staff learn key messages, decide local policy guidelines, and determine the training approach for local staff (UNICEF to be asked to coordinate through its country offices);
  - distribution by national ministries of health of at least one printed item with basic messages to each immunization delivery point;

11 The discussion on vial level freeze indicators never faded throughout the years, and today it is still brought up at the TechNet forum.

  - incorporation of at least a basic training component on VVMs and their use in all training sessions for polio NIDs; WHO should revise the relevant sections of the "Polio Eradication Field Guide" to cover the introduction, use and management of VVMs with OPV.
- WHO/GPV/VSQ will explore the possibility of getting all OPV manufacturers to add brief, non-verbal instructions for using VVMs to the *package insert*, as has already been done by Smith Kline Biologicals.
- Wherever feasible (and particularly in conjunction with other studies), substudies of health worker and supervisor knowledge, attitudes and practice relating to VVMs should be carried out to monitor the progress of training. Model study protocols will be prepared by PATH and EPI and made available to WHO and UNICEF offices.
- With assistance from WHO and UNICEF staff and TechNet members, countries should consider opportunities to incorporate basic VVM training into pre-service curricula for health workers.

Supervision

- Model items for supervisory checklists (measuring health worker knowledge and action with regard to VVMs) should be developed, pretested, shared with country programmes and incorporated into manuals and forms.
- Supervisory visits should be considered as opportunities for training on the use of VVMs.

Use of VVMs for management of vaccine delivery

- While the current training materials provided by WHO offer good support for point-of-use interpretation of individual vials, they give no guidance on use for the management of vaccine storage, handling and delivery. WHO/EPI should revise current materials, with the assistance of PATH and selected national EPI staff, to incorporate a set of guidelines on acceptable and unacceptable uses of OPV VVMs for enhancing management of vaccine delivery. These guidelines should point out the opportunities to use VVMs for the following purposes and give examples and discussion of the *rationale* and *limitations* of each use:
  - stock management at district and lower levels;
  - allocation of resources (equipment, supervision, training) to priority areas;
  - investigation of specific incidents or of patterns of problems;
  - stretching the cold chain for OPV beyond traditional limits;
  - taking OPV beyond the cold chain (i.e. without active cooling);

- broadening cold chain equipment purchasing options or relaxing equipment replacement schedules at the periphery, based on VVM indications.

These materials will be pretested and made available to UNICEF and WHO field offices and national EPI managers at various meetings.

Further studies

- Additional studies to decide whether or not to go forward with VVMs for other vaccines are no longer needed. However, *utilization studies*, to provide feedback on how VVMs are being used and to improve their use, should be carried out in accordance with a protocol approved by WHO/EPI. Such studies should include cost-effectiveness measures and should be designed in collaboration with experts in economic analysis. At least one study in each region where VVMs are used should be completed by mid-1999. TechNet assistance should be provided to interested countries.

Expanding VVM use to countries procuring OPV directly

- An advocacy package (including a summary paper on the potential impact of OPV VVM use on vaccine quality and cold chain management) and practical information on specification of VVMs in direct procurements of vaccine should be prepared by EPI and VSQ and distributed to those countries not using UNICEF/WHO procurement or expecting to begin independent vaccine procurement within the next five years.
- Work to encourage and assist qualified national vaccine manufacturers in adopting VVMs should continue (WHO/VSQ and PATH).

Priority activity 2: VVMs for all EPI vaccines

As stated in Recommendation 1, the development and deployment of VVMs for all EPI vaccines should proceed as rapidly as possible. A small product development team comprising representatives from WHO/GPV, UNICEF Technical Centres and PATH will coordinate efforts to develop and implement three VVMs with different specifications but with presentations consistent with the OPV VVMs, to cover all existing priority vaccines, for instance DTP, DT, TT, HBV, measles and BCG.

- On the basis of Artur Galazka's estimates of stability the group will elaborate specifications, in close collaboration with VVM and vaccine manufacturers, for three time/temperature indicators:
  - Category A - highly stable vaccines: toxoids and hepatitis B vaccine;
  - Category B - vaccines of moderate stability*: BCG, yellow fever and

- measles vaccines;
- Category C - stable vaccines: pertussis (whole cell), including DTP vaccines.

- It was decided that development efforts for all three VVMs should proceed in parallel and as quickly as possible. As soon as any one of them has been validated for use in the field it should be deployed. VVMs should be deployed as soon as they are available, even if any other additional indicators, such as threshold or freeze indicators, are appropriate for use on a given vaccine but are not available concurrently with the VVMs. Additional indicators should be added as they are developed.

Steps for introducing VVMs on all EPI vaccines *(not all the steps are needed for all vaccines; not necessarily in order of implementation):*

- Inform countries and other partners of the decision and likely time scale.
- Development of specifications for VVM manufacturers.
- Establishment of WHO minimum requirements (including matters relating to consistency of presentation).
- Vaccine manufacturers' agreement on specifications.
- Development and production of VVMs.
- Development of technology for label application.
- Vaccine manufacturers' validation of VVMs.
- WHO validation of VVMs.
- Field studies to validate usability of VVMs with lyophilized vaccines.
- Validation of correspondence between VVM performance and vaccine potency.
- Development of training materials for new VVMs.
- Development of a comprehensive introduction plan.

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* *Specification will include a requirement that the time/temperature indicators be removed or destroyed as the vial is opened for reconstitution. This may result in different manufacturers placing the VVM on different places on the vial/cap. It must be determined if this will present significant problem for training and use.*

Setting priorities for the next 10 years: implementation of known technologies

It was at the Harare, Zimbabwe, TechNet Consultation, that took place from 6-10 December 1999, that a clear message was sent out confirming that the management and implementation of existing technologies was to be the priority of health service logistics during the next 10 years, although not at the expense of innovation aimed at resolving new and existing problems.

Since the formation of the TechNet e-discussion forum in 1988, VVM had vied with injection safety as the hottest topic of discourse. In Harare, the TechNet members underlined some of the concerns regarding VVM implementation including the added cost burden that VVMs place on vaccines, the confusing messages surrounding the "fast chain" and other concepts, and the inability of health workers and to interpret and make decisions with them. A major worry was that the benefits of using VVM, such as in extending outreach, had not been made clear to managers. John Lloyd and Mary Catlin gave a joint VVM update presentation in which they stressed the criticality of adequate training in VVM procedures and referred to a PATH survey that found the following gaps in training programmes:

- *Training materials were not available.*
- *Available materials were not translated.*
- *Skilled trainers were not available.*
- *VVM training was not incorporated into routine EPI training.*

Robert Davis (UNICEF) reported on his experiences with multi-dose vial policy and VVM in Eastern and Southern Africa. Davis explained the difficulty of Kenyan health workers turning their back on the policy they had been pursuing for 20 years (one of discarding all vaccines that has been outside the cold chain for more than an hour) even if the vials have VVMs. This was an example of the big challenges faced when introducing such a drastic policy change.

USAID's Steve Landry outlined the imminent establishment of the Gavi, which was being set up as a radical solution to some of the serious issues surrounding the future of vaccination efforts. Gavi was subsequently take shape and grow into an internationally important organization with a critical role in shaping the market for VVM.

The Harare consultation recommended that a guide should be prepared on the management and supervision of vaccine distribution using VVMs by July 2000, that existing training materials should be included in this guide as appropriate, and special efforts should be made to disseminate these materials widely and to promote their use in training.

TechNet is dead, long live TechNet21

When I joined WHO at their headquarters in February 2001, I inherited the TechNet workload along with its e-discussion forum. Reviewing the progress since its establishment, I strongly believed it was time to make structural changes to the

entire network. My supervisor, Julie Milstien at the Access to Technologies group, strongly supported this change. And, as the technical responsible person for VVM and its implementation at WHO headquarters, I had plans to execute...

I gathered the TechNet group in New Delhi, India during 27-28 August 2001. At this gathering the group was reinvented and relaunched with its new name TechNet21. In fact, it had been the Harare consultation that have given the first signs of this change by agreeing on the technologies that were to result in the immunization services that are recognized; today it was just that the introduction and execution were lagging behind. The 1999 survey of the TechNet membership had indicated that although TechNet played a useful role, at the time it was not seen as providing a useful resource of expertise or information. When I took it over the body, the TechNet e-discussion forum had around 150 members, but with around 70% of postings coming from a few people. Participants of the survey indicated that TechNet's role should be more pragmatic and that it should not be concerned with policy development. In this sense, though it included quite a detailed agenda on all aspects of the immunization programme, recommendations of the TechNet21 New Delhi consultation were fully focused on the relaunch and reinvention of the network.

An intense round table session on the present and the future of the cold chain and VVMs was part of the New Delhi Consultation. Under Ticky Raubenheimer's moderation, Soren Spanner (WHO SEARO), Carib Nelson (PATH), Hans Everts (WHO HQ), Shanelle Hall; (UNICEF SD), and Debbie Kristensen (PATH) discussed different perspectives in relation to VVM implementation.

Carib Nelson gave an electrifying presentation on the possibilities of a more flexible cold chain with examples of storing vaccines in midwives' homes, of transporting vaccines without ice, and the storage of vaccines in air-conditioned rooms. Nelson highlighted the importance of VVMs as an important part of this flexible cold chain strategy since they gave health workers the ability to determine whether a vaccine has been exposed to too much heat over time. This allowed the freedom to deviate from the rigid cold chain without sacrificing vaccine safety. Nelson described his innovative flexible cold chain experiences in Indonesia:

Carib Nelson

"Indonesia has adopted an innovative national policy for hepatitis B vaccine in Uniject™ pre-filled injection devices. This

HepB vaccine in Uniject™

vaccine is typically used by midwives for neonatal home visits. They store the vaccine in their homes and carry it to home visits at ambient temperatures. Initially, when VVMs were not attached to Uniject devices, the vaccines were allowed to stay out of the cold chain for one month. As VVMs are introduced, the vaccines are allowed to remain out of the cold chain until the VVM, or the expiry date, indicates the need to discard. Over the last two years Indonesia has delivered about 1,000,000 hepatitis B doses in Uniject devices, following this flexible cold chain policy. PATH has been monitoring the use in three provinces and has found no VVMs indicating over-exposure to heat."

Debbie Kristensen gave an overview on the training requirements for the introduction of VVMs. Kristensen mentioned that VVM training to date had largely focused on the use of VVMs for polio NIDs. This training now had to be extended to all those who handled vaccines for both routine immunization and campaigns. Without training, the VVMs were likely to be ignored and the benefits would not be realized. By the time of the Harare meeting, a few countries were already using VVMs on vaccines other than OPV, and some countries were expecting to receive new vaccines with VVMs in the very near future.

Some of the examples given:

- *Indonesia currently uses VVMs on hepatitis B vaccine in a pre-filled mono-dose syringe format.*
- *Vietnam expects to receive 3 million doses of measles vaccine with VVMs from the JICS later this year.*
- *Japan BCG is prepared to deliver 1.5 million ampoules of BCG with VVMs for UNICEF orders.*
- *The Partnership for Child Health will provide 9 million doses of tetanus toxoid in pre- filled mono-dose syringes with VVMs to target countries, beginning with Burkina Faso in late 2001.*
- *At least two Indian producers of hepatitis B vaccine are incorporating VVMs onto their products.*

Kristensen summarized the benefits of VVM mentioning that if the policy makers and end-users clearly understood the benefits of this technology, they would undoubtedly be better motivated to devote time and effort into learning how to use it.

- ***Health workers can use VVMs to prevent delivery of heat-damaged vaccine.*** *VVMs provide a warning signal when vaccine has been heat-damaged and should be discarded.*
- ***VVMs can be used to manage stock*** *by identifying which vaccines have received some heat exposure, but are still good, and should be used first.*
- ***VVMs reduce unnecessary vaccine wastage.*** *They can identify useable vaccine after a cold chain failure or after an outreach trip.*
- ***VVMs can facilitate the relaxation of the cold chain,*** *where desired – with a side benefit of preventing freeze-damage to sensitive vaccines.*
- ***VVMs can be used to detect cold chain problems*** *if individual facilities document vaccine discards due to VVM status. The data can be used to identify where problems are occurring and to focus resources on the cold chains of those facilities.*
- ***VVMs facilitate outreach*** *– as seen during numerous polio NIDs. If OPV can be transported for days without ice, just imagine how long the other vaccines will last under similar conditions.*

Kristensen also summarized the information that should be conveyed in any learning programmes associated with VVMs:

1. *How to read and interpret the VVM*
2. *The location of the VVM*
3. *Reminders of the need to discard reconstituted vaccines within 6 hours or at the end of the session whichever comes first*
4. *VVMs are reliable tools and different vaccines will have VVMs that change color at a different rate.*

In addition to training, Kristensen discussed the programme implications of VVM including the fact that there were other steps that countries could take to prepare for the broader VVM introduction:

Procurement *– Those countries procuring their own vaccines or accepting donations can request that manufacturers supply all vaccines with VVMs that meet WHO specifications.*

Vaccine distribution *– There may be initial transition periods where countries receive a mix of vaccines with and without VVMs. Ideally, the vaccines with VVMs will be sent to areas with the poorest cold chains.*

Policy *– Countries may want to tie adoption of the multi-dose vial policy for liquid vaccines to the availability of VVMs on those vaccines. The VVMs will provide added information on the heat-exposure status of the opened vials of vaccines. Countries might also consider flexible cold chain policies for vaccines with VVMs. Note: Indonesia is already studying possibilities for relaxing storage temperatures for their mono-dose hepatitis B vaccine presentation. Such changes can help to overcome cold chain capacity constraints, prevent freeze-damage and decrease costs.*

Wastage monitoring *– If countries are monitoring vaccine wastage, it could be beneficial to include the reasons for discarding vaccines on their forms. Discards due to a VVM indication of excessive heat exposure could be specifically noted on inventory forms and reported to supervisors. Such data can be used to help identify cold chain problems. Note: 80,000 doses of heat-exposed OPV were discovered due to VVMs in Uttar Pradesh, India. A follow-up investigation revealed problems with the cold chain that were previously unknown and can now be corrected.*

Shanelle Hall reported that VVM specifications for all antigens had been completed and issued to vaccine manufacturers in August 1999. UNICEF's 1999 tendering round had included a request for the supply of vaccines with VVMs and the 2000 round had attracted VVM offers from two companies. The tender for 2001 to 2003 had also included a VVM requirement and a number of manufacturers had offered to comply.

Hall noted, however, that although the VVM requirement was in place, implementation was proving to be more difficult than had previously been thought. As a result, a work plan had been agreed with WHO, and discussions were underway with LifeLines and the vaccine manufacturers to deal with the various commercial and technical issues. No timeline was yet in place and she would report back when a programme had been agreed.

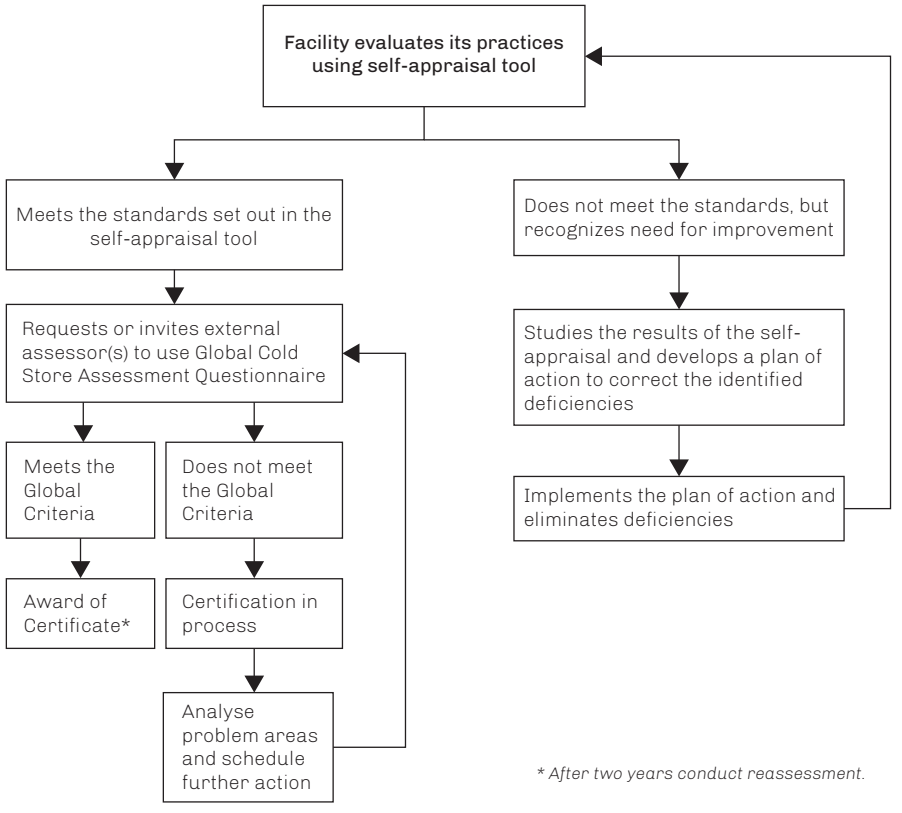
Cold store certification initiative is brought up for discussion at TechNet New Delhi

Since my arrival at the headquarters of WHO, I had been busy going through all immunization programme reviews to understand the extend of all the logistics and technology related problems at the country level. Immunization programme reviews conducted in many countries during the preceding few years had shown that logistics problems continued to be an obstacle to achieving substantial progress in immunization. In particular, poor management of the vaccine cold chain, one of the major components of the logistics of immunization, played a major role in the below-par performance observed by these review teams.

One of the factors that led Gavi to focus on infrastructure strengthening was the perception that cold chain and vaccine distribution mechanisms were beginning to disintegrate in many countries. The real need for better vaccine management practices could also be seen in the high levels of wastage observed (and recorded on Gavi fund application forms) and in the prevalence of adverse events. These adverse events arise, at least partially, as a consequence of incorrect vaccine storage and distribution practices. In addition, the failure of programmes to implement the multi-dose vial policy and to use VVMs were also contributing to the problem of vaccine wastage.

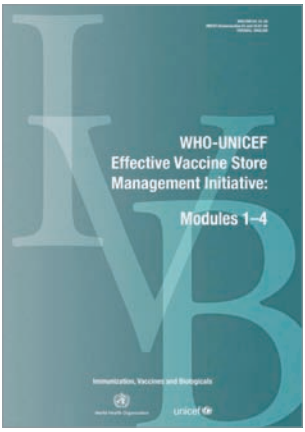
My idea was to gather an international working group to create an initiative with the goal of encouraging programmes to adopt practices that fully protect vaccines, promote efficient stock management, and support improved vaccine distribution systems in the current rapidly changing environment. The idea was to initially target national stores and gradually expand the initiative to cover the vaccine management system in the country.

Cold store certification process



** After two years conduct reassessment.*

Andrew Garnett



TechNet New Delhi was a perfect forum to bring this idea up for discussion and a dear colleague of mine, with whom I discussed the initial skeleton of the idea, agreed to do the presentation. Andrew Garnett explained the cold store certification process to an attentive audience and there was a general agreement that some sort of rigorous assessment of vaccine stores was required. However, there was considerable concern expressed about the implications of extending the formal certification process beyond the national level stores. Several contributors considered this to be an impractical ambition, and consequently, it was generally agreed that the initiative should initially concentrate on national level stores. Some contributors also expressed concern about the whole idea of formal certification. There was a worry that stores which failed to achieve certification might be blacklisted by donor agencies and deprived of vaccines. Other contributors argued that most, if not all, of the benefits of certification could be achieved through a process of self-assessment.

Following this debate, I gathered together the international task force in December 2001 with the plan to launch the initiative as the *WHO-UNICEF Cold Store Certification Initiative* in 2002.

Following discussions between WHO and UNICEF, the initiative was reshaped and launched as the *WHO-UNICEF Effective Vaccine Store Management (EVSM) Initiative* in 2004. This initiative was then supplemented by the "vaccine management (VM)" system component of the country and subsequently the two assessments were merged into one as today's *"Effective Vaccine Management (EVM)"* initiative.

VVM implementation accelerates

The Technical Review of Vaccine Vial Monitor Implementation meeting (27 March 2002) was a turning point in VVM implementation. The meeting was considered as a milestone as it resulted in a valuable exchange of information, clarification of issues, and assignment of responsibilities for all parties.

The next TechNet21 Consultation was held in Antalya, Turkey, during 23-25 March 2004. There was no need for a specific VVM session, but VVMs were brought up and/or referred to in a majority of the agenda items.

Robert Steinglass (BASICS, USA) gave a presentation on the impact of new delivery technologies on increased access. This was a Uniject report from Mali where community-based volunteers (CBV) had administered TT-Uniject with VVM. The correct reading of the VVM was among the eight-performance measures used to assess the correct use of TT-Uniject by the CBV. The study concluded that injection with TT-Uniject was correctly administered by female volunteers selected to participate in the campaign. This result was particularly remarkable since it was despite the fact that at least half of the volunteers could not read!

Serge Ganivet (WHO AFRO) presenting the sentinel reporting sites for vaccine wastage surveillance in Malawi, highlighted that vaccine discards due to VVM readings can be tracked through such sentinel reporting.

Samuel Sawa (UNICEF SD) gave feedback on the implementation of the vaccine arrival report (VAR) since its introduction in 2003 for all Gavi shipments. The initial VAR had referred only to the presence of the VVM. There was no reporting requirement on the status of the VVMs on arrival. TechNet members then raised the issue of having both VVMs and CCM cards in the shipments and questioned whether the CCM could be removed from the international shipment. It was clarified that VVM is not a transit or shipping indicator. It monitors heat exposure from the moment the vaccine is labelled up to the point of use. In the VVM's operational lifespan, the duration of transport tends to be minimal so it is almost impossible to notice a change with the naked eye unless shipment has been unduly long. It was explained that other devices will assist in determining whether the contractual agreement of UNICEF, in terms of temperature exposure, has been respected by the manufacturer and/or forwarder.

An "overcoming freezing in the cold chain" session, chaired by Steve Landry of The Vaccine Fund, was interesting from the point of view that despite their function as cumulative heat indicator over time, VVMs had been instrumental in the prevention of freezing simply by allowing vaccines to go beyond the 8°C limit. Since the TechNet members were all aware of a study that had been conducted to evaluate the use of cool water packs instead of icepacks during vaccine transportation, I presented the clear conclusion that the freezing of sensitive vaccines during in-country transport can be prevented by the use of cool water packs.

Carib Nelson in his case-study from Indonesia on a twin-temperature cold chain, concluded that the removal of vaccines from freeze-susceptible parts of the cold chain prevented freezing and did not result in excessive heat exposure. Nonetheless, Nelson underlined that VVMs are needed when taking vaccines out of the cold chain.

David Hipgrave from the University of Melbourne reviewed the existing data for HepB vaccine taken out of the cold chain. Hipgrave said that the attachment of VVMs to vials of HepB vaccine by manufacturers added a new dimension to this issue, and was confident in concluding that in the era of the VVM and with the available data, storage of HepB vaccine out of the cold chain must be considered completely safe and effective.

Steven Wiersma (WHO HQ) discussed WHO plans for HepB policy development. His conclusion was that vaccines with VVMs can be taken out of the cold chain only if health workers and others handling the vaccines have been trained to interpret VVM readings correctly and if any vial bearing a VVM that has reached its end-point is discarded.

The Antalya TechNet Consultation also featured a cartoon exhibition called "Training comes alive" by Kemal Gökhan, which introduced the Vaccine Management Training Cluster materials, including the VVM module.

In 2006, following the Antalya TechNet Consultation, and as a result of departmental restructuring, I handed over some of my responsibilities (including the management of TechNet21) to the EPI team.

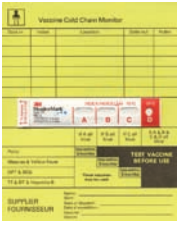
At next TechNet Consultation in October 2006 in Mexico City the subject of the role of VVMs in taking vaccines out of the cold chain again came up. Apart from this, there were no other sessions nor mentions of the miracle tool that was by now appearing in all vaccines. Holding the TechNet21 meeting for the first time in a country where PAHO was the dominant health agency presented an excellent opportunity for PAHO countries to be exposed to the international group and its experiences, but with only 10 out of 136 participants from PAHO countries in attendance (excluding the host), it was also a big missed opportunity.

VVMs back on the agenda

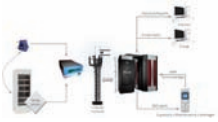
VVMs were back on the agenda at the 2-4 December 2008, Tunis (Tunisia) TechNet21 Consultation. There were two major exponents of VVM in this meeting, myself and Joanie Robertson from PATH. I gave a presentation on whether we really are monitoring temperatures in the vaccine cold chain and Joanie spoke on the issues surrounding out-of-cold-chain strategies.

The main focus of my presentation was not actually VVMs, but it served as a golden opportunity to spotlight this elegant tool and its role in temperature monitoring[12]. I focused on the temperature monitoring devices used at different levels of the vaccine cold chain, underlining the critical role of VVMs that they are the only tool that reflected the cumulative temperature effects on vaccines from the time of production all the way to the furthest points of delivery.

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

Description (Product specifications)	Examples (WHO prequalified)	Why to use
Electronic shipping indicators PQS performance specification, WHO/PQS/E06/TR07.1	 Vaxalert®	Used in international transport. WHO recommends inclusion of one device in each and every shipping carton. Two different type devices used with different vaccines (**Type I** with yellow backing card for DTP, DT, TT, Td, Hep B, IPV, liquid Hib and combination vaccines; **Type II** with blue backing card for OPV and all lyophilized vaccines of BCG, measles, MR, MMR, Hib, yellow fever and meningitis vaccine). These devices can also be used in in-country transport if the distribution takes more than a day between the primary vaccine store and intermediate vaccine stores.
Vaccine cold chain monitor PQS performance specification, WHO/PQS/E06/IN02.1	 Vaccine cold chain monitor card	Transit indicator. Used in international transport one device per shipping carton only if dry ice is used (electronic shipping indicators do not function with dry ice due to extreme cold). Continuous use with the same box of vaccines is limited within country. If new ones are activated, it can only check discrete levels of cold chain in the system. No use in storage facilities (data cannot be associated with vaccines for decision making).

12 A new temperature monitoring device, Fridge-tag® that revolutionized the temperature monitoring in refrigerators was the main focus of my presentation. For the record, I was talking to all temperature monitoring device manufacturers in an IQPC Cold Chain European Conference in 2006 explaining my dream temperature monitoring device for the vaccine refrigerators (literally explaining what the Fridge-tag looks like today). In six months, Andrea Berlinger came to WHO with a prototype Fridge-tag device in December 2006. With the establishment of the 30-day electronic temperature refrigerator logger product category in the PQS, the Fridge-tag® device from Berlinger would be the first product to be WHO prequalified on 30 September 2007.

Vaccine vial monitor PQS performance specification, WHO/PQS/E06/IN05.1 (19)	 HEATmarker®	The only tool among all time temperature indicators that is available at any time in the process of distribution and at the time a vaccine is administered indicating whether vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been heat damaged.
Irreversible freeze indicator PQS performance specification, WHO/PQS/E06/IN03.1	 Freeze Tag	Can be used both at storage facilities and during transport of freeze-sensitive vaccines. If electronic shipping indicator is used in international transport, there is no need to include irreversible freeze-indicator since the electronic shipping indicator has a freezing alarm function.
Programmable electronic temperature and event logger systems with integral alarm and auto-dialer options PQS performance specification, WHO/PQS/E06/TR03.1	 Fridgefone™	Programmable temperature and event logger systems with integral alarm and auto-dialler options, principally used for monitoring storage conditions in primary and intermediate vaccine stores.
Portable electronic thermometer PQS performance specification, WHO/PQS/E06/TH01.1	n/a	Hand-held electronic thermometer with internal sensor and/or one or two detachable probes suitable for monitoring air temperature in freezer rooms, cold rooms, vaccine freezers, vaccine refrigerators air-conditioned rooms.
Portable alcohol stem thermometer PQS performance specification, WHO/PQS/E06/TH03.1	n/a	Portable alcohol stem thermometer suitable for monitoring storage temperatures in vaccine refrigerators and freezers. These devices may also be used for supplementary temperature measurement in freezer rooms, cold rooms, and air-conditioned rooms used for storing vaccine in the vaccine cold chain.
Integrated electronic maximum-minimum thermometer, with factory programmed alarms, for vaccine refrigerators and freezers PQS performance specification, WHO/PQS/E06/TH06.1	n/a	Electronic maximum-minimum thermometer, with factory programmed alarms, for monitoring storage conditions in vaccine refrigerators and freezers.
Wall-mounted pen recording thermometer PQS performance specification, WHO/PQS/E06/TR04.1	n/a	Wall-mounted pen recording thermometers to be used to record the storage temperature in primary and intermediate cold rooms and freezer rooms containing vaccine stocks in situations where electronic logger systems are inappropriate.

User programmable temperature data loggers PQS performance specification, WHO/PQS/E06/TR05.1	 Libero®  LogTag Trix 8®	User-programmable electronic temperature data loggers to be used for study and commissioning purposes throughout the vaccine cold chain. They are not appropriate as main routine monitoring purposes.
30-day electronic refrigerator temperature logger PQS performance specification, WHO/PQS/E06/TR06.2	 Fridge-tag2®	Electronic refrigerator logger, with factory-programmed alarms and visual display for monitoring storage conditions in vaccine refrigerators. The LCD screen shows data over a 30-day period. The device may also be used as a secondary back-up in cold rooms.

Robertson spelled out that there was a great deal of experience with the use of OPV out of cold chain during NIDs that should be tapped into. She also explained that there was a need for clearer instructions in the field as to which vaccines could be kept out of the cold chain, for how long, and in what conditions. *"The issue of training cannot be too strongly emphasized for vaccines OCC. The use of VVM on vaccines that are used OCC is also very important, and it is vital that the performance of VVMs in different temperature scenarios is well understood, and scientifically verified."*

Is there a fatigue?

Fourteen years after their initial introduction in 1996, the Kuala Lumpur TechNet21 Consultation held from 30 November to 2 December 2010 reported that a degree of fatigue with the use of VVMs starting to set in at the country level. The TechNet21 group reported that challenges remained with improving VVM usage in the field as there were still health care workers who were unable to correctly interpret VVMs. Although there had been no particular report on the use of VVM in the field, some members cited anecdotal evidence of similar experiences. One reason given was that a high staff turnover as well as new staff joining the immunization workforce meant that many were not being trained on how to use the VVM.

On the other hand, the bulk of the training was focused only on how to read the VVM without touching upon all its other uses including the facilitation of effective stock management, enabling the outreach, the prevention of freezing, and the reduction in vaccine wastage. In reality, the use of VVM in the field was not achieving its full potential. But, despite this, the TechNet21 Consultation in 2010 failed to address this issue and focused more on the technological side of vaccine management. Jhilmil Bahl from WHO reported on recent discussions with the Technologies and Logistics Advisory Committee (TLAC) at WHO on the revision of MDVP and the visual cue. This emphasis was somewhat reminiscent of John Lloyd's summation from the proceedings of the TechNet conference way back in 1999.

New challenges

The increased introduction of new vaccines, especially the penta (DTP+HepB+Hib), brought new challenges to vaccine management. By the time of the next TechNet21 Consultation in Dakar, Senegal from 5 to 7 February 2013, there were three suppliers of pentavalent vaccine with two different types of VVMs. Health workers in the field were puzzled since VVMs on some vaccines were changing color faster than the others. They started to question the VVM rather than analyzing their cold chain. With the introduction of pentavalent vaccine, it was the first time that a liquid product with VVM7 had appeared in cold rooms. Because the reactivity of VVM7 being half as fast as VVM14, and despite the vaccines generally being kept at the higher end of the 2-8°C range, the VVMs did exactly what they were supposed to do, and changed color faster. This panicked the field workers. Souleymane Kone (WHO HQ) mentioned the challenge of having three suppliers with two different VVM types, but did not mention that VVM was simply pinpointing problems in the cold chain.

PATH's Simona Zipursky introduced a new concept of "controlled temperature chain (CTC)". She explained that many vaccines were more stable than their current licenses indicated and that the CTC approach takes advantage of known vaccine stability. Without requiring any reformulation, it enables the use of vaccines outside the standard 2–8°C range, a situation endorsed by regulatory consent. Many countries had already been taking advantage of this stability, using certain antigens outside the cold chain for limited periods of time by relying on the VVM. However, this use is considered 'off-license', even though field studies had confirmed the potency of vaccines used in this way. In 2012, the license for Serum Institute of India's Meningitis A vaccine, MenAfriVac®, was changed based on a thorough review of scientific data by regulatory authorities and WHO. The vaccine was allowed to be used for a period of up to four days, at temperatures of up to 40°C in CTC. Naturally, this approach raised some questions about whether the new CTC approach would now dictate how vaccines could officially be taken beyond the 8°C barrier with the help of VVM (despite this "off-label" practice having been 'de facto' for many years). Indeed, Bassabi Alladi and Claude Lodjo (MOH, Benin) made a presentation on the Meningitis A campaign that was understood to have successfully used vaccines at an ambient temperature of 40°C for up to four days following its removal from the 2°C-8°C cold chain.[13]

13 Although it was said "at ambient temperature of 40°C", the published study did not report any ambient temperature measurement (Simona Zipursky, et al. (2014). Benefits of using vaccines out of the cold chain: Delivering Meningitis A vaccine in a controlled temperature chain during the mass immunization campaign in Benin. *Vaccine.* Mar 14; 32(13): 1431–1435).

Performance on a poor foundation "would be wobbly"

At the Bangkok, Thailand (11-15 May 2015) TechNet21 Consultation, Diana Chang-Blanc (WHO HQ) emphasized the need to fix some of the basics of vaccine management as a necessary part of any work to strengthen immunization supply chain systems in the field: *"Network design, system optimization and innovations are important, but performance on a poor foundation would be wobbly".*

The focus of the presentation was to highlight the necessity to build a strong immunization supply chain system across all countries in order to sustain the performance of their national immunization programmes and to act as a clarion call to ensure that innovative solutions are implemented on a solid foundation of supply chain basics. In support of the need to fix and focus some of the basics, Chang-Blanc presented the key resources that were being developed at the global level to help countries build some of the fundamentals.

Among the ones listed were:

i) a comprehensive approach to vaccine management to enhance the ability of countries to comprehensively assess, plan and implement innovative changes to their immunization supply chain;
ii) a UNICEF Cold Chain Support Package (CCSP) which provided commercial and technical information to enable an efficient and effective procurement process for Cold Chain products and services through the UNICEF Supply Division;
iii) the WHO updated guidelines on Vaccine Vial Monitors (VVM), the multi-dose vial policy (MDVP), the immunization in practice book with module 2 on supply chain and logistics, the Vaccine Management Handbook and revised manuals and various e-learning materials.

In her presentation, Chang-Blanc underlined the critical role of learning and referred to the e-VVM based vaccine management course being offered through the EPELA platform. In closing, Chang-Blanc emphasized the growing complexity of immunization supply chain and that concerted efforts from all partners to standardize guidance was necessary in order to help countries consolidate the fundamentals of an immunization supply chain management system.

Pitch perfect

The 15th TechNet21 Conference which had the theme of "building the next generation of immunization supply chains" was held in Cascais, Portugal from 16-20

October 2017 and had more than 350 participants, an event record. Patrick Lydon from WHO headquarters set the scene at the opening ceremony:

"Business as usual just does not work anymore, we cannot keep doing the same things we've been doing before, the programmes have gotten a lot more complex, there are a lot more vaccines, a lot more products."

Patrick Lydon during the opening of TechNet21 conference, Cascais, Portugal

On many levels, the 15th TechNet21 Conference was a groundbreaking event. The five-day conference focused on three supply chain objectives: availability, potency, and efficiency. During the proceedings the participants discussed the enablers for the supply chain objectives and collaborative actions for change.

A 'Pitch Fest' on innovations in data use and visibility took place on Day 3. For this, participants were asked to come and witnessed new solutions and approaches to improving visibility and data use for the immunization programme and/or supply chain. Participants were given the opportunity to judge the approach and usefulness of each solution presented. Contenders ranged from open logistics management and information systems (LMIS) to the transportation of supplies with the help of drones, an immunization registry for global tracking, a passive vaccine storage system to blockchain technology. Ted Prusik gave the pitch for Temptime Corporation on 2D barcode and VVM:

"Hello, I am Ted Prusik, Senior Vice President and co-founder of Temptime, and sometimes the Chief Clown of Temptime." Prusik very smartly asked the participants to give a shout out for VVM and received a big applause and cheers even before giving his pitch.

Ted Prusik at Pitch fest, TechNet21 conference, Cascais, Portugal

"We are here talking about the next generation of supply chain, so I'd like to introduce you to the next generation of VVM. Our innovation fills the digital temperature gap at the vial level by integrating the VVM with the 2D barcode. With this, we are working with GS1, the global standards group, to develop the application identifier that contains the string of information so that interoperability, globally, becomes a reality. The VVM, as you know, is the only device available that can temperature monitor every vaccine from the time it's manufactured to the time it is administered. However, currently the VVM status is manually recorded, if it is recorded at all. The next generation supply chain is going digital, and we are aiming to develop VVM as a digital solution. With one scan by a smart phone or a scanner all the invaluable information that is contained in the bar code as well as the color shade of the VVM can be captured. This vial level information can then be linked to other electronic data in the system to provide a full temperature history of that particular vial. The technology is scalable and it is sustainable.

More than seven billion units have been used since 1996, and there are more than 2 billion smart phones in use globally. The technology can be extended easily to other medicines, cold chain medicines like insulin and oxytocin and even to test kits. So, this will help to make health care system more effective and efficient."

Prusik showed a short video to demonstrate how it would work.

"What you see on the screen is all of the information that is encoded in the 2D barcode as well as the status of the VVM. As you know with smart phones and technology you can design the screen to present information in a range of user-friendly styles, for example simple check marks, 'use' or 'not use' symbols, or as you see here a red "X" denoting that this VVM has reached its end-point. We believe this move away from the visual systems that are used now is going to be an industry game changer that will gradually be integrated into all health care systems."

There was a big applause from the audience.

Following all 11 innovations being presented and a final 'beauty parade' of the presenters, the participants were given electronic voting devices with which to rate each entry on a 5-point scale. When Lydon announced the results, it came as no surprise that Temptime's "VVM integration into 2D barcode" was the top scorer.

Next generation

From the very beginning of the TechNet establishment, VVM was always on the agenda. The TechNet community embraced the technology and contributed to its development by making sound recommendations. In a new era of digital supply chains, the 2D barcode rebirth of the VVM has proved itself to be the answer once more. I expect that in the future TechNet21 conferences, we will be hearing a lot more about the latest incarnation of this elegant tool.

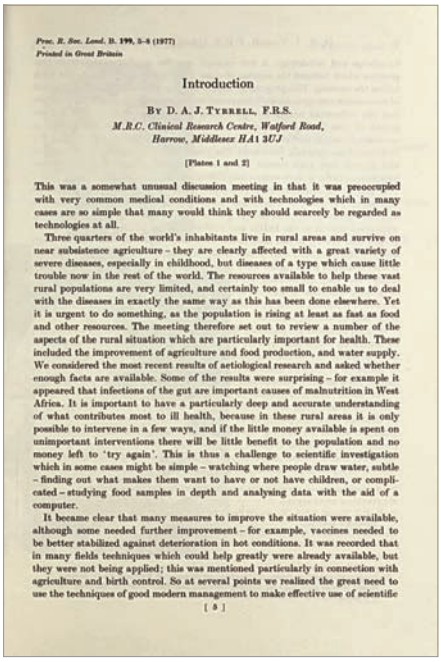
Professional hubris

Many initiatives and products have emerged that address problems of health care in low infrastructure, under-served, low- and middle-income countries. But, even with accepted as being highly successful, these solutions tended to be undervalued by many distinguished professionals living in the "other" part of the world, regardless of the quality of the underlying scientific research and support. Of course, it has always been the case. Forty-two years ago, in 1977, D. A. J. Tyrrell, F.R.S. M.R.C. of the Clinical Research Centre noted the following in his opening remarks to a discussion meeting and exhibit organized at the prestigious Royal Society in London:[14]

"It had to be faced however that obstacles often lay outside the realms of technology. For example, 'charismatic' and devoted individuals had inspired others and used great energy and skill to get rural development programmes moving with great benefit to the health and wellbeing of the people, who took up the project and ran it. It had been found difficult to reproduce this success when officially recruited staff were posted to do the same elsewhere. Another difficulty is that scientists often regard work done in this field as of little 'value' scientifically, and they particularly undervalue work done with simple methods in developing countries. In addition, scientists are often not interested in the

14 D. A. J. Tyrrell. Introduction. *Proceedings of the Royal Society of London,* Series B, Biological Sciences, 19 October 1977. Volume 199, Issue 1134 (https://doi.org/10.1098/rspb.1977.0113)

further work that is needed to ensure that the potential benefits of their discoveries are realized in developing countries."



Proc. R. Soc. Lond. B. **199**, 5–8 (1977)
Printed in Great Britain

Introduction

By D. A. J. Tyrrell, F.R.S.
M.R.C. Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ

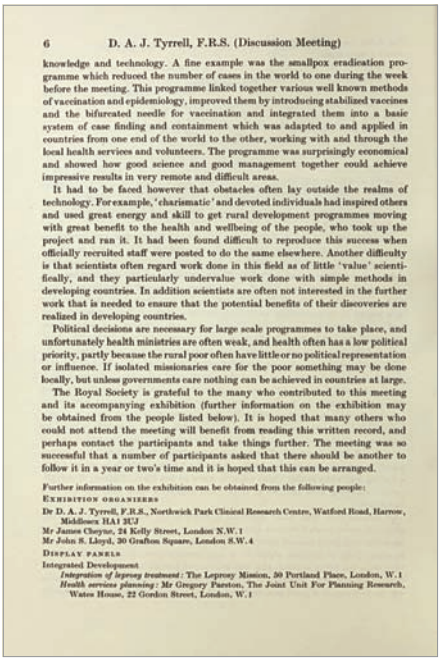
[Plates 1 and 2]

This was a somewhat unusual discussion meeting in that it was preoccupied with very common medical conditions and with technologies which in many cases are so simple that many would think they should scarcely be regarded as technologies at all.

Three quarters of the world's inhabitants live in rural areas and survive on near subsistence agriculture – they are clearly affected with a great variety of severe diseases, especially in childhood, but diseases of a type which cause little trouble now in the rest of the world. The resources available to help these vast rural populations are very limited, and certainly too small to enable us to deal with the diseases in exactly the same way as this has been done elsewhere. Yet it is urgent to do something, as the population is rising at least as fast as food and other resources. The meeting therefore set out to review a number of the aspects of the rural situation which are particularly important for health. These included the improvement of agriculture and food production, and water supply. We considered the most recent results of aetiological research and asked whether enough facts are available. Some of the results were surprising – for example it appeared that infections of the gut are important causes of malnutrition in West Africa. It is important to have a particularly deep and accurate understanding of what contributes most to ill health, because in these rural areas it is only possible to intervene in a few ways, and if the little money available is spent on unimportant interventions there will be little benefit to the population and no money left to 'try again'. This is thus a challenge to scientific investigation which in some cases might be simple – watching where people draw water, subtle – finding out what makes them want to have or not have children, or complicated – studying food samples in depth and analysing data with the aid of a computer.

It became clear that many measures to improve the situation were available, although some needed further improvement – for example, vaccines needed to be better stabilized against deterioration in hot conditions. It was recorded that in many fields techniques which could help greatly were already available, but they were not being applied; this was mentioned particularly in connection with agriculture and birth control. So at several points we realized the great need to use the techniques of good modern management to make effective use of scientific

[5]



6 D. A. J. Tyrrell, F.R.S. (Discussion Meeting)

knowledge and technology. A fine example was the smallpox eradication programme which reduced the number of cases in the world to one during the week before the meeting. This programme linked together various well known methods of vaccination and epidemiology, improved them by introducing stabilized vaccines and the bifurcated needle for vaccination and integrated them into a basic system of case finding and containment which was adapted to and applied in countries from one end of the world to the other, working with and through the local health services and volunteers. The programme was surprisingly economical and showed how good science and good management together could achieve impressive results in very remote and difficult areas.

It had to be faced however that obstacles often lay outside the realms of technology. For example, 'charismatic' and devoted individuals had inspired others and used great energy and skill to get rural development programmes moving with great benefit to the health and wellbeing of the people, who took up the project and ran it. It had been found difficult to reproduce this success when officially recruited staff were posted to do the same elsewhere. Another difficulty is that scientists often regard work done in this field as of little 'value' scientifically, and they particularly undervalue work done with simple methods in developing countries. In addition scientists are often not interested in the further work that is needed to ensure that the potential benefits of their discoveries are realized in developing countries.

Political decisions are necessary for large scale programmes to take place, and unfortunately health ministries are often weak, and health often has a low political priority, partly because the rural poor often have little or no political representation or influence. If isolated missionaries care for the poor something may be done locally, but unless governments care nothing can be achieved in countries at large.

The Royal Society is grateful to the many who contributed to this meeting and its accompanying exhibition (further information on the exhibition may be obtained from the people listed below). It is hoped that many others who could not attend the meeting will benefit from reading this written record, and perhaps contact the participants and take things further. The meeting was so successful that a number of participants asked that there should be another to follow it in a year or two's time and it is hoped that this can be arranged.

Further information on the exhibition can be obtained from the following people:

Exhibition organizers

Dr D. A. J. Tyrrell, F.R.S., Northwick Park Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ
Mr James Cheyne, 24 Kelly Street, London N.W.1
Mr John S. Lloyd, 30 Grafton Square, London S.W.4

Display panels

Integrated Development
Integration of leprosy treatment: The Leprosy Mission, 50 Portland Place, London, W.1
Health services planning: Mr Gregory Pearson, The Joint Unit For Planning Research, Wates House, 22 Gordon Street, London, W.1

I often give keynote speeches at pharmaceutical cold chain conferences. Quite often, the issues I bring to participants' attention concern the thorny realities in the field and the tools and approaches used to address these problems. Much of the time, participants react to these lectures as though they relate to a completely different world or even as if the issues presented are more imaginary than real. Crucially, they seem unable to form an affinity with the situations or the solutions under discussion regardless of the associated practical and scientific evidence. They do not query whether the same approach could be an answer to their own problems. The prevalent viewpoint is that these solutions are for "others" and not for "them". Two major tools that invariably attract this unfortunate response are VVM and the shake-test.

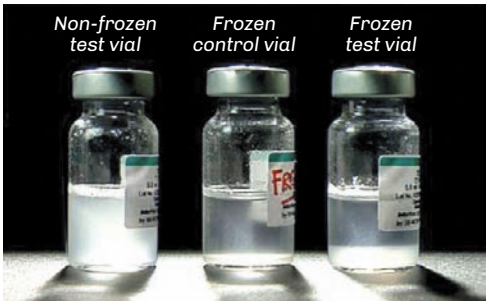
This book is about the VVM, and we will be talking a lot more about it, but let me briefly explain the case with the shake-test since the majority of opposition and disownment to this scientifically validated test procedure is basically down to professional hubris.

Why don't you shake it?

When a vaccine is damaged by freezing, the potency lost can never be restored – the damage is permanent. Freeze-damaged vaccines have a lower immunogenicity and are more likely to cause local reactions, such as sterile abscesses.

The shake-test is designed to determine whether adsorbed vaccines have been affected by freezing. After freezing, the lattice (made up of ionic bonds between the adsorbent and the antigen) in a vaccine is broken. Separated adsorbent tends to form larger, heavier granules that gradually settle at the bottom of the vial when this is shaken. When freezing and thawing cycles are repeated, the granules appear to increase in size and weight. In a typical demonstration of the shake test, two identical vials of a vaccine (i.e. from the same batch and the same manufacturer) that is suspected of having been exposed to freezing temperatures are selected; one of the two vials is purposely frozen and then thawed as the negative control, while the second vial serves as the vial to be "tested" against this negative control. The two vials are held together in one hand and shaken; they are then placed side by side on a flat surface. Provided the test vial has not been frozen, sedimentation is slower in the test vial than in the control vial that has been frozen and thawed. If the test vial has been frozen, the test and control vials will have similar sedimentation rates. The figure illustrates how the appearance of frozen (i.e. frozen and thawed, and therefore freeze-damaged) and non-frozen test vials compares to that of their frozen control vial, 1 minute and 28 seconds after shaking.[15]

The shake-test was validated and its specificity, sensitivity, and positive predictive value was established using phase contrast microscopy (PCM) in 2010. Further studies were also conducted with scanning electron microscopy (SEM) to document freezing damage on aluminum adjuvanted vaccines.[16-17] Shake test is a 100% specific, 100% sensitive test, and its positive predictive value is 100%, meaning that the probability that a vial identified as freeze-damaged by shake-test (fail test result) is absolute. So, what makes the shake-test such a precise method of distinguish-



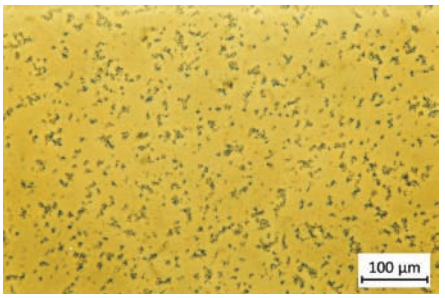
Differentiating the vaccine damaged by freezing through shake test

15 Kartoglu U, Ozguler N, Wolfson L, Kurzatkowski W. (2010) Validation of the shake test for detecting freeze damage to adsorbed vaccines. *Bull World Health Organ.* 88:624–631

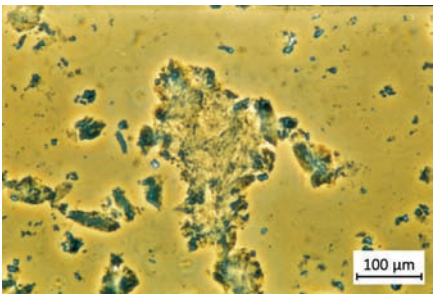
16 Kurzatkowski W, Kartoglu U, Staniszewska M, Gorska P, Krause A, Wysocki MJ. (2013) Structural damages in adsorbed vaccines affected by freezing. *Biologicals.* 41:71-76

17 Kurzatkowski W, Kartoglu U, Gorska P, Glowka M, Woznica K, Zasada AA, Szczepanska G, Trykowski G, Gniadek M, Donten M. (2018) Physical and chemical changes in Alhydrogel™ damaged by freezing. *Vaccine:* Nov 12;36(46):6902-6910

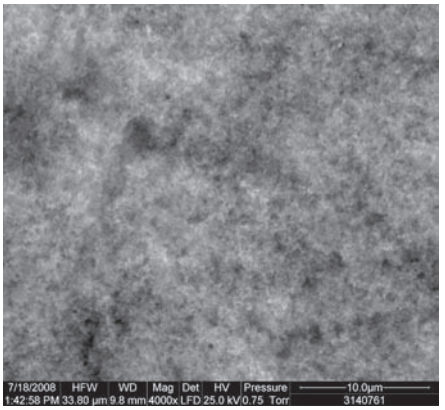
ing freeze-damage in aluminum adjuvanted vaccines? It is simply physics. Physics is one of the most fundamental scientific disciplines, and it helps us to understand how the universe behaves. It studies matter and its motion and behavior through space and time. The simple physics of the shake-test is that "heavy particles sediment faster than lighter particles". Here are both the PCM and SEM of non-frozen and freeze-damaged vaccines.



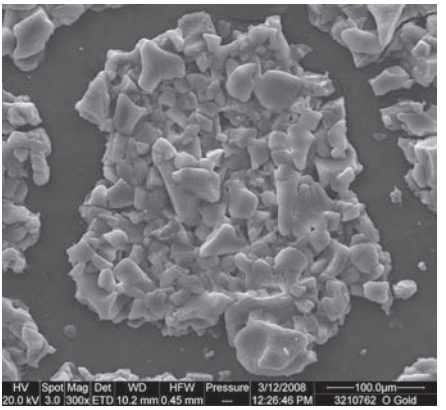
Fine-grain structure of dT vaccine kept between 2°C and 8°C (non-frozen)



Conglomerates of large precipitates with crystalline structure of dT vaccine affected by freezing (-25°C)



Non-frozen DTP-HepB vaccine under SEM 4000X with mesh-like homogeneous structure



Freeze-damaged DTP-HepB vaccine under SEM 300X with clutters of sediments

Now, on understanding the structural differences between a freeze-damaged vaccine (average particle size 350 µm) and non-frozen vaccines (average particle size 10 µm), which vial do you believe would have a faster sedimentation? And when you compare the sedimentation rates of these two vials against a vial that is purposely frozen (the negative control vial), you will find that the test vial of freeze-damaged vaccine will have behaved similar to your negative control. It's

that simple. I have always said that if the shake-test did not work, someone would had to rewrite the rules of physics regarding particle sedimentation in liquids.

With UNICEF shipments, when aluminum adjuvanted vaccines reach the destination countries and it is discovered that certain transport boxes (or perhaps the whole shipment) have been exposed to temperatures below 0°C, the receiving authorities are required to conduct the shake-test, and reject the affected boxes should they fail the shake test. Otherwise, with a positive shake-test (pass) result, regardless of what temperature the shipment has been exposed to, authorities will accept the shipment. This is not what happens in the western world. Here, all vaccines that are exposed to 0°C and lower temperatures are categorically rejected.

The obvious question this raises is why these countries simply don't adopt the shake-test as the determinant for a final decision on whether to accept or reject any shipments exposed to freezing temperatures? Since the basic science behind the shake test is fundamental physics, why would anyone believe that what works in, say, Ghana and Tanzania would not work in Germany or in Canada?

For example, the Canadian Immunization Guide (Part 1 – Key Immunization Information) advocates the following: "Before use, vaccines should be inspected and not used if the usual appearance is altered or a temperature recording device shows that the vaccine was exposed to temperatures below 0°C."[18]

In the original shake-test validation study, none of the vaccines that were exposed to -2°C for 24 hours were found to be frozen; all were in a liquid state. This was confirmation that the actual liquid-solid phase change associated with freezing depends on a number of factors, including low temperature, duration of exposure to low temperature and agitation during the exposure. Under the phase contrast microscope, vaccines exposed to -2°C looked identical to those kept at optimum temperatures – all showed fine-grain structure.

So, from a scientific perspective, what could be the rationale for not incorporating shake-testing into a country's vaccine practice and accepting the wastage associated with the wholesale rejection of all vaccines that have had any exposure to 0°C however transient?

Spoilage indicator

On January 21, 2016, Michal Chojnacky posted in the blog of the National Institute of Standards and Technology (NIST) blog on the importance of temperature control in vaccine viability. While explaining the NIST's role and responsibilities in this field, *"vaccines that are too warm will eventually spoil,"* she said, *"Unfortunately, there's no quick and easy way to determine whether a vaccine has been exposed to in-*

18 https://bit.ly/2XGMQ0E

appropriate storage temperatures, which means ineffective vaccines may be unknowingly administered to patients. Instead, pharmaceutical manufacturers, distributors, and immunization providers must rely on temperature monitoring devices placed in temperature-controlled storage units and shipping containers to assess vaccine viability."

The very first reaction to her posting came from a lay person on January 21. Ed Kostrna responded with the following:

"I was going to get a shot at my local VA and asked the tech about how the bottle she was using was maintained at the proper temperature. She could not answer and seemed quite annoyed that I would even ask. I left!

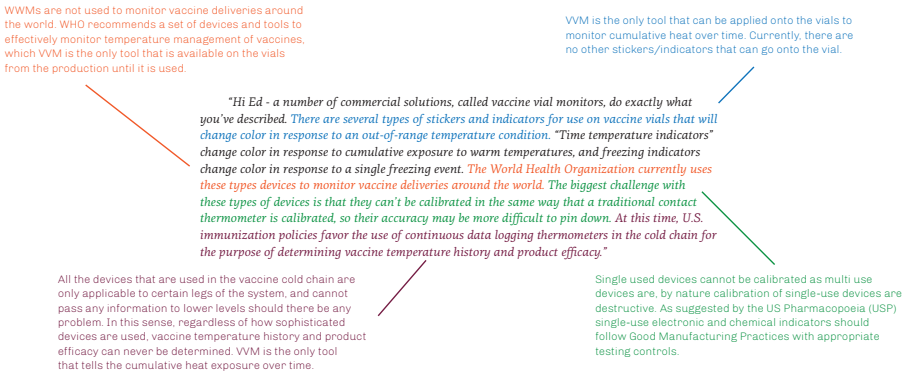
"Maybe you could put a 'spoilage' indicator on the bottles that would change color permanently if the temperature fell outside the acceptable range. A big RED dot that could not be removed by the clinic if the bottle ever froze or was exposed to higher than recommended temperatures."

On January 29, Ms. Chojnacky responded to Ed.

"Hi Ed – a number of commercial solutions, called vaccine vial monitors, do exactly what you've described. There are several types of stickers and indicators for use on vaccine vials that will change color in response to an out-of-range temperature condition. "Time temperature indicators" change color in response to cumulative exposure to warm temperatures, and freezing indicators change color in response to a single freezing event. The World Health Organization currently uses these types devices to monitor vaccine deliveries around the world. The biggest challenge with these types of devices is that they

can't be calibrated in the same way that a traditional contact thermometer is calibrated, so their accuracy may be more difficult to pin down. At this time, U.S. immunization policies favor the use of continuous data logging thermometers in the cold chain for the purpose of determining vaccine temperature history and product efficacy."

Before reacting to this inaccurate response, first I did a thorough analysis of the mishaps in the response.



Reading this inaccurate, misleading response, I sent the following as a response to Ms. Chojnacky, which triggered a couple of messages back and forth between her and myself. In the end, I decided there was no value in pursuing this particular exchange. However, I am copying below the full discussion to demonstrate how even a U.S.-based reference laboratory scientist perceives VVMs.

DR UMIT KARTOGLU on FEBRUARY 5, 2016 3:26 AM
Dear Ms Chojnacky,
I find your commentary comparing traditional contact thermometers to vaccine vial monitors (VVM) to be inaccurate and potentially misleading since the purpose of the devices is completely different. VVM is the only temperature indicator that is attached to the product at the unit level and monitors the entire cold chain from the manufacturer until the moment it is used at the service level. No matter how sophisticated, accurate (and calibrated) electronic devices are that are used along the supply chain, they can only be helpful at the particular level and leg of the supply chain where they are used. For example, the World Health Organization also recommends inclusion of electronic shipping indicators in all international shipments, despite the fact that VVMs are on each vial of vaccine. This is due to the fact that in an international shipment, the mission of these electronic devices is over when the consignee receives the package. If there are some deviations during the international shipment and product is accepted based on its "sta-

bility budget," there is no way that this information could be passed on to the lower levels in the system where additional excursions may be possible. When the products move into the central cold storage, they will be monitored through various other electronic temperature devices and systems. None of these devices will have the "memory" of what has happened to the product before it reached this point. This lack of accumulated temperature history perpetuates until the product reaches the practitioner at the service point. Even when the "best" temperature data logger is used at this level, these data cannot be used to determine the entire product temperature history and product efficacy since there is no information on the "actual" remaining stability budget of the product at time of receipt. Data generated using current devices that monitor storage and transport along the supply chain are not interconnected. In contrast, VVM brings a critical and novel approach to this: the health worker, the nurse, and the doctor can simply look at the color of the VVM on a particular unit of vaccine and can tell how the product was handled along the entire supply chain and assist in making an informed decision on product status.

It was surprising to read your supposition that VVMs cannot be calibrated in the same way that a traditional thermometer is calibrated and with the conclusion that "... their accuracy may be more difficult to pin down." Though VVMs are not and cannot be calibrated in the same way that a traditional thermometer is calibrated, it is not possible to calibrate any individual single-use device because the test is, by the nature of the time temperature integrators (VVM in our case), necessarily destructive. If you refer to "United States Pharmacopoeia (USP) Monitoring devices – Time, Temperature, and Humidity," under "Calibration of temperature – and humidity monitoring devices," it is clearly explained as follows: "Single-use electronic and chemical indicators should follow Good Manufacturing Practices with appropriate testing controls. Electronic indicators require proper calibration. Single-use indicator performance can be qualified by the supply chain user by sampling and testing of multiple production lots. For TTIs that calculate MKT, the performance of a batch can be assessed statistically by subjecting an appropriately sized sample to elevated temperature conditions for a set period of time and observing the results. Manufacturers should adopt appropriate acceptance criteria. It is acceptable to use the release test performed by the manufacturer of the indicator (based on the certificate of calibration or the certificate of analysis and the expiration date) in lieu of calibration or qualification." Therefore, the statement regarding the calibration of VVM is scientifically inaccurate.

VVM is a technology, explained in the same USP document, that provides early warning if the product (vaccine) is exposed to excessive heat over time before the expiration date. It is the only temperature monitoring tool that follows the product from manufacture to administration and accumulates the experience across the entire cold chain. VVM has had a profound impact around the globe. Due to the use of VVM, health workers can ensure that vaccines administered have not been damaged by heat. Importantly,

VVM also helps to reduce vaccine wastage; it facilitates immunization outreach and increases access and coverage; helps to pinpoint cold chain problems; help to manage vaccine stocks and dispatch; and it prevents inadvertent freezing of vaccines.

Finally, the technologies WHO recommends are not only for middle- and lower-income countries; WHO recommends technologies to be used in "programmes" by all Member States. In this sense, if the cold chain rules are global and VVM works, then VVM should also work in the U.S. as well. Given its important advisory role to the U.S. CDC, I suggest that NIST should be open to explore the benefits and proven experience of all temperature monitoring devices including VVM and demonstrate the difference VVM could bring to the U.S. immunization programme.

Warm regards,
Dr Umit Kartoglu, MD, DPH
Scientist, World Health Organization

MICHAL CHOJNACKY on FEBRUARY 5, 2016 4:37 PM
Hi Umit! Thank you very much for your insight on the role of VVMs throughout the global vaccine supply chain. I wholeheartedly agree – VVMs fill a unique and critical role in vaccine management, by providing a visual indication of cumulative time-temperature history throughout the transport, distribution, and storage of vaccines in the cold chain.

In terms of calibration, I am aware of lot testing and other sampling methodologies used to quantify VVM performance. These methods are useful for providing an estimate about device accuracy, and as you've stated, are compliant with USP requirements. At NIST, we have a slightly different perspective and vocabulary when it comes to "calibration," since we tend to think about device calibration in terms of establishing metrological traceability (http://www.nist.gov/calibrations/upload/Trace.pdf). For a measurement to be traceable, the measurement result must be "related to a reference through a documented unbroken chain of calibrations, each contributing the measurement uncertainty," according to the International Bureau of Weights and Measures (BIPM) definition. Since it's not possible to individually calibrate VVM devices (the test would be destructive, as you mention), it seems equally challenging to establish measurement traceability for these devices. By contrast, a contact thermometer with continuous logging capabilities can be calibrated on a periodic basis with documented uncertainty and measurement traceability.

There's another issue at play that prevents U.S. immunization programs from adopting certain approaches modeled by the WHO. U.S. vaccine providers are subject to the strict 2°C to 8°C storage temperature range specified on the product packaging. If there is any excursion outside this range, even half a degree, providers are instructed to call the

vaccine manufacturer for guidance on how to proceed. As you know, many vaccines can tolerate cumulative exposure to temperatures above 8°C for finite periods of time, depending on the product. VVMs take advantage of this fact, as the selected indicator is designed to approximate the properties of the vaccine inside the vial. However, current U.S. policies and laws don't really allow our providers to fully utilize vaccine stability data and VVM indicators for every-day decision making about vaccine efficacy. Instead, this authority rests with the pharmaceutical manufacturers, who make their decisions based on refrigerator temperature measurements provided by the physicians. In this scenario, traceable temperature measurements that accurately reflect stored vaccine temperatures play a critical role in preventing unnecessary vaccine waste as well as inadvertent administration of spoiled vaccine.

VVM technology has revolutionized safe vaccine distribution practices around the globe. In my opinion, VVMs play a critical, supportive role to continuous monitoring systems using calibrated contact thermometer sensors. Together, both products support improved vaccine management throughout the cold chain.

DR UMIT KARTOGLU on FEBRUARY 8, 2016 3:51 AM

Dear Ms Chojnacky,

I am aware of calibration in terms of establishing metrological traceability; however, this argument cannot be used for VVMs since its purpose is different than the contact thermometer. A thermometer is a measuring device for determining the temperature, but VVM is not a temperature measuring device. VVM reacts to the cumulative effects of time and temperature similar to how products like vaccine degrade with time and temperature. VVM develops increasing color with increasing cumulative temperature exposure and provides a simple visual cue to warn health workers to make informed decisions on the extent of temperature exposures and whether to use or not to use the vaccine. Thermometers cannot be compared with VVMs. VVM traceability from the certificate of analysis point of view (as described in the USP) is defined in WHO/PQS VVM performance specifications WHO/PQS/E006/IN05.2 (19 JAN 2012).

As for the strict 2-8 deg C temperature regime, there are examples in the U.S. market that products may be exposed to temperatures above 8 deg C for limited periods of time as defined by the manufacturers. For example, Gardasil 9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8 and 25 deg C) does not exceed 72 hours.

(http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf)

Similarly, Gardasil Qaudrivalent can also be used out of refrigeration (at temperatures at or below 25 deg C) for a total time of no more than 72 hours.

(http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf)

Prevnar 13 is allowed to arrive at temperatures between 2 to 25 deg C after shipping (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf)

Of course, these data are not recommendations for shipping or storage, but may guide decisions for use in case of temporary temperature excursions.

The most critical point is: Since none of the temperature monitoring devices used along the cold chain is interconnected, exposures to temperature excursions occurring at different legs of the cold chain cannot be mathematically accumulated to judge whether it is still below 72 hours. A vaccine manufacturer making a decision based on the refrigerator temperature measurement provided by the physician assumes that everything was OK prior to the vaccine reaching that particular service point, simply because the data logger used by the physician is not interconnected to other devices used upstream in the cold chain. Regardless of data coming from a calibrated data logger at the physician's office, it lacks the "full" history of temperature exposures of that particular vial. This approach gives only a "false security." At this point if VVM was attached it would have the entire history and be the answer.

The other issue is the belief that science is the same around the world. If vaccines with VVMs are safely used around the world, and these VVMs are affixed on the vaccines by vaccine manufacturers based on the stability profile of the product, why is this science ignored when it comes to U.S.? When there are no clouds during the day, the sky is blue both in Gabon and in the U.S. If we believe in science, why wouldn't VVM work in Gabon and also work in the U.S.? Would you agree that VVMs alone would prevent a lot of staff time unnecessarily spent on the phones even when there is half a degree C excursion for some minutes in a refrigerator?

Last month in New Hampshire it was determined that vaccines were not properly refrigerated for a period of 14 months. The hospital contacted the families of more than 800 patients, asking them to bring their children in to get new shots. VVMs used on those vials could have provided an early visual warning that vaccines weren't being stored correctly and the cost, concern, inconvenience, the loss of confidence in the cold chain at the hospital and the need for revaccination could have been avoided. Thermometers were used in the practice and were likely recording accurate temperatures but not identifying an obvious lingering problem.

Ed Kostyrna asked "Maybe you could put a 'spoilage' indicator on the bottles that would change color permanently if the temperature fell outside the acceptable range." The answer to Ed is that indicators exist and should be put on each vial of vaccine and other temperature sensitive medicines.

Warm regards,
Dr Umit Kartoglu, MD, DPH
Scientist, World Health Organization

MICHAL CHOJNACKY on FEBRUARY 9, 2016 4:46 PM

Umit, Vaccine manufacturing, packaging, and distribution processes are regulated by the FDA. As a result, widespread use of VVMs in the U.S. would require a joint effort from U.S. drug manufacturers and the FDA. In the U.S., these entities maintain vaccine stability data, and are jointly responsible for ensuring that vaccines are delivered to distribution sites and/or directly to providers under conditions that preserve drug potency.

Unlike the FDA, both NIST and CDC are non-regulatory agencies. The CDC oversees publicly funded vaccines distributed through the Vaccines for Children (VFC) program, which operates at the provider-office level. NIST provides technical expertise in the fields of measurement science, rigorous traceability, and standards development and use. By identifying and educating providers about easily implemented solutions for better vaccine management–from storage units to temperature monitoring devices, to calibration methods and storage and handling techniques–joint NIST-CDC efforts have prompted dramatic improvements throughout the provider-to-patient segment of the vaccine delivery chain.

Again, thank you for providing your input and the WHO perspective on the use of VVMs in the global vaccine supply chain. If you'd like to continue this discussion, please feel free to contact me directly.

Things are not okay

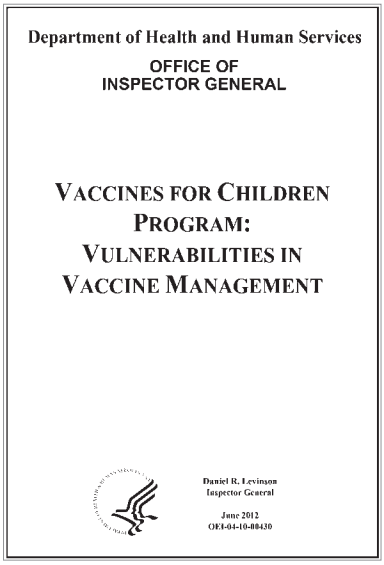
Following this last response from Ms. Chojnacky, I decided not to respond further. But, thinking about the professional hubris, many western countries, including the U.S. were automatically assumed to be operating safe storage and distribution practices of the vaccines. Looking at the literature, one will find studies mostly done in the "other" side of the world, creating a kind of illusion that all must be okay in the western world. The absence of information does not mean things are okay.

Dipika M. Matthias, et al, conducted a systematic literature review on freezing temperatures in the cold chain, and included a total of 35 studies in the analysis, 18 from the industrialized countries, including Australia, USA, Great Britain, Canada, Ireland and Spain.[19] The analysis highlighted that exposure of vaccines to freezing temperatures is pervasive, occurring in both developed and developing-country settings, as well as within both the storage and transport segments of the cold chain.

In 2011, the Office of Inspector General (U.S. Department of Health and Human Services) decided to conduct a study on vaccine management practices with-

19 Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. (2007) Freezing temperatures in the vaccine cold chain: A systematic review. *Vaccine*. 25:3980-3986

in the Vaccines for Children (VFC) programme. In 2010, approximately 82 million VFC vaccine doses were administered to an estimated 40 million children at a cost of $3.6 billion. Using CDC data, samples of 45 VFC providers from the 5 grantees with the highest volume of vaccines ordered in 2010 were selected as the basis. The study team conducted site visits at these providers' medical practice locations, interviewed their vaccine coordinators, and observed their vaccine management practices. These providers' vaccine storage unit temperatures were also independently measured for a 2-week period. Finally, the study team interviewed the five grantees' VFC program staff regarding their program oversight.


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
OEI-04-10-00430

And the results were pretty shocking:[20]

1. VCF vaccines stored by 76 percent of 45 providers reviewed were exposed to inappropriate temperatures for at least 5 cumulative hours during the 2-week period. It was found that all 45 providers had recorded temperatures that differed from the independently measured temperatures during the 2-week period.
2. Sixteen of forty-five providers (36%) had expired VFC vaccines kept in the refrigerator along with viable vaccines. Expired vaccines were an average of 186 days pat their expiration dates on the day of the visit, ranging from 6 to 673 days past expiration.
3. None of the 45 providers reviewed met the vaccine management requirements in all 10 categories. Specifically, in temperature monitoring, 40 of 45 providers (89%) failed to meet the requirements.
4. Thirty-eight of forty-five selected providers did not have all required documents
5. None of the five VFC grantees reviewed met all oversight requirements, and grantee site visits were not effective in ensuring that providers met VFC requirements over time.

Vulnerabilities in vaccine management reporting was a critical one, in documenting problems that are familiar to many immunization managers around the world.

20 Vaccines for Children Program: Vulnerabilities in Vaccine Management, OEI-04-10-00430, June 2012 (https://oig.hhs.gov/oei/reports/oei-04-10-00430.asp)

Provider Vaccine Management Requirements

VFC providers must perform required activities in 10 categories established in the Vaccine Management Module of CDC's *VFC Operations Guide*:

1. Vaccine Storage Equipment
2. Vaccine Storage Practices
3. Temperature Monitoring
4. Vaccine Storage and Handling Plans
5. Vaccine Personnel
6. Vaccine Waste
7. Vaccine Security and Equipment Maintenance
8. Vaccine Ordering and Inventory Management
9. Receiving Vaccine Shipments
10. Vaccine Preparation

In fact, in the WHO Effective Vaccine Management (EVM) initiative assessments conducted throughout the world, many agencies (in Africa and Asia) would score higher in temperature monitoring than the equivalent service level U.S. providers. But of course, the key issue is to accept that no countries are immune from cold chain related problems, and to understand that the solutions to address these problems are universal; there are no solutions that are applicable only to the developing world.

In 2017, I was engaged with a group of researchers to study temperature monitoring practices amongst retail pharmacies in the Magnisia and Sporades regional units in Greece.[21] Two-stage cluster sampling was used to obtain a representative sample of retail pharmacies. Twenty retail pharmacies were then selected as "intervention" group and another 20 retail pharmacies were selected as "control" group. Fridgetag® and Vaxtag® devices were randomly assigned to the intervention pharmacies and responsible pharmacists were trained accordingly either on the use of Fridgetag or Vaxtag through a series of demonstrations by the study team followed by drill and practice by the participants. No training was provided to the pharmacists from the "control" sites. Intervention sites used Fridge-tag and Vaxtag and a modified temperature control record sheet, while control sites continued with their routine operation with thermometers. All refrigerators in both groups were equipped with downloadable electronic data loggers to record temperatures for reference. Focus group sessions were conducted with participating staff to discuss temperature monitoring, intervention device uses and any other feedback.

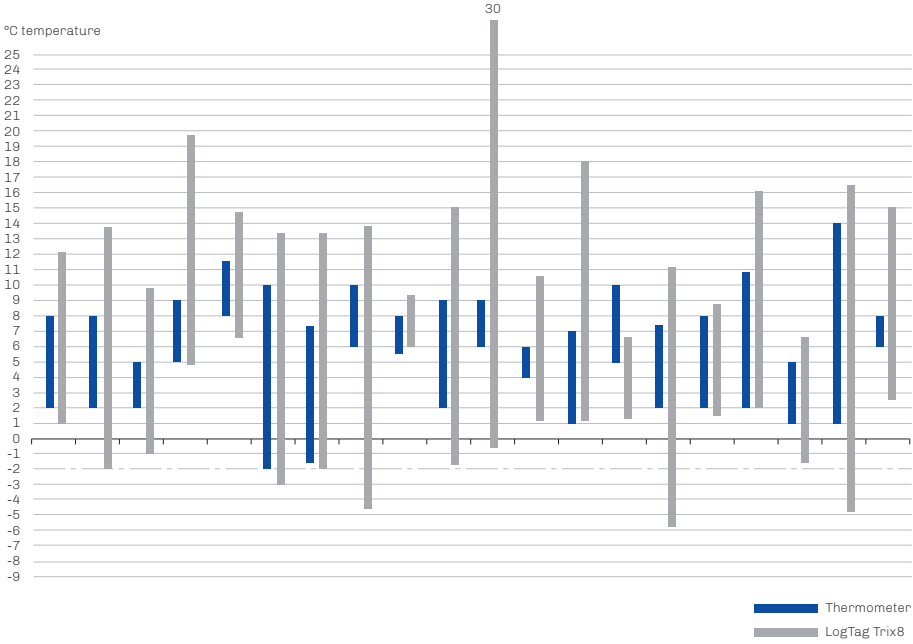
Again, the results were shocking. Significant discrepancies were observed between thermometer readings and the electronic data loggers in the control group - exactly, the same problem that was discovered in the vulnerabilities in vaccine management study in the U.S. In the U.S. the difference between measurements were at least 2.2°C. In one refrigerator the actual temperature with a datalogger

21 Kartoglu U, Birlirakis V, Vrachlioti-Botti MA, Gobina I. (2018) Improving Temperature Monitoring at the Last Mile in Pharmacies in Magnisia and Sporades Regional Units in Greece. *Journal of Pharmaceutical Care and Health Systems*, 5:3 DOI 10.4172/2376-0419.1000196

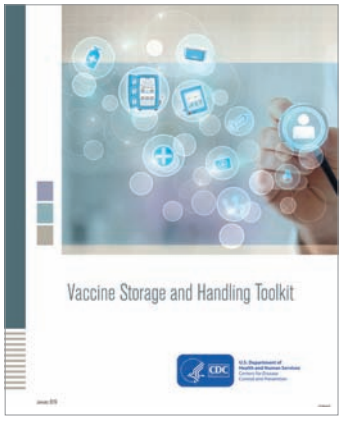
was measured as -5°C, but was measured by thermometer and recorded by the practitioner as +4.4°C.

Here is the difference between the thermometer and datalogger readings from the Greece study.

Comparison of thermometer readings and electronic data logger by pharmacy, control group (n=20)



If you think that the *2012 Vulnerabilities in Vaccine Management* report is old, and since then things must have changed, you are mistaken. Of course, the problems identified were addressed by the CDC which revised the VFC storage and handling guidelines to establish the following as programme requirements (previously these were federal recommendations, although some areas may already have established these as state/local VFC requirements):



- *VFC providers must use continuous temperature monitoring devices (digital data loggers or DDLs) to monitor VFC-supplied vaccines during routine onsite vaccine storage, vaccine transport, and mass vaccination clinics.*
- *Both primary and 'back-up' DDLs used to monitor VFC vaccines must include the following features:*
  - *Capacity for continuous temperature monitoring and the ability to record and routinely download data.*
  - *Temperature probe is 'required' to be buffered if purchased by a state/local immunization program. (The buffered probe is a 'recommendation' for DDLs purchased by providers.)*
  - *Active temperature display that can be easily read from the outside of the storage unit.*

However, despite these new requirements, we continued to hear similar reports.

A group of researchers at the CDC published a study in 2015 which found that 23 percent of the vaccination errors reported to the federal surveillance system from 2000 to 2013 involved improper storage or the use of expired vaccines.[22] In total there were 2,202 cases of incorrect storage of vaccines.

In 2017, officials from the New Jersey Department of Health announced that approximately 900 children who participated in a free or low-cost vaccine program in Ocean County might need to be revaccinated because the vaccines they received might not have been properly refrigerated.[23] The department suspended shipment of VFC vaccine to Dr. Bleiman on July 28, 2016, when, during a routine compliance visit, problems with refrigeration temperatures were discovered. Later that day, the State filed a complaint with the State Board of Medical Examiners alleging gross negligence, professional misconduct and other violations.

In another study, again a group of researchers at the CDC found that vaccines were kept outside the recommended temperatures ranged from 15 minutes to 6 months (median 51 hours).[24]

On 12 February 2019, Carmen Heredia Rodriguez reported on Kaiser Health News that vaccine storage fails to meet standards on too many occasions highlighting the problem of accountability where the federal government sets standards on the storage of vaccines. Yet not all health care providers are accountable under these guidelines.

22 BF Hibbs, PL Moro, P Lewis, ER Miller, TT Shimabukora. (2015) Vaccination errors reported to the Vaccine Adverse Events Reporting System, (VAERS) United States, 2000-2013. *Vaccine.* 33(28):3171-3178

23 https://abc7ny.com/1695486/

24 BF Hibbs, E Miller, J Shi, K Smith, P Lewis, TT Shimabukora. (2018) Safety of vaccines that have been kept outside of recommended temperatures: Reports to the Vaccine Adverse Events Reporting System, (VAERS), 2008-2012. *Vaccine.* 36(4):553-558

Vaccine storage too often fails to meet standards

By **Carmen Heredia Rodriguez** FEBRUARY 12, 2019

By correcting one potential error, the Ventura County (Calif.) Health Care Agency accidentally made another — and jeopardized vaccines given to thousands of people in the process.

In October 2017, county health officials, concerned that vaccines were getting too warm while being transported to clinics, changed their protocol. But a routine audit in November found that the ice packs they were using may have frozen some of the medicines and lowered their effectiveness. The agency then offered to reimmunize everyone who had received a vaccine that was delivered in faulty packaging.

"There's no way to tell whether or not they were ineffective," said Jason Arimura, director of pharmacy services for Ventura County Medical Center. Out of an abundance of caution, "we just notified everyone."

The number of patients affected: 23,000.

Ventura County is far from the only case of vaccines feared to be ineffective reaching patients. In the past 13 months alone, 117 children received possibly compromised vaccines against polio, meningococcal disease and the human papillomavirus at an Indian Health Service clinic in Oklahoma City because of improper refrigeration. Similar issues with temperature control prompted a health clinic in Indianapolis to send letters offering to revaccinate 1,600 people last January, according to local news reports.

On Feb. 1, Kentucky officials announced that potentially ineffective and contaminated vaccines were administered at multiple businesses across Kentucky, Ohio and Indiana. The statement did not disclose how many people were affected.

The federal government sets standards on the storage of vaccines. However, not all health care providers are accountable under those guidelines.

The Vaccines for Children (VFC) program, which offers these drugs at no cost for kids from low-income families, requires clinics, doctors and other providers to undergo annual audits and use top-grade equipment, such as continuous temperature-monitoring devices. It also requires that problems be reported to federal authorities.

More than 44,000 doctors participate in the program and provide vaccines to 90 percent of the children in the country, according to the Centers for Disease Control and Prevention.

But medical facilities outside of the program — like many pharmacies and internists with private practices who are treating adults or children not in the

VFC program — have no comparable federal oversight. In fact, storing vaccines and reporting cases of patients receiving ineffective drugs is largely up to their discretion. The vaccines involved in the Ventura County recall were not part of the Vaccines for Children program.

Experts said most hospitals, clinics and doctors are vigilant in properly storing their vaccines. And research suggests that compromised vaccines given to patients are not harmful.

L.J Tan, chief strategy officer for the nonprofit vaccination advocacy group Immunization Action Coalition, said the nation's vaccine stock is likely one of "the safest in the world."

But improperly handling these medications means wasting expensive drugs, and using compromised vaccines "could create a pocket of underimmunized individuals," said Dr. Julie Boom, a pediatrician and director of the immunization project at Texas Children's Hospital. "And we don't want that to happen."

In Ventura County, the temperature problems affected vaccines for flu, tetanus, diphtheria, whooping cough and hepatitis B. County health officials told patients who had received tuberculosis testing and some who had received penicillin to treat syphilis that their medicines also may have been compromised.

Through January, approximately 1,200 have come back to be revaccinated, Arimura said. Revaccinating all 23,000 people would cost $1.3 million, he added.

Vaccines are extremely sensitive to temperature fluctuations. In some cases, exposing a vaccine to the wrong environment once can effectively kill live viruses and harm proteins in the vaccines, said Tan. Generally, temperature problems occur during transportation of medicines.

(...)

Digital data loggers with buffered temperature probes might seem to be a high-tech solution to the problem, but we should not forget how the thermodynamics work. All vaccines are mono-dose in the U.S., meaning that the thermal mass of the vaccine is 0.5 ml. If you have a temperature sensor buffered in a 5 ml solution, it is almost impossible to accurately monitor "product temperature". When your data logger indicates that it is 0°C, a thermal mass of 0.5 ml (the vaccine itself) will have already reached a temperature below 0°C. And besides, none of the vaccine stability information is generated by using product temperatures, rather the temperature of the environment where the vaccines are kept are used in these tests. In addition, at no level of the cold chain supply system is the actual product temperature monitored. In this sense, solutions like the 30-day elec-

tronic refrigerator logger as suggested by WHO would be a better solution to monitor refrigerator temperatures (with no glycol embedded probes).

CDC guidelines also recommend that in the case of temperature excursions beyond 2°C to 8°C (with no specified time duration), any staff who hears an alarm or notices a temperature excursion on the DDL should notify the primary or alternate vaccine coordinator immediately or report the problem to their supervisor. They must also alert staff by marking the exposed vaccines, "DO NOT USE," and placing them in a separate container apart from other vaccines (these quarantined vaccines not to be discarded).

Kelly Lynn Moore visiting the Institute of Public Health, Tirana, Albania in October 2014

You may wonder what supervisors do when they are contacted by staff experiencing an alarm. *"CDC's guidance, if you go by the book, is that you should contact the manufacturers for each vaccine in the fridge and provide the details of the temperature excursion and get guidance from them about what to do"* says Dr. Kelly Lynn Moore, *"In my old program at Tennessee, I had a nurse on the team who did those temperature excursion calls on behalf of the clinics, so the clinics would report to her. In other states, clinics were expected to make the calls themselves and not to use vaccine until they verified it was usable. In practical terms, the "Do Not Use" was often applied to the entire unit."*

Naturally, in these calls, there is always a big assumption - that all storage and handling of the vials prior to the temperature excursion in question was totally okay. Any decisions as to the appropriate response is based only on the specific temperature excursion that is the subject of the call. The resulting disruption the waste of staff time, the attendant costs and any consequent interruptions to the vaccination programme could have been eliminated if the vaccines had VVMs. And besides, the VVMs would effectively contain the cumulative record of other possible temperature excursions that may have taken place at earlier stages of the supply chain, and therefore, giving a clear visual indication as to whether the vaccines can be used or not.

Inertia

Knowing the widespread and inherent vulnerabilities implicit in all medical cold-chains throughout the world, you cannot help asking why all countries do not simply adopt time and temperature integrator (TTI) technology for temperature sensitive products, starting with vaccines. Why has VVM not been picked up more widely and why is it still perceived as a solution for the developing world only?

Senior Advisor Emeritus for PATH and Affiliate Instructor in Global Health at the University of Washington, Dr. Michael Free explains that in the early days programme managers used to think of these new warning devices as 'social' technologies, and then somewhere around the mid-80s began to face the reality that these technologies were basically not going to succeed unless or until they were commercially successful.

"And to be commercially viable they essentially had to be in a market place where people perceived the need, demanded the technology and were prepared to pay for it. Paradoxically that was more possible in the developing world because of the influence of the health and humanitarian agencies and also the aggregate purchasing and entire mechanism of change that aligned all these players. But the market place in the developed world never perceived VVM as an essential need and therefore did not demand it as a value-add to their vaccines. We realized at the time that we needed to put aside in our minds any worries about whether these technologies could fulfil the needs of more developed markets and just focus on the needs of our target populations. It was purely a market place issue."

Dr. Free further explains this in terms of professional hubris:

"Professionals in industrially advanced countries feel that they have got things under control and do not need these aids - particularly they don't feel the need for tools that are used in less well-developed low infrastructure regions."

I showed Dr. Free the results of the Greece study and told him that if I hide the location of the study and give four options (one industrialized and three developing countries) to readers to guess, the likelihood of selecting the industrialized one would be very slim. Dr. Free believes that it would take a lot of studies and the raising of these studies up into the so-called political consciousness.

Dr. Michael Free

"Somebody has got to take it on, have the resources and unwavering goal to carry out a campaign, that is every bit as vigorous as the original campaign to get the VVMs into developing countries. The resistance will be high and different in nature from the global effort. It is not the question of resources or infrastructure or training but more a question of people's perceptions and assumptions around the adequacies of their systems."

Associate Director, Reproductive Health at PATH and Affiliate Professor of Epidemiology at the School of Public Health, University of Washington, Dr. Vivien Tsu tells that they (PATH) looked into why the U.S. market (vaccine and pharma) didn't seem to require them.

"And the answer was 'we think we already take good care of our vaccines'" says Dr. Tsu, *"But it wasn't true."*

Here Dr. Tsu also touched upon the binding effect of professional conceit.

"Pediatricians said 'we always keep our vaccines in the fridge.' But I think that the thing about far more expensive drugs is, they weren't, and many cases still aren't, generally supplied in settings where the availability of refrigeration is a problem. People naturally assume that if we have these expensive drugs, then we must have refrigeration, and a functioning cold chain. It's all of course supposition."

"I agree," I told Dr. Tsu, *"Look at the Vulnerabilities in Vaccine Management report from the Inspector General."*

We both agreed that the centralized purchasing power of UNICEF had been instrumental in bringing VVM to scale, whereas in the private market you do not have a centralized control, and you have many more manufacturers involved.

"It is different market" says Dr. Tsu, *"But the thing that's ironic is these are much more expensive products so adding a TTI is a much smaller fraction of price than it is with low-cost vaccines."*

Temptime still sells VVMs below the target price that was established 40 years ago when the idea was first conceived. When the vaccines are in cents, you can imagine the impact VVMs, despite themselves only costing a few cents each, could have on the vaccine price. Although the request for such indicators originally came from WHO, at one point WHO themselves started to question the technology. For that very particular reason, Dr. Gordon Perkin, President of PATH during the years 1980 to 1999, includes WHO among the naysayers:

"At one point WHO in Geneva said, 'we cannot endorse this, because our mission is to reduce the cost of vaccines, and what you are proposing is something that will increase the cost.' So, we had to get over that boundary with a one-year study in Bhutan showed that use of the marker could reduce the cost of programme by more than 70% and that vaccines could be used well beyond prescribed usage parameters."

I discussed the very same issue with Jonathan Colton, professor of mechanical engineering, industrial design, and international affairs at the Georgia Institute of Technology. We spoke about many examples of cold chain problems from the western world that mirror those faced by the rest of the world. Prof. Colton agreed that the prevalence of professional hubris brings a different perspective to the private market.

Jon Colton in Rwanda, visiting a test farm, helping with agricultural mechanization

"The reasons why advanced countries don't want this had to do with the fact that VVM was instigated for the developing world. By inference this means we don't need it in the advanced world, because the assumption is 'our system works', even though the facts tell us that it doesn't (like the studies you are referring to)."

Prof. Colton continues that scientific and technical studies are an insufficient stimulus of action because most western countries are driven by lawsuits rather than technologies.

"If a whole bunch of batches went bad, if there was harm to people, then maybe that would drive the companies involved to incorporate them. The people that I've talked to about these things, doctors, nurses and such in the U.S., they agree it would be a great idea to have it. But although most of the medical profession would want it, I think it is the medical industry and the U.S. government that is saying we don't need it, that our system works well. In other words, the acceptance of VVM would be some sort of admission that our system isn't working well. And, everywhere in the capitalistic world, things are driven by cost. Take the making of safety changes to cars, it costs money, and the companies do an analysis and sometimes conclude that it is cheaper to pay the court cases rather than initiating the change. Remember the Pinto case?"

The explosive Pinto

Ford Pinto was one of the automotive industry's hottest-selling subcompacts during the 1970s. Its success enhanced the reputation of Lee Iacocca - until hundreds of deaths and injuries were linked to a faulty design that made the gasoline tank vulnerable to explosion after rear-end collisions.

Mother Jones

Mother Jones, a left-wing magazine that specialized in investigative journalism, reported in its September/October 1977 issue that Ford knew - and did nothing about - pre-production crash tests that showed that rear-end collisions easily ruptured the Pinto's fuel system.

"Ford allegedly knew that there was a flaw in the tube leading to the gasoline-tank cap of pre-1976 Pintos. A rear-end collision would rip the tube away from the tank and gasoline would pour onto the road.

The gasoline tank itself would buckle after being jammed up against the differential housing, which contained four sharp, protruding bolts, according to Mother Jones. *A spark from a cigarette, ignition or scraping metal would do the rest.*

But because assembly-line machinery already was tooled when engineers found the defect, the magazine said, top Ford officials decided to manufacture the car anyway - exploding gasoline tank and all - even though Ford owned the patent on a much safer gasoline tank. Iacocca's $2,000 limit on the car's costs left no money to protect the fuel system, not even a $1 piece of plastic that would have protected the gasoline tank from being punctured, Mother Jones *asserted.*

What caught the public's eye in the Pinto cases was the disclosure that Ford found it cheaper to pay off the families of the victims of Pinto fires than the $137 million it would cost to fix the Pinto immediately, according to an internal Ford memo introduced during a civil trial. That meant it was not cost-effective to do the repairs.

There is no way of knowing how much Ford paid in Pinto suits because some were settled quietly out of court."

From https://www.motherjones.com/politics/1977/09/pinto-madness/

"For some reason, the car market is allowed to make safety changes without admitting they are wrong," says Prof. Colton, *"because, normally, a manufacturer owes its customers a duty of care and if it acts wrongly or fails to act appropriately this can create a tort – a legal term meaning the company has committed a wrong or acted negligently towards someone, automatically creating a liability for injuries or damage. In the medical field, it seems there is something similar to the car industry, in that changes to safety-related technology might be deemed an admission of liability in the event of customer injury or loss."*

Prof. Colton undertakes legal consulting in the field of machinery and he told me that companies don't want to make changes since this would open them up to lawsuits. He also agrees that excessive professional vanity is part of the problem:

"The other reason for the disdain around VVM in the developed regions is the blinkered inertia which is omnipresent. 'Everything is fine' they say."

Prof. Colton's explanation reminds me of Dr. Perkin's comments regarding PAHO's refusal of VVMs. PAHO had trained all health workers in its countries to immediately discard any vaccines that had been heat-exposed. By introducing VVM, which allowed health workers to see that some vaccines do not instantly go bad when they are exposed to certain heat for certain periods, Dr. Quatros (PAHO) thought health workers would think they had been deceived.

This was something that had literally been experienced by Dr. Tsu, when she was managing the early country studies with PTS VVM.

"People were very skeptical about whether health workers could recognize the color difference, and also whether their introduction would undermine training. So, these were the big questions by the time I came along in 1981, and the main issues when we talked to the folks in EPI, which in those days was John Lloyd and James Cheyne. The response to both questions was 'take it out to field and see'. That was why we got this small grant to go to these 10 different countries in different regions and see what the reaction was. I think people were surprised at how willing health workers were to use it, and the fact they did not seem to have the same concerns as we had. I mean they did raise worries such as "but we have always been told to throw them away". We told them, well, yes, that was because we didn't have any way before to tell whether the vaccine was good or not, but now we do. The idea of cumulative heat exposure was a concept that was hard at first for people to grasp because they thought if they put it back in the freezer, it should be okay. However, that doesn't work because this is cumulative exposure. So, those ideas were the ones we took out to the field."

Following PATH producing and refining measles VVMs based on PTS technology, between 1982 and 1985, validation field studies were conducted in Argentina, Brazil, Egypt, Kenya, Nepal, Pakistan, Peru, Philippines, Yemen and Zimbabwe. It sounds surprising to have had three PAHO countries among these validation field studies, Argentina, Brazil and Peru. And furthermore, these validation field studies were co-sponsored by the PAHO/EPI and PAHO's Programme for Health Technology Development.

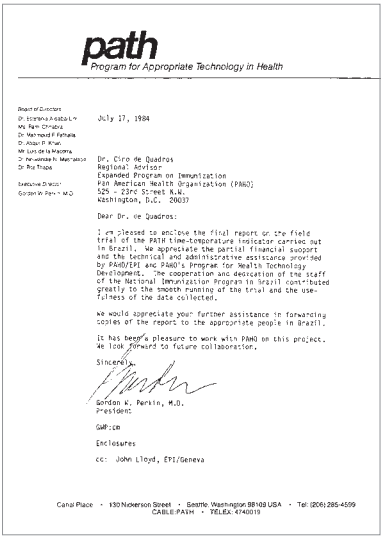
The Brazil report, as it was communicated to Dr. Ciro de Quadros by Dr. Perkin, noted the following under *User Acceptability*:

"The Regional Supervisor reported that health workers had a positive reaction to the indicator during his monthly field visits to each participating basic health units (BHU). Workers were unanimously in considering that the indicator provided the secu-

rity of knowing they were administering an effective vaccine. (...)

"Local level health workers thought the indicator was valid for its designed purpose, and there were no problems with color interpretation. However, all those questioned believed the indicator was not very sensitive to heat due to the observed delay (12 days) in color change to black. Perhaps this skepticism can be reduced if future training includes more information on vaccine stability and the explanation that the indicator color change corresponds to WHO-recommended minimum standards for vaccine stability."

Of course, conducting a study in a country, and introducing policy changes are two different things, especially when the policy goals in a region are monopolized by a central power.



path
Program for Appropriate Technology in Health

July 17, 1984

Dr. Ciro de Quadros
Regional Advisor
Expanded Program on Immunization
Pan American Health Organization (PAHO)
525 - 23rd Street N.W.
Washington, D.C. 20037

Dear Dr. de Quadros:

I am pleased to enclose the final report on the field trial of the PATH time-temperature indicator carried out in Brazil. We appreciate the partial financial support and the technical and administrative assistance provided by PAHO/EPI and PAHO's Program for Health Technology Development. The cooperation and dedication of the staff of the National Immunization Program in Brazil contributed greatly to the smooth running of the trial and the usefulness of the data collected.

We would appreciate your further assistance in forwarding copies of the report to the appropriate people in Brazil.

It has been a pleasure to work with PAHO on this project. We look forward to future collaboration.

Sincerely,

Gordon W. Perkin, M.D.
President

GWP:ce

Enclosures

cc: John Lloyd, EPI/Geneva

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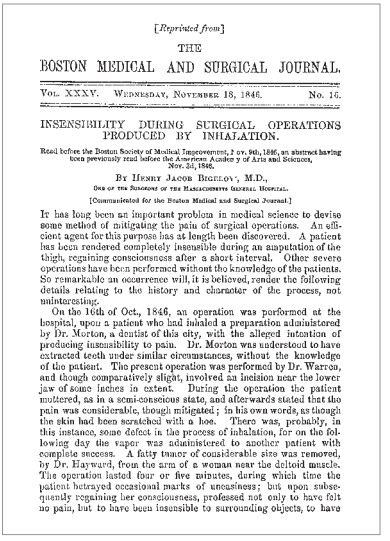
Was VVM a slow idea?

A Harvard surgeon and contributing editor for *The New Yorker*, Dr. Atul Gawande questioned why do some innovations spread so swiftly and others very slowly. In his article, published in *The New Yorker* on 29 July 2013, Gawande considers the very different trajectories of surgical anesthesia and antiseptics, both of which were discovered in the nineteenth century.



[*Reprinted from*]

THE

BOSTON MEDICAL AND SURGICAL JOURNAL.

Vol. XXXV. Wednesday, November 18, 1846. No. 16.

INSENSIBILITY DURING SURGICAL OPERATIONS PRODUCED BY INHALATION.

Read before the Boston Society of Medical Improvement, 7 ov. 9th, 1846, an abstract having been previously read before the American Acadee y of Arts and Sciences, Nov. 5th, 1846.

By Henry Jacob Bigelow, M.D.,
One of the Surgeons of the Massachusetts General Hospital.

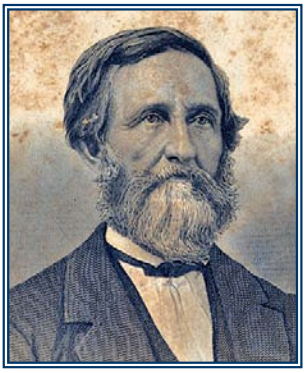
[Communicated for the Boston Medical and Surgical Journal.]

It has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An sufficient agent for this purpose has at length been discovered. A patient has been rendered completely insensible during an amputation of the thigh, regaining consciousness after a short interval. Other severe operations have been performed without the knowledge of the patients. So remarkable an occurrence will, it is believed, render the following details relating to the history and character of the process, not uninteresting.

On the 16th of Oct., 1846, an operation was performed at the hospital, upon a patient who had inhaled a preparation administered by Dr. Morton, a dentist of this city, with the alleged intention of producing insensibility to pain. Dr. Morton was understood to have extracted teeth under similar circumstances, without the knowledge of the patient. The present operation was performed by Dr. Warren, and though comparatively slight, involved an incision near the lower jaw of some inches in extent. During the operation the patient muttered, as in a semi-conscious state, and afterwards stated that the pain was considerable, though mitigated; in his own words, as though the skin had been scratched with a hoe. There was, probably, in this instance, some defect in the process of inhalation, for on the following day the vapor was administered to another patient with complete success. A fatty tumor of considerable size was removed, by Dr. Hayward, from the arm of a woman near the deltoid muscle. The operation lasted four or five minutes, during which time the patient betrayed occasional marks of uneasiness; but upon subsequently regaining her consciousness, professed not only to have felt no pain, but to have been insensible to surrounding objects, to have

On 16 October 1846, a Boston dentist named William Morton administered ether anesthesia before a medical audience at the Massachusetts General Hospital in Boston, Massachusetts. Both Morton, and the Boston Surgeon Henry Jacob Bigolow, who helped Morton to demonstrate his claim of a discovery of a gas that could render patients insensible to the pain during surgery were unaware of Crawford Williamson Long's prior work with ether during surgery.[25]

25 Crawford Williamson Long was an American surgeon and pharmacists best known for his first use of inhaled sulfuric ether as an anesthetic. The first historical surgery was him removing a tumor from the neck of a patient, James M. Venable on 30 March 1842. Despite continuing using ether in surgeries and expanding its use to his obstetric practice, Long did not immediately publish his findings. Bigolow's article and several others made Long documenting the details of his experiments, collecting patient accounts, and notarizing their letters. Finally, he published his work in the Southern Medical and Surgical Journal in December 1849.



Crawford Williamson Long

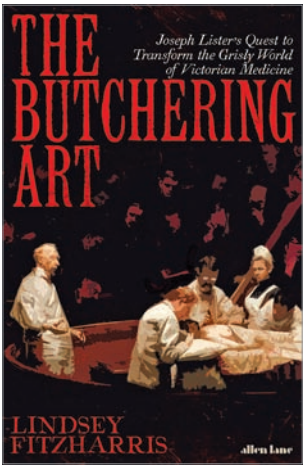
On 18 November 1846, Bigolow wrote about this groundbreaking discovery in the Boston Medical and Surgical Journal:

"It has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose has at length been discovered."

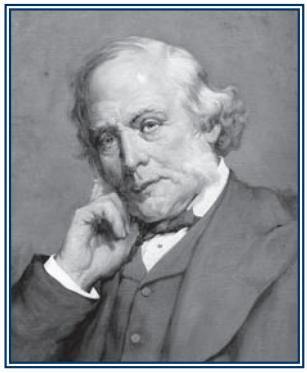
Credit for the discovery of anesthesia became even more complicated when Crawford Williamson Long, Charles Jackson and Horrace Wells staked claims for the use of ether in pain management. Long, despite an extensive documented proof, never received full credit for his discovery during his lifetime. The issue here is not who has discovered ether as a surgical anesthetic, but how fast it spread. Following the 1846 public demonstration, by mid-December of that year, surgeons were already using it in Paris and London. By June 1847, anesthesia had been used in almost all regions of the world.

On 21 December 1846, just a few days before Christmas, Scottish surgeon Robert Liston (known for his strength and speed in surgeries) from the University College Hospital in London gave his first public appearance with using ether and conquering pain. Interestingly, the hero of the antiseptics in Gawande's article, Joseph Lister was a young man who had seated himself quietly at the back of the operating theatre.

Lindsey Fitzharris in her most recent book, *The Butchering Art* tells the story of Joseph Lister's quest to transform the grisly world of Victorian medicine. *"With Robert Liston's ether triumph, Lister had just witnessed the elimination of the first of the two major obstacles to successful surgery – that it could now be performed without inflicting pain"* writes Fitzharris, *"Inspired by what he had seen on the afternoon of December 21, the deeply perceptive Joseph Lister would soon embark on devoting the rest of his life to elucidating the causes and nature of postoperative infections and finding a solution for them. In the shadow of one of the profession's last great butchers, another surgical revolution was about to begin."*



Two decades after the anesthesia becoming so popular, with the confidence of operating without perpetrating pain, the surgeons became more willing to operate, which led to an increase in postoperative infection and shock. In summary, pain was conquered, but not the filth. It might sound terrible, but in those days, surgeons took pride in the stains



Joseph Lister

on their unwashed operating gowns as a display of their experience. They were not required to wash hands for anything, not even before operations. People believed that damage from exposure to bad air was responsible for infections in wounds. With the advent of the painless operations, surgeons with no understanding of the causes of infection were even operating on multiple patients in succession using the same unwashed instruments.

Lister, as a professor of surgery at the University of Glasgow became aware of French chemist Louis Pasteur's paper showing that if micro-organisms were present, under anaerobic conditions food spoilage could occur. Pasteur suggested three methods to eliminate micro-organisms: filtration, exposure to heat or exposure to chemical solutions (e.g. carbolic acid). Lister believed that the same could apply to prevent infections. Lister tested the results of spraying instruments, the surgical incisions, and dressings with carbolic acid solution. He observed a remarkably reduced incidence of gangrene and sepsis. He published his observations in *The Lancet* in a series of six articles in 1867.

Gawande rightly points out that you would have thought that, after Lister publishing his results in *The Lancet*, his antiseptic method would have spread as rapidly as anesthesia – which was not the case, and he questions why anesthesia spread very rapidly and not the aseptic surgery. I summarize Gawande's points below with his words:

1. Anesthesia combatted a visible and immediate problem (pain); aseptic surgery combatted an invisible problem (germs) whose effects wouldn't be manifest until well after the operation.
2. Second, although both made life better for patients, only one made life better for doctors. Anesthesia changed surgery from a brutal, time-pressured assault on a shrieking patient to a quiet, considered procedure. Listerism, by contrast, required the operator to work in a shower of carbolic acid. Even low dilutions burned the surgeons' hands. You can imagine why Lister's crusade might have been a tough sell.

Gawande concludes that this has been the pattern of many important but stalled ideas. Although, I know that the VVM story is a successful one, I also know that developing today's VVM took just a couple of years, and then more than 15 years were needed to get it on all the vaccines for UNICEF purchase. This does not make VVM a slow idea although the problem it tackled was an invisible one – it

is impossible to differentiate a heat damaged vaccine vial from a vaccine that is not heat damaged. Of course, the scene with the development of VVM was quite different compared to the 1800s. First of all, VVM was developed upon a request by WHO, and UNICEF as a central purchasing power was ready to adopt what WHO recommended regarding its use.

Sharing his Facebook posting from 2014 with a photo at returnees' camp, Moyen-Chari, Chad, Robert Davis, checking the VVM on a polio vaccine vial, says *"This takes me back"* on his 16 February 2019 posting. *"For the non-specialist, the vaccine vial monitor, applied to the vaccine vial changes color when the vial is exposed to temperatures higher than 8 degrees Centigrade. It is of immense use in tropical settings, where the vaccination team needs to know, yea or nay, whether the vaccine can be used.*

"Mike Reich, of Harvard U., has written a fine article on how the VVM came to be. It was the work of many hands.

"I once asked a well known figure in PATH, the Program for Appropriate Technology for Health, why it took so long for the VVM to move from conception to realization. "The gate keepers," he explained. Readers of C. Northcote Parkinson will understand.

"Good ideas go into committees," exclaims Robert Davis, *"They do not always come out unscathed".*

The pharmaceutical industry did not like to be dictated what to do by WHO and UNICEF. They also thought that they would lose control by revealing their stability information to end users in the field on products that are labelled as "store and transport at 2°C to 8°C". In the very early days, many of them came back with all types of reasons why they could not adopt the technology.

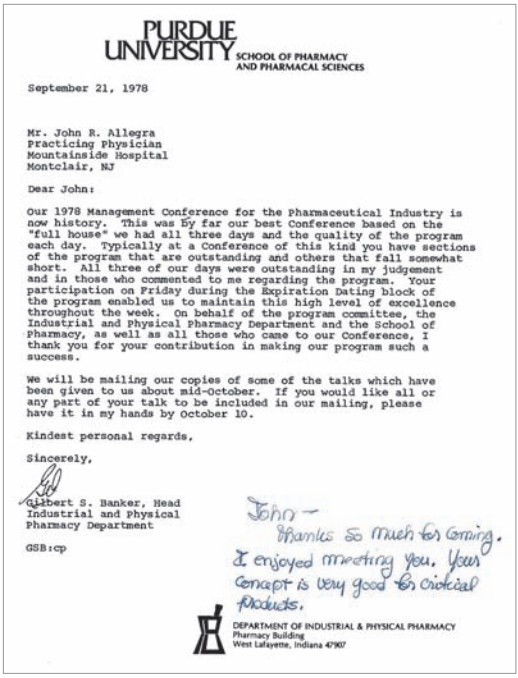
The initial concept, which was mooted during the early 1970s, and independent from WHO came from Ray Baughman and John Allegra who sought out potential customers for their new concept but sadly none of their efforts resulted in any real opportunities.

On 13-15 September 1978, John Allegra was invited to talk on time and temperature integrators at the Management Conference for the Pharmaceutical Industry at the Purdue University, West Lafayette, Indiana. Although Dr. Allegra did not refer to it as a "smart expiry date," his motive for having the time and tem-

perature integrators was the necessity of having an indicator that could overrule the expiry date. Dr. Allegra says that his talk was very well received, and generated a lot of interest. But Dr. Allegra also heard participants hinting that they would not want more government control over what they were doing.

"So, nobody wanted to push it, and, unfortunately by time it faded away."

Dr. Allegra's talk was praised by Gilbert S. Banker, the head of the Industrial and Physical Pharmacy Department, School of Pharmacy and Pharmaceutical Sciences at Purdue University. Banker writes to Dr. Allegra, appreciating his talk with a handwritten note on 21 September 1978.



PURDUE UNIVERSITY
SCHOOL OF PHARMACY AND PHARMACAL SCIENCES

September 21, 1978

Mr. John R. Allegra
Practicing Physician
Mountainside Hospital
Montclair, NJ

Dear John:

Our 1978 Management Conference for the Pharmaceutical Industry is now history. This was by far our best Conference based on the "full house" we had all three days and the quality of the program each day. Typically at a Conference of this kind you have sections of the program that are outstanding and others that fall somewhat short. All three of our days were outstanding in my judgement and in those who commented to me regarding the program. Your participation on Friday during the Expiration Dating block of the program enabled us to maintain this high level of excellence throughout the week. On behalf of the program committee, the Industrial and Physical Pharmacy Department and the School of Pharmacy, as well as all those who came to our Conference, I thank you for your contribution in making our program such a success.

We will be mailing our copies of some of the talks which have been given to us about mid-October. If you would like all or any part of your talk to be included in our mailing, please have it in my hands by October 10.

Kindest personal regards,

Sincerely,

Gilbert S. Banker, Head
Industrial and Physical
Pharmacy Department

GSB:cp

John –
Thanks so much for coming. I enjoyed meeting you. Your concept is very good for critical products.

DEPARTMENT OF INDUSTRIAL & PHYSICAL PHARMACY
Pharmacy Building
West Lafayette, Indiana 47907

I find Dr. Allegra's Purdue talk historical, revolutionary, innovative and pioneering. For this reason, I believe it is important to reproduce it in full here.

The Use of Time-Temperature Indicators to Insure the Quality of Pharmaceutical Products

By *John R. Allegra, M.D., Ph.D. Mountainside Hospital*
Montclair, New Jersey

My interest in expiration dating and the use of time-temperature indicators to insure the quality of pharmaceutical products dates back to my experience as a mission doctor in Africa. Although we frequently had the latest drugs, I often wondered how many of the pharmaceuticals had lost significant potency due to thermal abuse, even if they were used before their labeled expiration date.

Vaccines present a particularly difficult problem because of their refrigeration requirements. Yet, the need for expanded vaccination programs was made abundantly clear to me as large numbers of children die from measles each year in Africa, despite the availability today of an excellent measles vaccine.

The World Health Organization (W.H.O.) has recently expanded its efforts in promoting vaccinations worldwide. One of their most vexing problems is insuring that the vaccines do not lose their efficacy because of thermal abuse. W.H.O. officials have estimated that over 50% of the vaccines used in underdeveloped countries are not effective at the time of administration due to thermal abuse. W.H.O. is currently using time-temperature indicators in field trials to detect thermally abused vaccines. Indicators are also working for W.H.O. as management aids to detect deficiencies in the cold chain.

In the USA, where the cold chain is relatively good, isolated epidemics have been attributed to vaccine which had become ineffective due to mishandling. A study by Lerman and Gold[26] attributed an epidemic of measles in Ohio to thermally abused vaccines. Apparently, vaccine stored in the door of a refrigerator was inactivated from the high temperature exposures experienced by frequent opening and closing of the door. A study by Krugman et.al.[27] showed that for live virus vaccines in the USA one specimen in five had lost significant activity because of abuse during transport or storage in the community.

Besides vaccines, many other pharmaceutical products can lose their efficacy from thermal abuse. This is particularly true for frozen and refrigerated products, those derived from plasma proteins and certain suspensions and emulsions.

Despite current major efforts by drug houses to insure the quality of their products and to establish reasonable expiration dating; unrecognized thermal abuse can take place. To guard against this, it would seem only natural that as suitable time-temperature indicators become available they be placed on each drug container to screen out thermally abused products.

What type of time-temperature indicators would be most desirable?

Basically, what is needed is an “integrating” device which would take into account the accumulated effects of thermal exposure in a way that corresponds to the thermal degradation behavior of pharmaceuticals. For example, it is known that short times at high temperatures can have the same negative effect on product quality as long times at lower temperatures. An integrating device would differ markedly from a temperature-only device which shows only that a particular temperature has been exceeded. Such an integrating device would also differ from a temperature-only indicator with a built-in delay which would fire only when a given temperature had been exceeded for an extended period of time.

26 *S.J. Lerman, E. Gold. JAMA, Vol. 216, No.8, May 24, 1971*

27 *R.D. Krugman, B.C. Meyei, J.C..Enteiline, P.D. Parkma.n, J.J. Witte, and H.M. Meyer, J.Pediatrics 85.,512.Cl9.7.1 L*

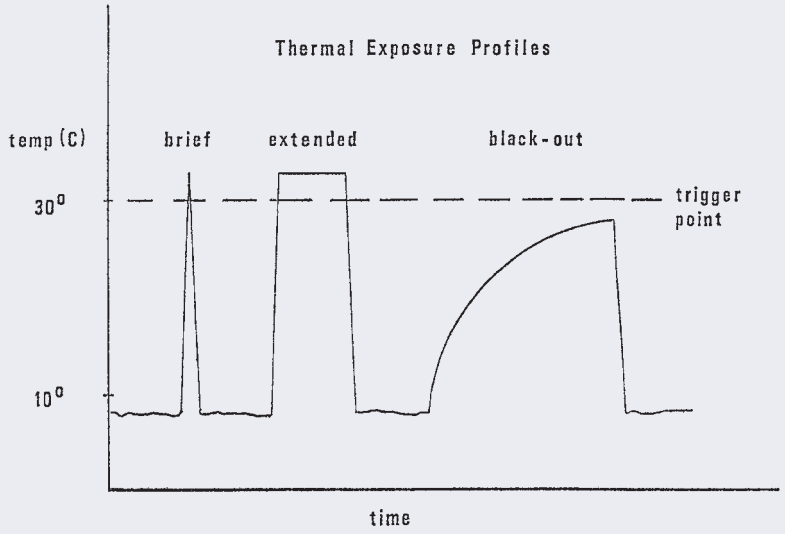


Figure 1

Figure 1 shows schematic thermal exposure profiles. The first profile represents a drug taken out of a refrigerator for a brief time. This would trigger a temperature-only device yet may not result in significant loss of product quality. The second profile shows a drug taken out of the refrigerator for an extended period. This would cause a response from a temperature-only device with a built-in delay. Such devices may be helpful for monitoring sharp transitions such as defrosting and critical stability temperatures for emulsions and suspensions. The third curve reflects a black-out condition where the temperature of the refrigerator slowly reaches ambient temperature.

This exposure may correspond to significant thermal abuse, yet it would not trigger the temperature-only devices.

A time-temperature integrating device would take into account all of these thermal exposures in the same way as they affect product quality.

Figure 2 demonstrates numerically how a time-temperature integrating device functions. A hypothetical product loses its efficacy at different time intervals depending on temperature. The integrating indicator should trigger when any combination of time-temperature exposures corresponding to the total thermal lifetime of the product is reached.

Currently, devices which integrate the accumulated effects of time and temperature can be placed into three general categories: enzyme, diffusion, and chemical devices.

The enzyme device is represented by i-point's product.

It consists of two pouches. One contains the enzyme; the other contains the indicating substrate. Device response is a color change produced as the enzyme interacts with the substrate.

Several patents exist for diffusion type devices. Perhaps the most advanced is that made by 3M. It consists of a chemical which migrates along a paper strip. Using such a device one can determine how much of the lifetime has expired by noting how far the chemical substance has migrated along the paper strip. These are being used in several applications such as inventory aids and to detect flaws in the cold chain.

Degradation Characteristics
for a
Hypothetical Product

time		temperature
3 years	at	3°C
3 months	at	21°C
3 days	at	50°C

EXAMPLES:

Product has degraded under the following exposures

2 years at 3°C and 1 month at 21°C

2 years at 3°C and 1 day at 50°C

2 months at 21°C and 1 day at 50°C

1 year at 3°C, 1 month at 21°C, and 1 day at 50°C

Indicator response should be the same for each example

Figure 2

The most recent type of device is the chemical indicator developed by Allied Chemical Corporation. This indicator consists of a special thermally responsive substance deposited on paper which undergoes a sharp color transition upon expiration of the product's shelf life. A multi-tab device may be employed to indicate fractional expiration of shelf life.

The Allied Chemical device can be made arbitrarily small and can be easily incorporated into labels. Allied is also developing temperature-only devices with built-in delay for handling problems such as defrosting and phase transitions on emulsions and suspensions.

The use of time-temperature indicators would result in economy from decreasing the insulation or refrigeration needed during shipping, decreasing the size of the built-in safety factor used for expiration dating, making a more

efficient use of inventory, and to pinpoint areas of thermal abuse. In addition, a pharmaceutical company may have a good drug which can- not be introduced because 'of limited thermal stability. Perhaps the use of an indicator to insure against thermal abuse would make such a product marketable.

The moral and ethical considerations of insuring. good product quality must be weighed apart from the economic advantages. All of us after hearing the previous speakers can appreciate the substantial efforts that currently go into insuring product quality and into expiration dating. Yet, we physicians still cannot be sure that the pharmaceutical we are about to administer has not lost its true effectiveness due to thermal abuse despite its use before the labeled expiration date.

Why not go one step further now that the technology is available and use time-temperature indicators to insure the quality of pharmaceutical products?

The reactions to Kockums's enzyme pouch indicator was very similar in late 1970s both in the U.S. and in Europe. John Lloyd explains:

"In the first trials of enzyme indicators from Kockums in the U.S. they wanted to demonstrate to the companies that there were still problems with the cold chain. Food companies were initially very interested. They did some trials with the apparent conviction that they had a perfectly good cold chain and this was just confirming it. The results were terrible. So, Kockums was very pleased with the results for a brief period, in that their product had a market. But the companies concerned said that the studies had shown them a lot but that was enough. 'We will now pay attention to the cold chain, but we do not want people to use it.' There was also the issue of a degree of regulation in the system, and the companies did not want any regulation based on this indicator. I think there were two issues here. One is the liability issue, the other is simply money. If they had this device, people could come back to them and ask for replacements. Of course, Kockums thought that it was being interpreted by the industry in the wrong way. Instead, they went to the European market; they went to Italy. Fiat were giving lunch to their employees in packs, lunch comes in a tray. And these trays are supposed to be kept cold (and some warm). People were complaining about the quality of the food. They decided to experiment with the Kockums indicator to demonstrate to their workers that the food they picked was good. Same thing happened. Fiat was convinced that it was a way of reinforcing food quality perception among the workers, and in fact there were so many problems raising from it that they stopped being used, because they did not want this to be seen."

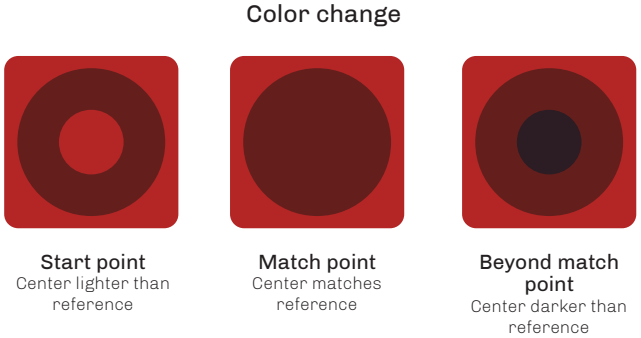
TTIs on daily rations and rapid skin decontamination lotion for soldiers of the U.S. army

While the U.S. public health services refused to acknowledge that the VVM could be an instrumental tool in the U.S. immunization programme, another cluster in the country had been using (VVM-like) TTIs for many years. *"We have had these since the mid-1990s"* says Chris Caufield (Vice President, Global Customer Development, Temptime Corporation), *"The first time the U.S. Army went into Iraq, and into the desert they quickly realized how extremely hot it was there, with many things melting. So, at that time, they began to evaluate the use of TTI for the ready-to-eat daily rations for soldiers. At the Natick Soldiers Centre, which is located in Massachusetts, they evaluated our TTI technology, and since 1997 it's been part of the supply contract for all their suppliers delivering ready-meals to the army."* The performance criteria for daily rations is 27°C for three years.

The U.S. Army also uses cumulative TTIs on a medical treatment, reactive skin decontamination lotion (RSDL). Chris explains: *"It's a lifesaving item that each warfighter carries on their person, in the field, in any of those theatres of war where chemical or biological warfare can occur. It is a chemical warfare counter measure, so if you are exposed to chemical warfare, you can rub it onto your skin, and it actually pulls the chemical agent from your skin, and allows you some hours to get to water to rinse it off. The TTI used on the rapid skin decontamination lotion is 27°C for nine years. This shows us the wide range of capability available from Temptime devices. We can make TTI for 2 days and we can make TTI for 9 years. That's the capability range and our ability to match a lot of different stability profiles."*

The TTI used for these different purposes have a different look and colors.

Nonetheless, it is an awkward fact that the temperature excursion risks have been studied in detail for the military, but not for the public health services.



Quality oriented vs. quality driven

Does applying such indicators to perishables and biologicals really increase the liability of the manufacturer? I believe, it makes it more transparent, that's all. In general, when a product is handed over to a recipient (e.g. a supermarket, a wholesaler, a country MOH) by the manufacturer, the manufacturer cannot be held liable if the product is not stored and handled as recommended resulting in damage, to whatever degree, of the product. When there are no indicators, and something goes wrong with the product, it is not possible to tell whether the product was off label quality to start with or if it suffered mishandling in the hands of other parties. With such indicators, when the initial status of the indicator is recorded at the outset, any further changes would be indicating downstream storage/handling damage and the manufacturer could not be deemed liable. This was made clear in a 2002 technical review of VVM implementation meeting that if there is a problem of this nature, VVM would serve to make it visible. In this historic VVM meeting held at WHO headquarters in Geneva, the following comment/question was responded by the IFPMA spokesperson Mr. Walter Vandersmissen (I know this would be a repetition, but repetition is good):

Comment: *"We all recognize that there is some liability. It is a fact of life. However, we would like vaccine manufacturers to clarify for what reason they feel that VVMs could make the situation worse, i.e. bearing in mind that the risk of exposure to unacceptable temperatures exists no matter what?"*

Answer: [by Mr. Vandersmissen] *"It doesn't make the situation worse. It makes it literally visible. Before the VVM, there was no way of telling if vaccine was heat abused. Now it will be traced. The positive is that vaccine will be discarded, but the negative is that people will want compensation for it."*

Question: *"Isn't there the risk anyway? Isn't VVM a tool to reduce the use of unacceptable quality vaccines?"*

Answer: [by Mr. Vandersmissen] *"Yes, it may reduce the risk, but it won't take it away."*

Take Gardasil® (quadrivalent), the U.S. product insert indicates that it can be used out of refrigeration (at temperatures at or below 25°C) for a total time of no more than 72 hours. But, if you are the end-user of the product, how would you know whether this amount of time has ever been used partially, or exceeded totally unless you have a VVM type indicator attached to every single vial? You may have sophisticated temperature monitoring devices in place throughout the cold

chain, but these instruments are not smart and cannot pass cumulative information to lower levels.

In the U.S. if a vaccine refrigerator is exposed to temperatures above the 8°C, practitioners are advised to cease the immunization activities, and to contact every single manufacturer of the products that they have in the refrigerator in order to get clearance as to whether they can continue using the vaccine. This takes time. Something that can be simply solved with a device like VVM, while saving money and unnecessary vaccine wastage.

Liability is not the only issue that gets in the way with the regulations concerning VVM however. The use of VVM is a dependable means of determining the issues relating to handling from a quality perspective, but unfortunately, companies are largely ambivalent to this. Because, although they maintain they are totally focused on quality, at the same time they don't want to contemplate the additional scrutiny on quality which a more visible product monitoring regime might engender, where they, as manufacturers are not in charge.

The science behind

The chemistry

The color change that takes place in the reactive square of HEATmarker® VVMs is based on the solid-state polymerization reaction of proprietary, substituted diacetylene monomers. The monomers are very lightly colored once they are synthesized, and as a result of the polymerization reaction they become darkly colored.

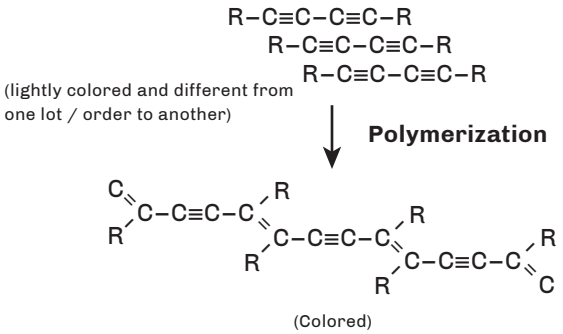
As with many polymerization reactions involving molecules with conjugated triple bonds, the polymerization reaction can be accomplished as a result of time and temperature exposure, but can also be accomplished by actinic radiation[28] in the visible but mostly UV portion of the light spectrum.

Certain crystalline diacetylenes monomers undergo a dramatic color change upon prolonged storage under ambient conditions. Gerhard Wegner was the first to understand this reaction more than a century ago and stimulated much chemical and physical research on these intriguing compounds. Wegner concluded that the color change must be the result of a polymerization reaction. He based this upon the principles of topochemical reactions developed by GML Schmidt and coworkers. The polymerization process was explained by C1 and C4 carbon atoms of adjacent diacetylene moieties in a molecular stack linking together. Furthermore, Baughman's work showed that according to the following scheme elongated poly-

28 Electromagnetic radiation that can produce photochemical reactions.

mer chains are formed under preservation of the single crystalline phase structure provided that the molecular motions accompanying the chemical transformation compensate each other in a way as to minimize the overall changes of the crystallographic parameters.

Polymerization of diacetylene monomers



The rate of the polymerization reaction can be matched to the rate of product degradation, so that integrated time-temperature exposure affects the indicator color in the same way that this exposure effects the quality of products, like vaccines. When the average rate of color change (or the number of days to end-point) is plotted against the temperature, with a logarithmic scale, a linear relationship is obtained. This suggests that the polymerization reaction (the color change) follows the Arrhenius equation.

Arrhenius equation

In physical chemistry, the Arrhenius equation is a formula for the temperature dependence of reaction rates. It was proposed by Swedish scientist, 1903 Nobel prize laureate in chemistry, Svante August Arrhenius (1859-1927). Chemical reactions are typically expected to proceed faster at higher temperatures and slower at lower temperatures. Quantitatively this relationship between the rate a reaction proceeds and its temperature is determined by the Arrhenius equation. At higher temperatures, the probability that two molecules will collide is higher. This higher collision rate results in a higher kinetic energy, which has an effect

on the activation energy of the reaction. The activation energy is the amount of energy required to ensure that a reaction happens.

The effect of temperature on reaction rates using the Arrhenius equation can be calculated as follows:

$$K = A_0 e^{(-E_a/RT)}$$

In this equation, A_0 and E_a are experimentally determined constants specific to the reaction, and R is the universal gas constant (with a value of 8.314×10^{-3} kJ $mol^{-1}K^{-1}$). The activation energy, E_a, determines how the rate changes with temperature, T, which is expressed in degrees Kelvin.

For example, for a VVM30, the optical density changes essentially linearly with time and reaches its end-point by 30 days at 37°C, so the rate constant equals 1/30 per day at this temperature. The end-point is the stage where the difference between the optical density of the reference ring and the optical density of the active surface (center square) of the VVM reaches zero. The experimentally determined activation energy of 27.1 kcal/mole is used to determine the optical density change for any other time–temperature combination or to plot an Arrhenius chart of the end-point as a function of temperature.

From Kartoglu, U. (2016) Pharmaceutical and Vaccine Quality Illustrated, EPELA

The rate of the chemical reaction of the polymerization follows the Arrhenius equation and predicts shelf-life in units of time (e.g. days) across various temperatures. The "energy of activation" factor in the equation depends on the specific chemistry of the VVM, and determines the slope of the standard plot of shelf-life (time on logarithmic y axis) versus temperature (x axis, often converted to °C from the equation's reciprocal of absolute °Kelvin).

The match

WHO requires that vaccine shelf-life and/or release criteria establishment should be supported by real time studies. Such studies are conducted during the development of vaccines on commercially packaged product to examine the kinetics of vaccine potency and other attributes. WHO *'Guidelines on stability evaluation of vaccines'* document (WHO/BS/06.2049) indicates the following: *"Stability studies on commercially packaged product should support planned exposures of vaccine to temperatures associated with expected temperature excursions, as well as the labeled storage temperature. This includes conditions for labeling, packaging, and inspection, as well as*

shipping of vaccine to commercial distributors. Accelerated and long-term stability studies can be conducted in parallel rather than consecutively, when the vaccine is stable at a particular storage condition, or when it has been demonstrated that storage at one temperature does not affect stability under a subsequent storage condition. Long term stability studies on commercially packaged product should yield sufficient information to reveal the product kinetics, as well as to establish shelf life. Thus, if preliminary studies of packaged vaccine indicate nonlinear kinetics, with early rapid change in the product characteristic, more early time points should be taken to better characterize the kinetics, while later measurements may be taken at wider intervals. More regular intervals may be employed when vaccine kinetics is linear. Studies may be likewise designed to provide reliable early evidence of product stability."

Stability data from both accelerated and long-term studies are used to establish recommended storage conditions and expiration dating for pharmaceutical and biological products including vaccines. The manufacturer assures the quality of the product as long as the product remains in its approved container within the specified temperature range until the date of expiration. However, as the product passes through the distribution chain it is likely that it will be exposed to temperatures outside of its specified storage. To understand the impact of such excursions on the product, mean kinetic temperature (MKT) has been proposed as a means of evaluating thermal excursions occurring during the storage and shipment. The use of MKT is included in controlled room temperature (CRT) and controlled cold temperature (CCT) definitions of the United States Pharmacopeia (USP).

USP definitions of CRT and CCT	
Controlled room temperature	A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40 are permitted as long as they do not exceed 24 hours. Spikes above 40°C may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°C", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations.
Controlled cold temperature	temperature maintained thermostatically between 2° and 8°C (36° and 46°F), that allows for excursions in temperature between 0° and 15°C (32° and 59°F) that may be experienced during storage, shipping, and distribution such that the allowable calculated MKT is not more than 8°C (46°F). Transient spikes up to 25°C (77° F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise.

Based on their stability characteristics vaccines are categorized in following groups for assignment of corresponding VVMs.

VVM reaction rates by type

Type (vaccines)	Maximum time to end-point at 37°C	Maximum time to end-point at 25°C	Maximum time to end-point at 5°C	Time to end-point at 5°C
VVM30: High stability	30 days	193 days	na*	≥4 years
VVM14: Medium stability	14 days	90 days	na*	≥3 years
VVM11: Intermediate stability	11 days	71 days	na*	≥2.5 years
VVM7: Moderate stability	7 days	45 days	na*	≥2 years
VVM2: Least stable	2 days	na*	225 days	na*

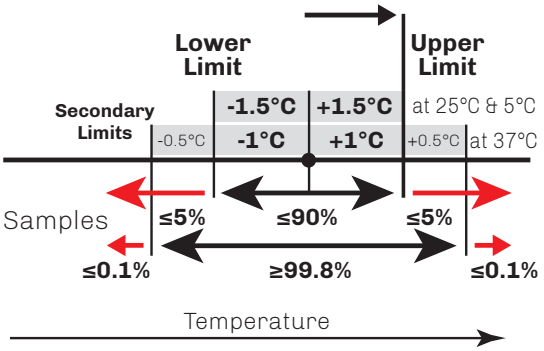
*VVM (Arrhenius) reaction rates determined at two temperature points

WHO PQS performance specifications for VVM (WHO/PQS/E006/IN05.3) indicates the following explanation on the specifications related to the above table.

- *At +37°C, RH 33% ± 5% and RH 75% ± 5%, the primary limits are set such that at the specified time no more than 5% of VVMs shall reach end-point at the lower temperature limit of 35°C and no less than 95% shall reach end-point at the upper temperature limit of 37°C. Further, secondary limits are applied to restrict how far beyond the primary specification the end points are allowed to be. At the specified time no more than 0.1% of VVMs shall reach end-point at the lower secondary temperature limit of 34.5°C and no less than 99.9% shall reach end-point at the upper secondary temperature limit of 37.5°C.*
- *At +5°C and +25°C specifications (ambient humidity in submerged foil/polythene pouch): Limits are set such that at the specified time no more than 5% of VVMs shall reach end-point at the lower temperature limit (2°C or 22°C, respectively) and no less than 95% shall reach end-point at the upper temperature limit (5°C or 25°C, respectively).*

The above information from the table on the VVM reaction rates can be illustrated as follows:

Stability limit criteria by sample group



VVM reaction rates by type

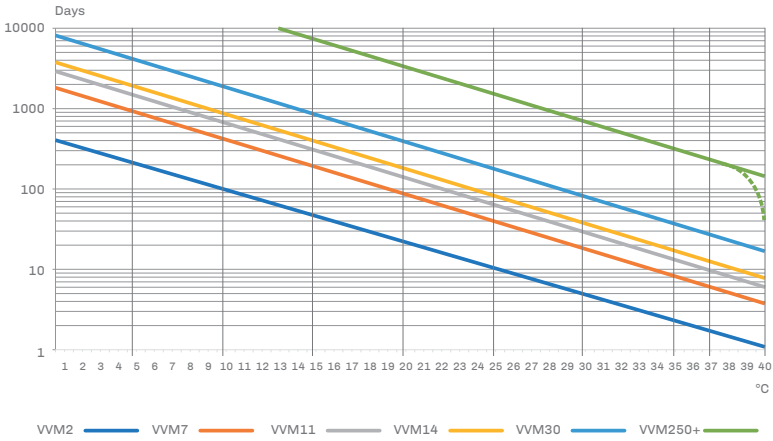
Type (vaccines)	Maximum time to end-point at 55°C	Maximum time to end-point at 45°C	Maximum time to end-point at 37°C	Time to end-point at 25°C
VVM250: Very high stability	17 days	73 days	250 days*	≥900 days

*VVM (Arrhenius) reaction rates determined at 55°C and 45°C, the 37°C values are approximate

- *At +55°C, RH 33% ± 5% and RH 75% ± 5%, the primary limits are set such that at the specified time no more than 5% of VVMs shall reach end-point at the lower temperature limit of 53°C and no less than 95% shall reach end-point at the upper temperature limit of 55°C. Further, secondary limits are applied to restrict how far beyond the primary specification the end points are allowed to be. At the specified time no more than 0.1% of VVMs shall reach end-point at the lower secondary temperature limit of 52.5°C and no less than 99.9% shall reach end-point at the upper secondary temperature limit of 55.5°C.*
- *At +45°C specifications (ambient humidity in submerged foil/polythene pouch): Limits are set such that at the specified time no more than 5% of VVMs shall reach end-point at the lower temperature limit (42°C) and no less than 95% shall reach end-point at the upper temperature limit (45°C).*

These end points can be illustrated in a logarithmic scale as follows. VVM250+ includes a threshold indicator for 40°C, and this is illustrated by dashed line indicating that with the activation of the threshold indicator at 40°C the VVM will be considered as unusable:

HEATmarker VVMs – time to end-point



H series TTIs

In addition to HEATmarker VVMs, Temptime Corporation also produces H series time and temperature integrators. H series is a subset of HEATmarkers which incorporates an orange UV-blocker film as an overlaminate, and uses the same monomer technology, manufacturing materials and processes as VVM. H series also utilizes similar tests and release procedures as the VVM and includes more categories than VVM.

Specified temperatures for H series differ from type to type. In principle, the target time is about the half way between the upper limit and the lower limit. For Hu, the specified temperature is 25°C, and for Hx the specified temperature is 37°C.

HEATmarker H series TTIs

°C	5°C	12°C	25°C	37°C	60°C
Category	**Target time in days**				
Hu14	350	110	**14**	2.5	0.12
Hu21	530	160	**21**	3.7	0.19
Hu28	710	220	**28**	4.9	0.25
Hu41	1,100	330	**41**	7.0	0.33
Hx9	1,400	430	**53**	9.0	0.43
Hx12	1,900	570	**71**	12	0.57
Hx18	2,800	850	**110**	18	0.86
Hx24	3,800	1,100	**140**	24	1.1
Hx36	5,700	1,700	**210**	36	1.7

For example, Hx24 has the target time of 24 days at 37°C, while the upper limit is 30 days, in this sense, Hx24 is the H series equivalent of VVM30.

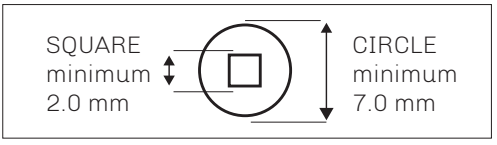
H series are used on some vaccines where the indicator is on the outer carton box. It is also used on biologicals in the Middle East, India and (soon) in China. The H-series is also used on rapid diagnostic test kits in India based on National AIDS Control Organization requirement.

An example of H series HEATmarker

The anatomy of HEATmarkers

The format and dimensions of VVM is defined by WHO PQS in the specifications. The specifications indicate that the VVM must take the form of an inner active surface at the centre of an outer reference circle. In this sense, the design does not need to be a square in a circle, it can be circle in a circle. The VVM must be large enough for the shade change to be readily apparent but small enough to fit onto the vial label or vial cap. The recommended outer reference surface must not to exceed 11 mm across. The ratio of the area of the inner active area to the area to the outer reference area (including the inner active area) is to be no smaller than 1:10. This ratio is satisfied by the below example.

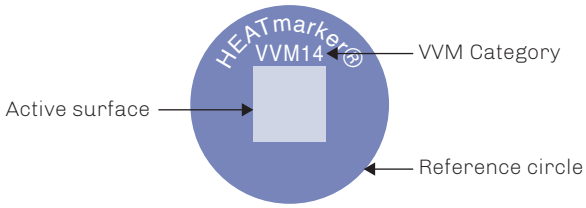
Format and dimensions of VVM



The circle of the VVM comprises a static, reference surface, and the square comprises the active surface. The color change of the active surface is limited to a change of shade, from light to dark. Although mauve color is the color of HEATmarker VVMs, the specifications allow any other color in the design.

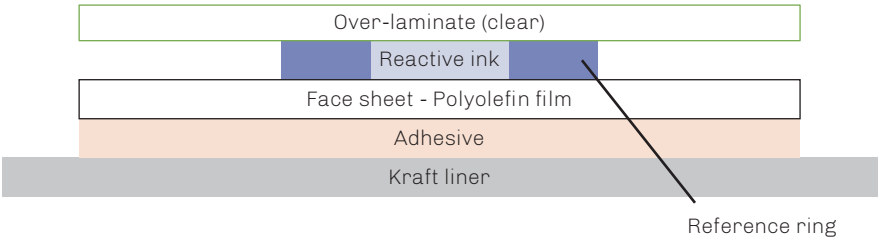
The shape of the current HEATmarker VVM is also a trademark of Temptime Corporation.[29] However, Temptime allows any other (potential) VVM manufacturers to copy the shape (square in circle) on products for WHO prequalified vaccines for the UN market.

HEATmarker VVM

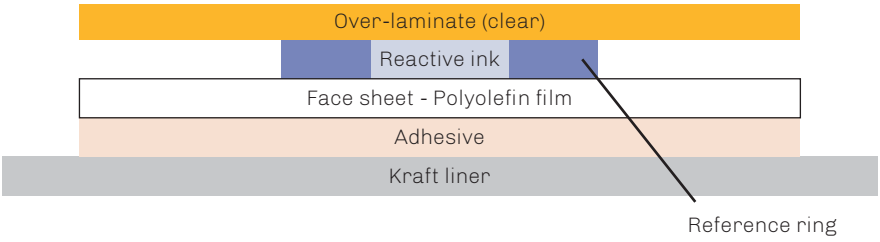


HEATmarker VVM and H series device compositions are shown in the following illustrations as cross-sectional view of the markers.

HEATmarker VVM cross sectional device composition



HEATmarker H series cross sectional device composition



29 At the time of such intention to trademark the HEATmarker shape, Temptime approached WHO. However, they received no response from the WHO legal department.

Measurement of VVM reaction

VVM color-change by time and temperature is measured by the reflected optical density (OD) using a specific spectrodensitometer with a 2-mm diameter measurement aperture. It should be noted that not all spectrodensitometers have the ability to measure spectral data or display colorimetric information. It is also critical that owing to the small size of the VVM's reference ring and indicator area, it is necessary to ensure the target and aperture centering of the spectrodensitometer is suitable for measuring the reference and the active surfaces. All devices are calibrated on a daily basis or before the measurement process. Temptime uses an X-Rite 500 series spectrodensitometer. Normally the measurement is done both for reference (outer circle) and indicator (the square) on minimum of two points that are averaged. The status of VVM is given by the difference of the optical densities of the reference and indicator surfaces. At the start-point, the optical density of the active surface (indicator) must be lower than the optical density of the reference surface by a difference of at least 0.23 OD. The end-point is reached when the difference in average optical density obtained from readings at two different points on the reference surface and the optical density of two different points of the active surface is 0.00. The end-point is exceeded when the OD of the active surface is higher than OD of the reference surface.

Using X-Rite 500 series spectrodensitometer

VVM validation and quality control processes

In a typical VVM application by vaccine manufacturers, the very first step is for WHO to agree on the assignment of an appropriate VVM category to the vaccine based on the submitted stability data from the vaccine manufacturer. All steps for the implementation are summarized in the following Table.

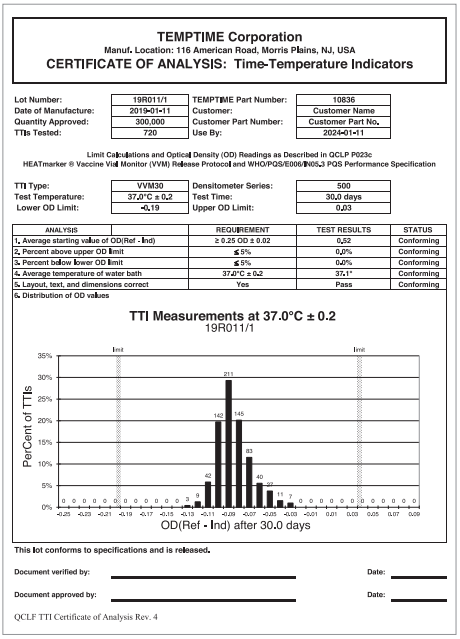
Process and validation/quality control tests performed during VVM implementation

Step	Description of the process	Validation and/or QC tests
Manufacturer's request and approval of VVM type by WHO	Manufacturer's request to Temptime	
	WHO review of stability data	Manufacturers have to validate their stability tests
	WHO approval of VVM type based on stability data (communicated to both the manufacturer and the Temptime)	
Validation of VVM reactivity by the manufacturer	Vaccine manufacturer procures necessary equipment (water bath tanks, densitometer, and special temperature monitoring devices)	
	Conduct initial validation test	Initial validation test conducted at vaccine manufacturer's facility
Determination of VVM position on the vial and approval of the artwork	Vaccine manufacturer provides artwork to Temptime	
	Temptime confirms that the artwork is satisfactory	
	For special applications, validation tests are performed for application (e.g. better adhesion)	Application validation tests conducted at vaccine manufacturer's facility
VVM printing and slitting	Prepare ink base and run pilot tests (Temptime)	
	Conduct accelerated tests for the ink base	Testing of ink base
	Run actual printing	
	Take samples from each master roll for kinetic tests	Kinetic tests
	Take master rolls for slitting	
	Visual check and samples taken for homogeneity tests	Visual check and homogeneity tests
	Conduct lot release test	Testing VVM reactivity at 37°C or 55°C
	Ready for shipment	

Packaging and shipment	Give sequential numbers and pack in corrugated boxes	
	Make necessary booking for shipment	
	Inform customer and advise on arrival	
VVM application on vial	Vaccine manufacturer to check the indicator which is placed on shipping carton, and measure color of the sample indicator	
	Conduct lot acceptance test using Temptime lot release protocol and recommended sampling plan according to vaccine manufacturer's quality system	Acceptance tests (by vaccine manufacturer on arrival) using Temptime lot release protocol and sampling plan
	Store goods in freezer at -24°C	
	Apply VVM to label and/or vial	
	Store at specified temperatures as required by the type of vaccine until shipment	

VVM printing press, Temptime Corporation

VVM batch release by Temptime is documented in a release certificate and communicated to the vaccine manufacturer.



TEMPTIME Corporation
Manuf. Location: 116 American Road, Morris Plains, NJ, USA
CERTIFICATE OF ANALYSIS: Time-Temperature Indicators

Lot Number:	19R011/1	TEMPTIME Part Number:	10836
Date of Manufacture:	2019-01-11	Customer:	Customer Name
Quantity Approved:	300,000	Customer Part Number:	Customer Part No.
TTIs Tested:	720	Use By:	2024-01-11

Limit Calculations and Optical Density (OD) Readings as Described in QCLP P023c
HEATmarker ® Vaccine Vial Monitor (VVM) Release Protocol and WHO/PQS/E006/IN05.3 PQS Performance Specification

TTI Type:	VVM30	Densitometer Series:	500
Test Temperature:	37.0°C ± 0.2	Test Time:	30.0 days
Lower OD Limit:	-0.19	Upper OD Limit:	0.03

ANALYSIS	REQUIREMENT	TEST RESULTS	STATUS
1. Average starting value of OD(Ref - Ind)	≥ 0.25 OD ± 0.02	0.32	Conforming
2. Percent above upper OD limit	≤ 5%	0.0%	Conforming
3. Percent below lower OD limit	≤ 5%	0.0%	Conforming
4. Average temperature of water bath	37.0°C ± 0.2	37.1°	Conforming
5. Layout, text, and dimensions correct	Yes	Pass	Conforming

6. Distribution of OD values

TTI Measurements at 37.0°C ± 0.2
19R011/1

This lot conforms to specifications and is released.

Document verified by: _____ Date: _____

Document approved by: _____ Date: _____

QCLF TTI Certificate of Analysis Rev. 4

VVM testing

VVMs are generally tested in water baths since they provide much better temperature control. The temperature of the water bath and/or the incubator is maintained at the target mean kinetic temperature (MKT) within a tolerance of ±0.2°C. This temperature requirement is verified by test environment validation or with an array of temperature sensors around the test sample area. The temperature of the water bath is monitored at least every 15 minutes (if an incubator is used, temperature monitoring is done at least every minute). Since VVM samples are sensitive to light, the tests are done under no-light conditions. For this reason, sample VVMs are sealed in waterproof aluminum pouches.

VVMs in sealed pouches transferred to water baths in metal cages to sink

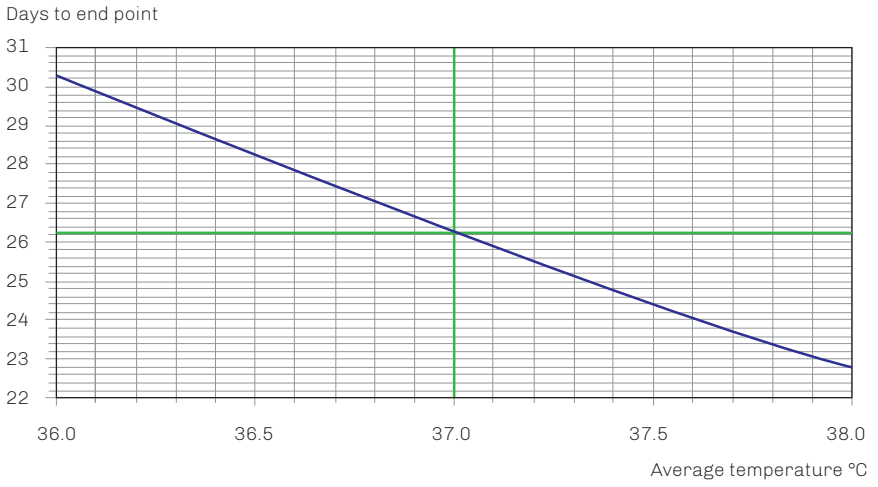
Allowable ranges of OD difference between the reference and the indicator areas at the specified time-to-end point is given in the following table. It should be noted that the cyan mode is measured with the spectrodensitometer.

Allowable ranges of R-I at the specified time to end-point (cyan mode measured)				
VVM type	**Primary limits: ±1°C measured at 37°C/55°C (including overall uncertainty)**		**Secondary limits: ±1.5°C measured at 37°C/55°C (including overall uncertainty)**	
	Lower limit AQL = 5%	**Upper limit AQL = 5%**	**Lower limit AQL = 0.1%**	**Upper limit AQL = 0.1%**
VVM30	-0.19	0.03	-0.23	0.06
VVM14	-0.15	0.03	-0.18	0.06
VVM11	-0.13	0.03	-0.16	0.05
VVM7	-0.11	0.03	-0.13	0.05
VVM2	-0.09	0.03	-0.10	0.04
VVM250	-0.10	0.03	-0.12	0.05

AQL = acceptance quality limit

The expected total uncertainty for measuring the difference between the OD of the reference and active surfaces is ±0.03. The measurement uncertainty for a single measurement is ±0.02. Major sources of uncertainty are instrument error both for the reference and active surfaces, repeatability, and variation in end-point caused by an allowed temperature tolerance of ±0.2°C in the temperature bath. This temperature control is extremely critical in water baths, because, for example, if the temperature variation is 0.5°C, this will skew the days to end-point by approximately 2 days.

Temperature dependency of VVM30



VVM integrity and location

VVM resists removal from the vaccine vial to the same degree as a label meeting current vaccine labeling requirement. In this respect, before a vaccine vial or ampoule is opened for use, the VVM should not be removable. One other requirement for VVM integrity is that the VVM should remain intact after soaking in water for 8 hours, and the OD of water-exposed samples should conform to within ±0.4 or ±10% of initial (R-I) whichever is greater.

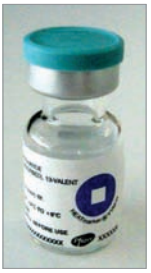
The positioning of the VVM on the vial depends upon whether the vaccine must be discarded at the end of the immunization session in which it is opened, or whether any remaining doses in an opened vial can be used in subsequent sessions. In this sense, the location of the VVM is directly linked with the WHO's MDVP requirements, VVM being the visual cue. This is explained in detail in the WHO/PQS VVM product specifications:

- *For multi-dose vials containing a vaccine that can be used in subsequent sessions: Regardless of the vaccine presentation (liquid, freeze-dried or two vial combinations of liquid and freeze-dried), the VVM must be permanently attached to the label of the vaccine vial and must remain readily observable before, during, and after use, until the entire contents of the vial have been used.*
- *For vaccines that must be discarded at the end of the session or within 6 hours, whichever comes first: The VVM must be attached to the vaccine vial or ampule and must remain readily observable until the vial or ampule is opened, but not observable after opening. In order to achieve this requirement, the VVM must be located on the flip-off top of a vial or on the neck of an ampule.*
- *On a product by product basis, WHO will advise both the vaccine and the VVM manufacturer where the VVM is to be located. Locating the VVM on the bottom of a vial or ampule is never acceptable – it must always be in a visible location.*

VVM applications

The proper adhesion of the VVM onto the designated place on a vial or ampoule is the responsibility of the vaccine manufacturer. To ensure this the vaccine manufacturer should conduct studies if necessary since the surfaces to which the VVMs are applied can vary.

VVM application surfaces

				
Glass (neck of an ampoule)	Vial labels	Plastic containers (for which permeation of adhesive components is not a risk)	Foil pouches	Vial cap (smooth, flat plastic surfaces, no embossed, recessed areas or ridges)

As for plastic containers, there are also vaccines in attached tubes that come as a conjoined strip. Each tube can be removed from the strip in two different ways. In the first example, when a tube is broken off the strip, it still remains unopened. In such presentations, each tube requires a VVM as is the case with the oral cholera vaccine produced by EuBiologics Co. Ltd., South Korea. In the second example, where the tube is broken away from the plastic conjoined strip, it is opened (and must be administered immediately). In this design, one VVM is applied to the holding section of the conjoined strip, which remains until the very last tube is broken away, as is the case with new design of monodose Rotarix by GSK.

Conjoined strips of vaccine tubes

Do users read VVM correctly?

Although the validation and quality related studies are conducted with the use of densitometer readings, VVMs in practice (i.e. in the field) are evaluated visually. In this evaluation, the color of the active surface (the square) is compared to color of the outer reference circle, and vaccine is usable if the active surface color is lighter than the color of the outer reference circle. The VVM is considered as having reached its end-point when the two colors match and from this time onwards the vaccine should not be used. WHO/PQS VVM product specifications indicate that the VVM color change must be monochromatic in its response to cumulative time-temperature exposure within the limits of the allowed color variation. It is also required that the observer must be able to distinguish between an unchanged indicator, and intermediate color change and the end-point of the indicator.

The WHO/PQS independent type testing protocol requires an observer perception test. In this test, 15 VVM samples are attached to 2 ml empty vials (5 of them at start-point, 5 of them at approximately 50% color change to end-point, and 5 at the end-point). They are put in random order and five untrained observers are asked to work independently under tungsten or fluorescent light at 100 lux on the working plane, and sort the vaccine vials into three groups with 100% accuracy. One can imagine that this is not a particularly difficult exercise which only becomes challenging when the color change is close to the end-point and the user has to correctly identify the usable and unusable ones.

VVM is not a potency indicator. Therefore, it does not directly measure vaccine potency but, instead, gives information about the main factor that affects potency: heat exposure over a period of time. When it comes to the assignment of VVM categories, vaccine stability data is provided only up to defined limits. For example, in the case of OPV vaccine, in addition to 5°C, WHO receives data at 37°C only for 48 hours, showing that vaccines conform to the release specifications. No data is available beyond these defined periods. In reality, vaccine potency does not go precipitously bad beyond 48 hours. This is similar to the establishment of expiry dates - vaccine potency does not abruptly drop the day after the expiration date. However, expiry dates for vaccines are based on a decision relating to the level of risk that is acceptable when setting a rigid cutoff for what is actually a gradual waning of potency. In reality, potency remains acceptable well beyond the expiration date.

In statistical terms, this cut-off point is not a juncture that signifies a dichotomous good/bad, positive/negative level of potency. Because of this, stability tests conducted only in defined periods cannot be considered as a “golden test” for comparing VVM reactions in order to evaluate “false negatives”. Designed as an early warning signal, all VVMs, including the VVM2 used on OPV, are designed to

reach their end-point early, in order to avoid using vaccine that would potentially not be potent.

VVM is designed to match the given stability data as an early warning so health workers can take managerial decisions to consume the most heat-exposed vaccines first and to take appropriate corrective actions in their supply chain systems. Where vaccine management practices are optimal, vaccines with VVMs indicating heat exposure (but before their end points) will have been used first and corrective actions taken, thus preventing heat damaged vaccine reaching vaccinee candidates at the periphery.

Visual VVM readings can also be successfully carried out by health workers that exhibit color vision deficiency (commonly called color blindness). The below table illustrates how different stages of VVMs are seen by persons with different color vision deficiencies.

How color vision deficient health workers see VVMs

Type of color vision deficiency	How VVMs are seen
Normal view (no deficiency)	
Rad weak - Protanomaly	
Green weak - Deuteranomaly	
Blue weak – Tritanomaly	
Red blind – Protanopia	
Green blind - Deuteranopia	
Blue blind - Tritanopia	
Monochromacy - Achromatopsia	
Blue cone monochromacy	

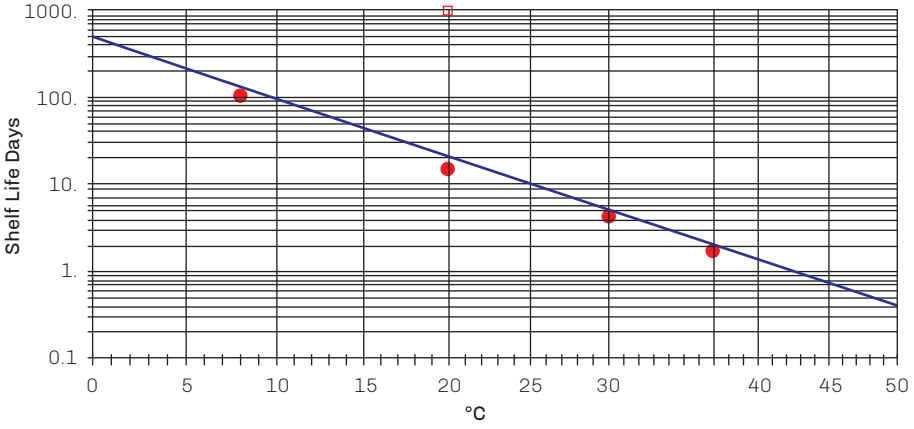
Since the visual reading is based on the comparison of the active surface to the outer reference circle, the distortion in colors are all proportional and therefore color-blind health workers are able to successfully read the VVMs.

Correlation between vaccine potency and VVM reaction

The well-known 1997 NIBSC correlation study of the VVMs with vaccine (OPV) showed that there was good correlation between vaccine potency and VVM color change for vaccines produced by all four manufacturers that were supplying OPV to UN procurement agencies. The conclusions of the NIBSC correlation study also included the fact that a simple visual inspection of VVMs against the standard scale that measures change in color is a realistic test for widespread application.

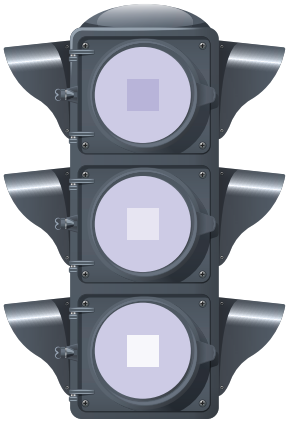
In fact, the very first study of VVM reaction and stability data comes from 1992, an early PATH-funded report by Strasburger and Siegel, in which sets of 12 VVMs were each stored at 8°C, 20°C, 30°C, and 37°C and observed for end-point conversion at 20 equally-spaced time-points within and somewhat beyond the expected conversion time. When an unspecified measure of central tendency of the time until endpoint conversion of the 12 VVMs observed at each temperature are plotted in a graph, plot of shelf life versus temperature, and these four points are compared to the log degradation curve between two points of the VVM2 specification (2 days at +37°C and 225 days at +5°C), we reach the conclusion that VVM2 reaction occurs as defined in the stability studies.

Perfect match of OPV potency and VVM reaction
by Strasburger and Siegel, 1992



The most recent study on OPV and VVM comes from Chad on assessing the potency of mOPV3 kept outside of the cold chain during a national immunization campaign (S. Zipursky et al. (2011), *Assessing the potency of oral polio vaccine kept outside of the cold chain during a national immunization campaign in Chad.* Vaccine, 29:5652-5656). This study is the first systematic documentation of potency of mOPV3 kept at ambient temperatures during a polio immunization campaign. During the study test vials were exposed to temperatures up to 47.1°C, and kept outside of the 2-8°C range for a maximum of 86.9 hours. Post campaign laboratory testing confirmed that vaccines were still potent and in conformity with the defined release specifications. All twenty vials tested at the laboratory fell within the batch release specifications for monovalent OPV type 3 of $10^{5.80}$ CCID50/dose, with a confidence interval lower or equal to ±0.3 log CCID50 (p = 0.95) for the estimated virus concentration of the reference preparation for the three replicates combined. The vials ranged in potency from $10^{5.60}$ CCID50 to $10^{6.40}$ CCID50/dose. 17 of the vials tested above at $10^{5.80}$ CCID50/dose, 2 tested at $10^{5.80}$ CCID50/dose, and 1 tested at $10^{5.60}$ CCID50/dose, which although below the specification of $10^{5.80}$ CCID50/dose, when considered with the CI of ±0.3 log cannot conclusively be determined to be outside the acceptable limits of the release specification or as lacking the potency to result in seroconversion. These results matched with VVMs reaching their endpoint in six vials.

Vaccine wastage and VVMs



Routine vaccine wastage data at countries is not gathered and examined, therefore it is not possible to see what really contributes to the wastage levels. There are two field studies (unpublished) confirming extremely low vaccine wastage as a result of VVM monitoring.

Vaccine wastage rates were monitored through 40-sentinel surveillance sites in Malawi in 2004-2005, with the OPV wastage rate found to be ranging from 5% to 16% throughout the year. Over 99% of this wastage came from opened vials. Less than 1% of vials were discarded unopened, where expiry, breakage and missing inventory were the principal reasons. There was not a single vial discarded due to VVM indication.

A second unpublished study comes from Uttar-Pradesh in 2003, which showed 24% wastage during campaigns. By far the bulk of the wastage was simply due to vials not being returned. Wastage due to VVM indication represented 7% (45/643) of the returned vials. 7% of 24% wasted represents about 1.5% wastage due to VVM indication.

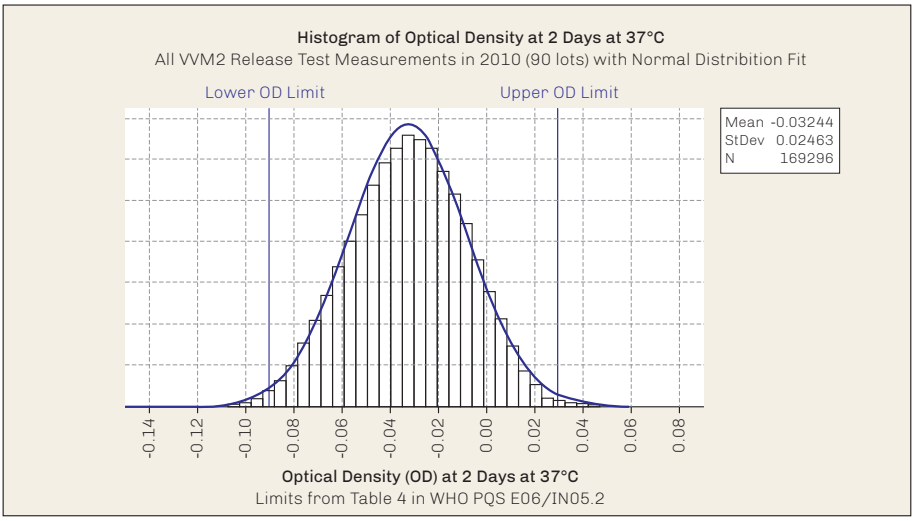
VVM is a predictable reaction

VVM reaction is a predictable reaction and any scenario can be mathematically calculated. This has been verified by the clearance provided by the USFDA 510(K) pre-market notification (15 August 2007, registry no. K063759). *"The importance of the 510(K) clearance by the USFDA confirms that HEATmarker TTI technology changes color in a predictable manner when exposed to cumulative temperature exposure and the indicators follow the Arrhenius relationship regarding time and temperature exposure"* says Ted Prusik, *"The TTI demonstrates whether the medical device to which it is affixed has been exposed to a quantity of heat characterized by a specified time-temperature profile."* This review and acceptance by the FDA for the diacetylene technology as a time-temperature sensitive indicator provides assurance that the indicators behave in a predictable manner over a wide range of time and temperature exposures as covered in the clearance.

Device Classification Name	Indicator, Physical/Chemical, Storage Temperature
510(K) Number	K063759
Device Name	HEATMARKER TIME TEMPERATURE INDICATOR
Applicant	TEMPTIME CORPORATION 116 AMERICAN ROAD Morris Plains, NJ 07950
Correspondent Contact	Richard Phillips
Regulation Number	880.2800
Classification Product Code	OCI
Date Received	12/19/2006
Decision Date	08/15/2007
Decision	Substantially Equvalent (SESE)
Regulation Medical Specialty	General Hospital
510k Review Panel	General Hospital
Summary	Summary
Type	Treditional
Reviewed By Third Party	No
Combination Product	No

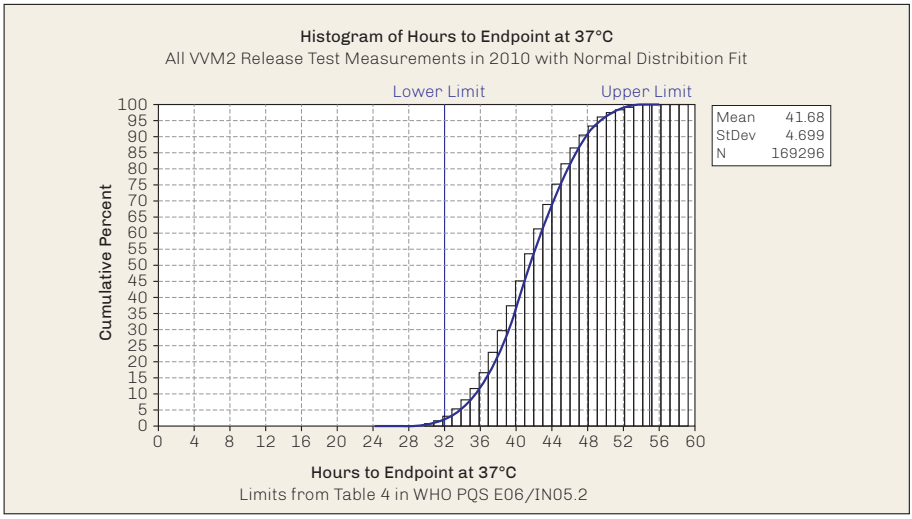
Low-variance

The following two graphs are developed based on 169,296 VVM2 readings sampled from 90 lots produced in 2010 by Temptime Corporation. The first graph shows 169,296 data points taken for release of VVM2 after 2 days storage at 37°C



and comparison to specification limits. The tolerance limits include all errors as defined in the specification.

The second graph shows the data in an integrated form based on first graph on page 198 for the time to reach endpoint at 37°C (cumulative percent).



Coefficient of variation (also known as unitized risk) is a normalized measure of "dispersion" of a probability distribution and is used widely in probability theory and statistics. Coefficient variation (CV) of VVM2 reaction at 37°C from the first graph is calculated to be 0.75. Any CV that is <1.0 is statistically considered low-variance.

Conclusion

VVM is the only tool that is available throughout the entire process of distribution and at the time a vaccine is administered that indicates whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged. It provides a clear, unequivocal signal to health work-

ers as to whether a vaccine can be safely used. With its established science and the clearance by the USFDA with 510(K) approval, VVM reaction is a predictable reaction and any scenario can be mathematically calculated. Since its introduction in 1996, more than 8 billion units have been used successfully, saving millions of U.S. dollars and millions of young lives.

VVM induced vaccine management policies

Amongst all the temperature monitoring devices and tools, VVM is the only one that has dramatically changed the course of vaccine management practices as well as shaped the future of the cold chain. 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.

Multi-dose vial policy and VVM

The concept of "open-vial policy" was first introduced in 1995,[30] and after several revisions, it is now known as the "multi-dose vial policy". In its first version, WHO announced that sufficient data had been collected on the safety and potency of vaccines recommended for use in immunization services to warrant a change in the organization's policy on the use of multi-dose vials of vaccine. The intent of this policy statement was to emphasize the safe use of opened multi-dose vials of vaccine. It was a policy revision that had the potential to reduce vaccine wastage rates by up to 30%, resulting in annual savings worldwide of $40 million in vaccine costs.

30 WHO. (1995) *WHO policy statement: The use of opened vials of vaccine in subsequent immunization sessions,* WHO/EPI/LHIS/95.01

At the time of the policy change, the prevailing EPI policy stated that all vaccine vials which had been opened for an immunization session had to be discarded at the end of the session, regardless of the type of vaccine or the number of doses remaining in the vial. The revised WHO policy applied only to vaccines which met WHO requirements for potency and temperature stability, that were packaged according to ISO standards, and that contained an appropriate concentration of preservative, such as thiomersal (injectable vaccines only).[31]

The revised policy stated that for opened vials of OPV, DTP, TT, DT and hepatitis B vaccines could be used in subsequent immunization sessions until the arrival of a new shipment of vaccines, provided that the vial expiry date had not been passed, and the vaccines had been stored under appropriate cold chain conditions (0°C to 8°C). Any opened vials of vaccine which had been taken outside of the health centre for immunization activities (e.g. outreach, NIDs) had to be discarded at the end of the day. The policy indicated that opened vials of measles, yellow fever and BCG vaccines were to be discarded at the end of each immunization session. In addition, further warnings were issued to the effect that if sterile procedures had not been fully observed, if there was even a suspicion that the open vial had been contaminated, or if there was visible evidence of contamination, such as a change in appearance, floating particles, etc., an open vial had to be discarded immediately.

Although VVMs were not directly mentioned as part of the conditions of the policy application, the policy statement mentioned that linking the policy change to vials which are supplied with a VVM might simplify the introduction of the new policy and the associated training tasks. The policy further elaborated that *"In problem areas where implementation of the new policy might increase the risk of heat-damaged vaccines being administered, managers may choose to delay introduction of the policy until such time as vials are being supplied with VVMs."*

The policy was revised in 2000 and published with the same title.[32] The revised policy indicated a specified time frame of four weeks for the use of opened multi-dose vials for subsequent immunization sessions. In addition, the conditions were changed as follows, this time including VVMs among the conditions.

- *The expiry date has not passed;*
- *The vaccines are stored under appropriate cold chain conditions;*
- *The vaccine vial septum has not been submerged in water*
- *Aseptic technique has been used to withdraw all doses;*
- *The vaccine vial monitor (VVM), if attached, has not reached the discard-point.*

31 Vaccines supplied via UNICEF met all these requirements.
32 WHO/V&B/00.09

The recommendations for the handling of vaccines that must be reconstituted remained the same with the only clarification being that the vials of these vaccines must be discarded at the end of the session or at the end of six hours, whichever comes first. The change of the time limit for liquid injectable vaccines was made in this policy for managerial reasons only. The imposition of any time limits of less than four weeks, nationally or sub-nationally, according to the interval between immunization sessions and the average number of children immunized at a session, were left to the discretion of Member States.

The most recent change to the policy were made in 2014 including a change of title to "Multi-Dose Vial Policy (MDVP)[33]". In this revision, some quite comprehensive changes were introduced.

Multi-dose vial policy

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 for up to 28 days after opening. The criteria are as follows.

1. The vaccine is currently prequalified by WHO.
2. The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO.*
3. The expiry date of the vaccine has not passed.
4. 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.

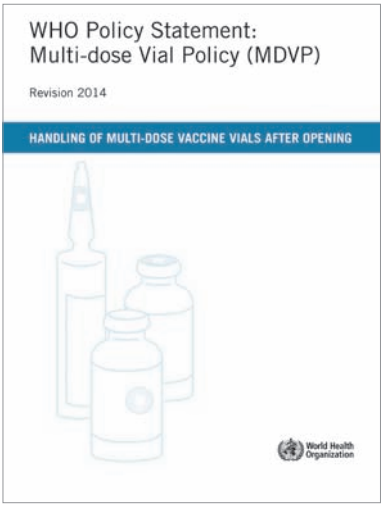
For vaccines that are not prequalified by WHO, independent determinations on preservative efficacy, sterility, presentation and stability may not have been made by a functional national regulatory authority. Consequently, this could mean that the vaccine does not meet the WHO requirements on safety and efficacy, which form the minimum recommended standard for keeping multi-dose vaccine vials opened for more than six hours. Therefore, WHO recommends using non-WHO-prequalified vaccines as soon as possible after opening, and

33 WHO. (2014) *WHO Policy Statement - Multi-dose vial policy (MDVP): Handling of multi-dose vaccine vials after opening.* WHO/IVB/14.07

respecting the time limit for using opened vials as indicated by the manufacturer's instructions in the package insert. If this information is not indicated in the package insert, WHO recommends discarding all non-WHO-prequalified vaccine products within six hours after opening or at the end of the immunization session, whichever comes first.

* Consult each individual vaccine product sheet at the WHO prequalification website, referencing the description "Handling of opened multi-dose vials" https://bit.ly/2KLgk7B

You may be surprised and wondering what has happened to the VVM reference in the MDVP. Although VVM is not specifically mentioned in the main policy points, the status of VVM was greatly reinforced by the new MDVP. This perspective is outlined further in the policy for safe implementation of the MDVP. But let's first visit the reasons that led WHO to introduce such dramatic changes.



With the steady increase in vaccine prices, wastage was becoming a growing concern for many immunization programmes. It was therefore important to ensure that countries could access information on which multi-dose vials of vaccines could be kept open for extended periods of time in order to minimize vaccine wastage while at the same time ensuring vaccine safety. The 2000 policy statement separated vaccines by type and specified that liquid vaccines could be kept open for re-use for up to four weeks, while lyophilized vaccines were to be discarded at the end of each immunization session or six hours after opening, whichever came first. By this time many new vaccines had been developed and many of them were already incorporated into EPI programmes. So, by the time of the 2014 policy revision, the WHO prequalification list of vaccines contained more than 30 types of vaccines, comprising over 120 different products. Due to the peculiarities of these new vaccine formulations, it was not possible to fit all vaccines into the simple categorization of "liquid = keep for four weeks" or "lyophilized = discard within six hours". The prequalified vaccines list had liquid vaccines in presentations of greater than one dose that did not contain preservatives, and ones that did contain preservatives but which did not meet the required standard of preservative efficacy (keeping these vaccines for four weeks was too risky from a bacterial growth perspective). Now, the reference for such information was included in the product pages that appeared on the

WHO website for prequalified vaccine products, with a special section referring to "Handling of opened multi-dose vials". The same information was also given in the WHO-approved package inserts for all prequalified vaccines. For example, Human Papillomavirus (bivalent) vaccine Cervarix® from GSK is a 2-dose liquid presentation and does not include any preservative. The product page on the WHO website indicates that opened vials of this vaccine must be discarded six hours after opening or at the end of the immunization session, whichever comes first.

By the time of the policy change, WHO was also engaged in developing a visual cue for MDVP for inclusion in the vial label. This kept the Immunization Practices Advisory Committee (IPAC) pretty busy. Several designs were developed and field tested.

Proposed visual cues for MDVP

To be used for vials that should be discarded within 6 hours of being opened.

To be used for vaccine vials that may be kept open under specific conditions for 28 days and used in subsequent sessions.

For me, this was a wasted effort. First of all, vaccine labels had very limited space available for any new signalization. Secondly, these icons were going to be extremely small on printed labels. Thirdly, and most importantly, we already had a visual indicator: VVM. All we needed to do was to explain this new role of VVM to all health workers. WHO did not listen to this argument; they wanted to pursue graphical icons and test them in the field. However, after they had conducted field trials with potential indicators in Uganda, Cambodia and Peru WHO finally decided to drop the idea and turn to VVM (it took WHO more than a year to do this). VVM placement on vaccine vials/ampoules proved an excellent reference for health workers to tell whether MDVP with 28-days applied to a particular type or that the vaccine needed to be discarded within six hours. And, the new MDVP policy confirmed and recommended VVM as a visual cue. It was quite simple. Vaccines with VVMs on the label could to be kept for subsequent immunization sessions for up to 28 days. Vaccines with any other placement of the VVM other than the label (e.g. on the neck of an ampoule, or on the cap) were to be discarded in six hours or at the end of the session, whichever came first.

Let's go back to our example of Human Papillomavirus (bivalent) vaccine. Cervarix from GSK is a 2-dose liquid presentation, and opened vials of this vaccine should be discarded six hours after opening or at the end of the immunization session, whichever comes first. I am sure you have already guessed where the VVM

is located on the vial: on the cap. So, a multi-dose liquid vaccine with a VVM on the cap means that it must be discarded within six hours after opening. This is how the VVM as a visual cue is explained in the most recent MDVP policy:

How to implement the MDVP policy safely

Use of visual triggers

A VVM can be found on nearly all vaccine vials supplied to national immunization programmes and procured through UNICEF. The WHO vaccine prequalification programme has worked with vaccine manufacturers to define VVM placement guidelines so that the VVM, if attached to the vial, can serve as a visual trigger to assist a health worker in properly applying the MDVP. There are two different locations for VVMs and each is associated with specific guidance for handling opened multi-dose vials of vaccine.

1. WHO-prequalified vaccines where the VVM, if attached, is on the label of the vaccine. The vaccine vial, once opened, can be kept for subsequent immunization sessions for up to 28 days, regardless of the formulation of the product (liquid or lyophilized).
2. WHO-prequalified vaccines where the VVM is attached in a different location than on the label (e.g. cap or neck of ampoule). In this instance, the vaccine vial, once opened, must be discarded at the end of the immunization session or within six hours of opening, whichever comes first. This is regardless of the formulation of the product (liquid or lyophilized) and would apply, for example, to a reconstituted product of which the vaccine vial cap, which has a VVM attached, has been discarded after opening.

WHO/PQS VVM specifications (WHO/PQS/E006/IN05.3) under the "integrity and location of VVMs" section now indicates the following:

4.0.8 Integrity and location of VVMs:

(...)

The location of the VVM on the vial depends upon whether the vaccine must be discarded at the end of the immunization session in which it is opened, or whether any remaining contents in an opened vial can be retained for use in subsequent sessions. The following cases apply:

For multi-dose vials containing a vaccine that can be used in subsequent sessions: Regardless of the vaccine presentation (liquid, freeze-dried or two vial combinations of liquid and freeze-dried), the VVM must be permanently attached to the label of the vaccine vial and must remain readily observable before, during, and after use, until the entire contents of the vial have been used.

For vaccines that must be discarded at the end of the session or within 6 hours, whichever comes first: The VVM must be attached to the vaccine vial or ampule and must remain readily observable until the vial or ampule is opened, but not observable after opening. In order to achieve this requirement, the VVM must be located on the flip-off top of a vial or on the neck of an ampule.

On a product by product basis, WHO will advise both the vaccine and the VVM manufacturer where the VVM is to be located. Locating the VVM on the bottom of a vial or ampule is never acceptable – it must always be in a visible location.

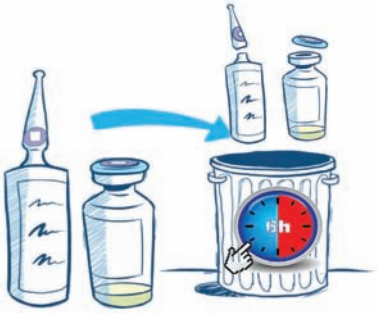
Here is an example from how Albania immunization programme effectively uses the new MDVP. All health workers are trained on the visual cue role of the VVM for MDVP implementation.

Things are simple for them. If the VVM is located on the label, when they open the multi-dose vials of vaccines such as Td vaccine, they write down the opening date on the label as a reminder to them so they keep it only for 28 days.

Any other vaccine having the VVM located on the vial cap or on the neck of the ampoule, regardless of the vaccine being liquid or freeze dried, are kept only for six hours. This particular Td vaccine multi-dose vial was opened on 9 March 2019, and will be kept until 6 April 2019.

10-dose Tetadif (Td vaccine) marked with the opening date to observe MDVP, Tirana, Albania

The Albania immunization programme also prepared posters as reminders to health workers on the role of VVM as visual indicator of correct MDVP implementation.



NESE MONITORI I FLAKONIT TE VAKSINES (VVM) ESHTE I VENDOSUR NE KAPAKUN APO MAJEN E AMPULES:

VAKSINA DO TE MBAHET DERI 6 ORE PAS HAPJES E ME PAS DUHET TE HIDHET

Doza e dytë në flakonin e vaksinës së penumokokut mbahet vetëm 6 orë pas hapjes. Monitori VVM ndodhet mbi kapak.

NESE MONITORI I FLAKONIT TE VAKSINES (VVM) ESHTE I VENDOSUR NE ETIKETEN E FLAKONIT : VAKSINA DO TE RUHET PER 28 DITE NE TEMPERATURAT +2 +8^{0}C DHE NE FLAKON SHENOHET DATA E HAPJES.

Managing stocks with VVM

One of the basic rules of inventory management relates to the concept of "first-in-first-out (FIFO)". In FIFO management, material requirements are serviced in the order of items with the date of entry or acquisition. FIFO does not consider the expiry date of the product; it assumes that the expiry date of the last arrival of a product will have a longer expiry date compared to earlier arrival of the same product - which is not always the case. Because of this and with the increasing complexity of supply arrangements EEFO (earliest expiry, first out) is now the preferred way to manage stocks.

However, with the advent of VVM the managing of stocks based on EEFO or earliest expiry date has changed. In the cases of vaccines having darker VVMs (meaning that they have been exposed to higher temperatures – but are still usable) the VVM reading overrules the EEFO principle and best practice dictates

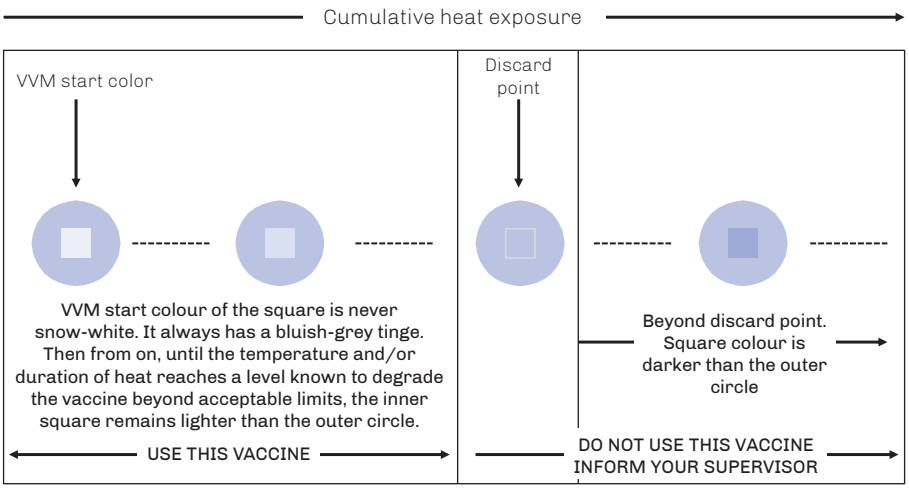
that vials with darker VVMs must be dispatched or used first regardless of the expiry date shown. In this scenario you may be using vaccines with a later expiry in advance of ones with an earlier expiry. Otherwise, the VVM on a particular vaccine vials may indicate a product discard before it has been used.

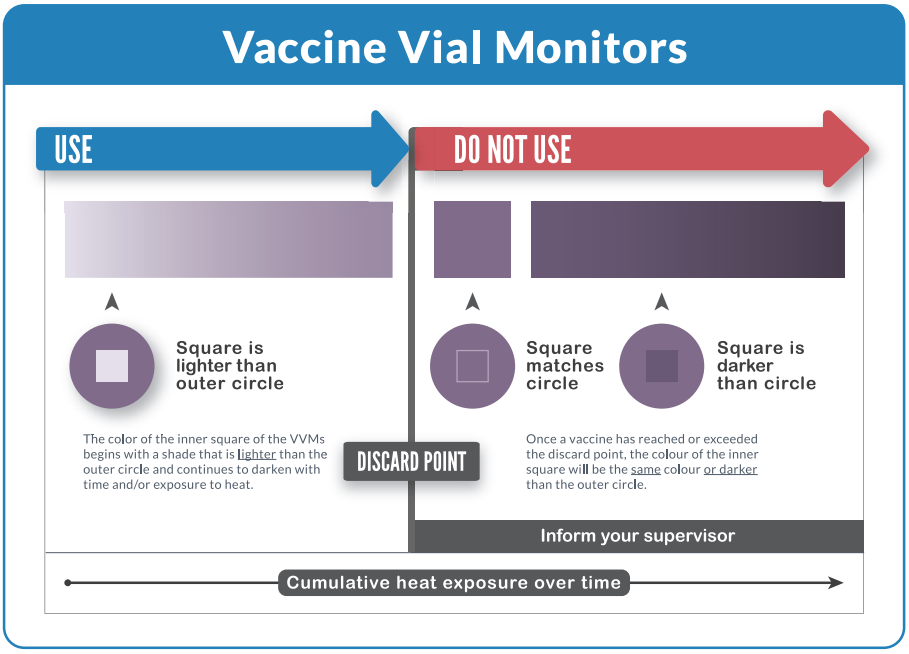
This principle facilitates stocks to be rotated based on a combination of EEFO and VVM readings, resulting in reducing vaccine wastage, as well as prioritizing vaccines based on their temperature excursion history.

The immunization programme in Albania gives us another excellent example. In this case an electronic immunization registry indicates the expiry period of the vaccines as well as the VVM status. When stage 2 is indicated in the registry, even though there may be batches from the same vaccine with an earlier expiry date showing stage 1 VVM, the stage 2 VVM vaccines automatically go to the top of the usage list.

Here it is worth explaining the logic behind the staging of the VVM reaction. In principle, VVM color change is a "continuous" process. The combined effects of time and temperature cause the inner square (active surface) of the VVM to darken gradually and irreversibly. The rate of color change increases with temperature. The inner square is initially lighter in color than the outer circle (but the inner square is never white). It remains so until the temperature and/or the duration of heat reaches a level that is likely to degrade the vaccine beyond the acceptable limit. The inner square continues to darken as heat exposure continues, until it is much darker than the outer circle. If the inner square becomes as dark as or darker than the outer circle the vial must be discarded. Therefore, the whole interpretation of whether to use the vaccine depends on whether the inner square is lighter than the outer circle. Since VVM color change is a continuous process, all stages that are referred to are fully arbitrary. In reality, there is an almost infinite number of hues between the start-point of the inner square and the discard-point. This was the reason why the four-part VVM "use it -don't use it" image was changed to a three-part VVM image recently.

When it comes to recording the status of the VVM for record-keeping purposes at storage and health facilities, you need to somehow be able to differentiate, as objectively as possible, lighter and darker VVMs in the stock. Since everything is based on visual readings, staging makes sense in order to identify VVMs that are usable. In a continuous scale between of the starting point and the end-point, stage 2 would correspond to 50% shade of the outer circle being in the square. Since marking the exact 50% shade level can only be diagnosed with the help of a spectrodensitometer, health workers have developed practical expertise in the good VVM interpretation and what falls under stage 2.





Here is an example of such manual records from the Albania immunization programme.

In this instance, although there is only one batch of DT pediatric and one batch of IPV, here you see how the health centre records look like in #4 Health centre in Tirana, Albania with the VVM status information.

VVM status in immunization registry (last column), Albania EPI

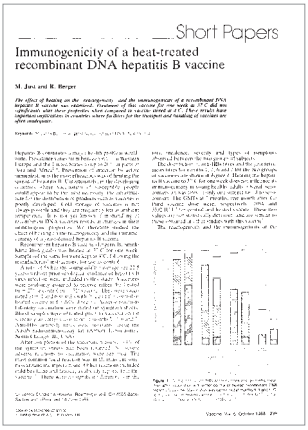
For more details in how managing stocks and dispatch of vaccines can be arranged with the help of VVMs, please refer to the "VVM based vaccine management" chapter on Page 245.

Taking vaccines beyond the 8°C

Building and maintaining a cold chain is an expensive business. *"In lower-income countries, the efforts to meet immunization targets are often hampered by poor health delivery systems, low political commitment, low levels of investment, poorly maintained cold chains, lack of human resources, and effective disease surveillance and reporting systems among other issues"* reports PATH.[34] *"One of the main constraints for lower-income countries to achieve immunization targets is maintaining a cold chain. Based on several studies, explained in more detail in this paper, the introduction of an OCC strategy for heat stable vaccines has the potential for increasing immunization coverage by allowing short term transport of these vaccines OCC. In addition, this strategy may avoid problems with freezing, noted to be one of the primary cold chain problems threatening vaccine integrity. VVMs can be an important tool for monitoring heat exposure when vaccines are taken OCC."*

34 Villadiego S. (2008) Outside of the Cold Chain. Seattle, PATH

Literature has many peer-reviewed articles on the use of vaccines OCC. Although many of the early studies did not have any VVMs included, the results supported the possibility of heat stable vaccines being stored and used at the last mile without any compromise in seroconversion rates. In the end, these studies supported recommendations from WHO for taking vaccines beyond the cold chain in special circumstances as described in their VVM policy statement. Later studies included VVM readings as part of the research protocol. I will summarize these studies here, but before doing so, it is worth underlining the "repeatability" feature of the findings from these studies. When a striking result emerges from a research project, the first question that is usually raised is whether the results are simply the result of chance. The only way to prove otherwise is to demonstrate repeatability of the results by other researchers. In this sense, the studies below should be read with this repeatability feature in mind.


Short Papers

Immunogenicity of a heat-treated recombinant DNA hepatitis B vaccine

M. Just and R. Berger

Just M, Berger R. (1988) Immunogenicity of a heat-treated recombinant DNA hepatitis B vaccine. Vaccine. 6:399-400.

This controlled study compared the anti-HBs response of 58 healthy, HBV- seronegative volunteers (average age 22.5 years, but no other details given). Twenty-seven participants received three 20 mg doses of the yeast-derived Engerix- B vaccine (Smith-Kline Biologicals, Belgium) exposed to a temperature of 37°C for1week, at 0,1 and 6 months; 31 received three doses stored at 4°C according to the same schedule. No serious adverse reactions or between-group differences in side-effects were reported. There was no significant difference in the rates of protection (above 95% for all groups) and geometric mean titres (GMTs) between the groups, and results were similar to other studies of this vaccine.

Van Damme P, Cramm M, Safary A, et al. (1992) Heat stability of a recombinant DNA hepatitis B vaccine. Vaccine. 10:366-367

The effects of antibody response following administration of an HepB vaccine (Engerix-B, SmithKline Beecham Biologicals) that had been stored at elevated temperatures were studied on 138 healthy adults in this clinical trial. They were randomized into three groups to receive the same lot of vaccine stored in three different ways: the first (control) group received vaccine kept at the normal storage temperature (4°C), the second group received vaccine heated at 45°C for 1 week, and the third group received vaccine heated at 37°C for 1 month. Blood anal-

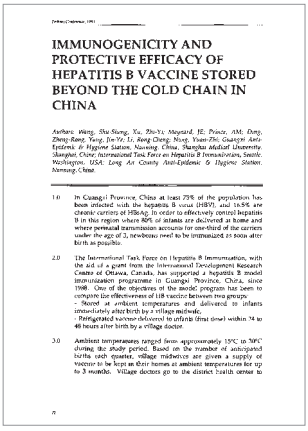
ysis were conducted for all subjects prior to vaccination for measurement of anti-HBc, anti-HBs, and HBsAg; and at months 1, 2, 6, 7 and 12 for analysis of antibodies. One month after the three vaccine doses, 95-100% of subjects had seroconverted. Six months after the third vaccination, 97-100% of subjects still had measurable titers of antibodies. There was not a statistically significant difference between the groups receiving heated vaccines versus the control group. The heat-treated vaccine groups did not include a greater frequency, severity, or different type of reaction when compared to the control vaccine group.


Heat stability of a recombinant DNA hepatitis B vaccine

P. Van Damme, M. Clement, A. Safary, P. Vandepapeliere, and A. Meheus

These results show that the reactogenicity and immunogenicity of the vaccine, including its ability to elicit antibody titers considered protective, are not altered by heating at the stated temperatures and durations.

Wang SS, Xu ZY, Maynard JE, et al. (1993) Immunogenicity and protective efficacy of hepatitis B vaccine stored beyond the cold chain in China. Presented at the 1993 TechNet conference

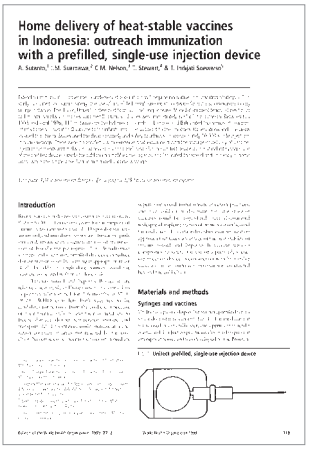

IMMUNOGENICITY AND PROTECTIVE EFFICACY OF HEPATITIS B VACCINE STORED BEYOND THE COLD CHAIN IN CHINA

Authors: Wang, Shu-Xiang, Xu, Zhi-Yi, Maynard, JE, Prince, AM, Dong, Zheng-Rong, Yang, De-Yi, Li, Rong-Dong, Ning, Yuan-Zhi, Guangxi Anti-Epidemic & Hygiene Station, Nanning, China, Shanghai Medical University, Shanghai, China; International Task Force on Hepatitis B Immunization, Seattle, Washington, USA; Long An County Anti-Epidemic & Hygiene Station, Hennago, China.

This study was performed in Long-An county, China and sponsored by China's EPI. The study compared the seroconversion rates of hepatitis B (HepB) vaccine stored and used at room temperature by village midwives and vaccine maintained in cold storage and used by the village doctors. The second and the third doses of the vaccine were given with other EPI vaccines as part of mobile outreach services.

Seroconversion rates of HepB antibodies were measured after the infants had received the three doses of HepB vaccine (in babies who received birth-dose vaccine stored at room temperature versus under refrigeration). Of the study group, 358 infants received their birth-dose from vaccine stored at ambient temperatures and administered by a village midwife, and 232 infants received vaccine stored in refrigerators and administered by a village doctor. The seroconversion rate was 81.6% in the OCC group and 81,9% in the refrigeration group. Maternal HB surface antigen (HBsAg) rates were 15.4% and 20.7% respectively. No difference was found between HBsAg rates amongst vaccinated infants in the OCC (1.1%) and refrigeration groups (2.2%). All HBsAg positive infants were born to HBsAg positive mothers. The estimated protective efficacy of

vaccination[35] was similar at 84.5% and 77.8%, respectively in the two groups. Preliminary findings in this study demonstrated that HepB vaccine stored OCC for up to three months can remain effective and be delivered to infants at birth.


Home delivery of heat-stable vaccines in Indonesia: outreach immunization with a prefilled, single-use injection device

A. Sutanto, I.M. Suarnawa, C.M. Nelson, T. Stewart, & I. Indjadi Soewarso

Introduction

Materials and methods

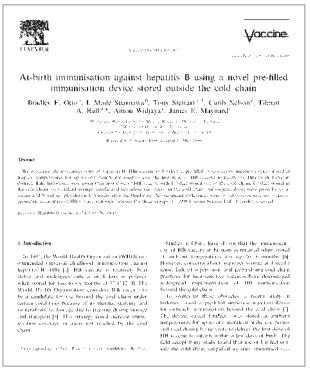
Syringes and vaccines

Uniject prefilled, single-use injection device

Sutanto A, Suarnawa IM, Nelson CM, Stewart T, Soewarso I. (1999) Home delivery of heat–stable vaccines in Indonesia: Outreach immunization with a prefilled, single-use injection device. Bulletin of the World Health Organization. 77(2):119–126

This study evaluated the use of a prefilled, single-use injection device for outreach immunization by village midwives stored at ambient temperatures for up to one month in midwives' homes versus vaccines delivered by standard syringes and kept at refrigerator. Between July 1995 and April 1996, 110 midwives on the Indonesian islands of Lombok and Bali visited the homes of newborn infants to deliver hepatitis B vaccine to the infants and tetanus toxoid to their mothers. Observations and interviews showed that the midwives used the device properly and safely to administer approximately 10,000 sterile injections in home settings. There were no problems with excessive heat exposure during the storage or delivery of vaccine (checked with threshold indicators). Infants received the birth dose of HB vaccine delivered either with a standard syringe and vaccine stored in the cold chain, or with the Uniject device prefilled with vaccine stored for one-month OCC. Seroconversion rates were identical for the two groups.

Injection recipients and midwives expressed a strong preference for the UniJect device over a standard syringe. Use of the prefilled device outside the cold chain simplified the logistics and facilitated the speed and efficiency of home visits, while the single-dose format minimized vaccine wastage.


Vaccine

At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain

Bradley F. Otto, I. Made Suarnawa, Tom Stewart, Carib Nelson, Tilman A. Ruff, Anton Widjaya, James E. Maynard

Abstract

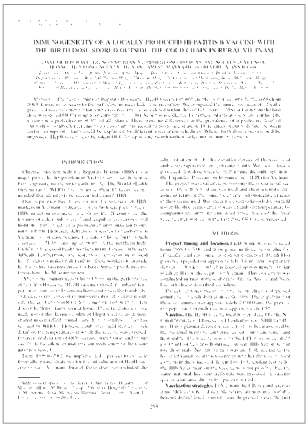
1. Introduction

Otto BF, Suarnawa IM, Steward T, et al. (2000) At-birth immunization against hepatitis B using a novel prefilled immunization device stored outside the cold chain. Vaccine. 18:489-502

This study evaluated the immunogenicity of HB vaccine in UniJect, a pre-filled, non-reusable injection device, stored at tropical temperatures for up to one month and used to give

35 The percent reduction in HBsAg attributable to vaccination amongst infants exposed to hepatitis B virus.

the first dose of HB vaccine to newborns. Infants in Tabanan district, Bali, Indonesia, were given their first dose of HB vaccine with UniJect stored out of the cold chain, UniJect stored in the cold chain; or standard syringe, needle and multidose vial stored in the cold chain. Subsequent doses were given by usual means and blood samples drawn 4±6 weeks after the third dose. No significant differences were found in seroconversion rates or geometric mean titres of HB surface antibody between the three groups.



Hipgrave DB, Huong VM, Tran TN, et al. (2006) Immunogenicity of a locally produced hepatitis B vaccine with the birth dose stored outside the cold chain in rural Vietnam. American Journal of Tropical Medicine and Hygiene. 74(2):225–260

This study compared the immunogenicity of a locally produced vaccine among infants who received three doses stored within the cold chain (n = 358) or for whom the first dose was stored OCC for up to one month (n = 748). Serum was collected from these infants at age 9–18 months. The vaccine was protective in 80.3% of all infants. There were no differences in the prevalence of a protective level of antibody or antibody titer among groups of infants according to storage strategy. Differences in antibody titer between certain groups of infants could be explained by different vaccination schedules. The study concluded that where birth dose coverage will be improved, HepB vaccine can be taken OCC for up to one month without affecting its immunogenicity.

Huong V, Hipgrave D, Hills S, Nelson C, Sy Hien D, Van Cuong N. (2006) Out-of-cold-chain delivery of the HB birth dose in four districts of Vietnam. PATH (Unpublished data)

This study evaluated the coverage, safety, immunogenicity, and logistics of an out-of-cold-chain delivery strategy for the HB vaccine birth dose in areas where the cold chain does not function. Two groups were compared: In the control group, newborns born at district hospitals were vaccinated with HB vaccine stored in the cold chain. Subsequent doses were stored in the cold chain and delivered during regular monthly EPI days at commune health centers. In the out-of-cold-chain group, infants born at commune health centers and at home were vaccinated with

HB vaccine stored at room temperature at commune health facilities. The subsequent doses were stored in the cold chain and delivered during regular monthly EPI days at commune health centers. The single-dose HB vaccine for the birth dose was delivered to the health center twice per month and stored at room temperature in a dark box to protect it from sunlight.

During the 14-month study, over 10,000 children in the four study districts received the birth dose, approximately one-third within the cold chain and two-thirds out of the cold chain.

Compared to a pre-study baseline, on-time birth-dose coverage doubled with the introduction of the out of cold chain strategy. Baseline data was available only for birth doses delivered within three days of birth. Using the three-day definition, baseline coverage was 45%, while study coverage increased to 90% for all children born within the four districts.

Using the out of cold chain approach, health centers were able to achieve the same on-time birth dose coverage as cold chain- equipped hospitals. On-time coverage was 83% for the health center-based out-of-cold-chain group and 82% for the hospital-based in-the-cold-chain group and (no significant difference).

Serology was conducted on children from both groups. The in-the-cold-chain group showed a protective efficacy level of 86% while the out-of-cold-chain group showed a protective efficacy level of 92% ($p<0.001$). This was a surprising finding, although reasons for the higher seroconversion in the out-of-cold-chain group are not clear, the most likely possible scenario could be the freezing of the vaccine in the cold chain group thus resulting in lower seroconversion rates.


Hepatitis B vaccination of newborn infants in rural China: evaluation of a village-based, out-of-cold-chain delivery strategy

Introduction

Wang L, Chen H, Li F, Armstrong G, Nelson C, Ze W, Shapiro C. (2007) Hepatitis B vaccination of newborn infants in rural China: Evaluation of a village- based, out of cold chain delivery strategy. Bulletin of the World Health Organization. 85(9):649–732

Rural townships in three counties in China's Hunan Province were randomized into three groups with different strategies for delivery of the first dose of HepB vaccine. In group 1, vaccine was stored within the cold chain and administered in township hospitals. In group 2, vaccine was stored out of the cold chain in villages and administered by village-based health workers to infants at home. Group 3 used the same strategy as group 2, but vaccine was packaged in a prefilled injection device. Training of immunization providers and public communication conveying the importance of the birth dose was performed for all groups.

Among children born at home, timely administration (within 24 hours after birth) of the first dose of HepB vaccine increased in all groups after the study: group 1, from 2.4% to 25.2%; group 2, from 2.6% to 51.8%; and group 3, from 0.6% to 66.7%; P < 0.001 in each case. No significant difference in antibody response to vaccine was observed between the groups. The study concluded that timely administration of the first dose of HepB vaccine was improved by communication and training activities, and by out-of-cold-chain storage of vaccine and administration at the village level, especially among children born at home.


ScienceDirect

Vaccine

Overcoming the need for a cold chain with conjugated meningococcal Group C vaccine: A controlled, randomized, double-blind study in toddlers on the safety and immunogenicity of Menjugate®, stored at room temperature for 6 months

Schondorf I, Banzhoff A, Nicolay U, Diaz- Mitoma F. (2007) Overcoming the need for a cold chain with conjugated meningococcal group C vaccine: A controlled, randomized, double-blind study in toddlers on the safety and immunogenicity of Menjugate, stored at room temperature for 6 months. Vaccine. 25:1175–1182.

In this study the safety and immunogenicity of a single dose of the conjugated meningococcal Group C vaccine, Menjugate, stored for 6 months at room temperature (25±2°C, N=250) or at 2-8°C (N=250) when administered to 12-23 months toddlers was investigated. In the two respective groups, 87 and 88% of toddlers reached bactericidal antibodies titers of at least 1:8. The immunogenicity of Menjugate stored at room temperature was not inferior to that stored at 2-8°C. The safety profile and immunogenicity of the vaccine was not influenced by the storage condition.

All the studies summarized above did not include VVM. However, the results, naturally have many implications when the VVM steps into the picture. Two following studies using vaccines outside the cold chain included VVM readings and measurements, bringing even stronger encouragement for a new innovative approach WHO would develop in coming years: Controlled temperature chain.


Vaccine

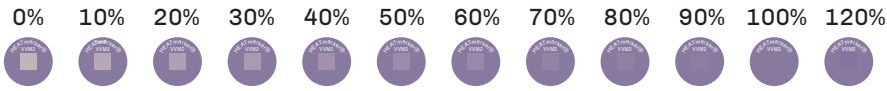
Using oral polio vaccine beyond the cold chain: A feasibility study conducted during the national immunization campaign in Mali

Halm A, Yalcouye I, Kamissoko M, et al. (2010) Using oral polio vaccine beyond the cold chain: A feasibility study conducted during the national immunization campaign in Mali. Vaccine. 28:3467-3472

This study is the first systematic documentation of using OPV out of the cold chain during NID campaigns in Mali. Using a crossover intervention design, vaccinators compared the transport of OPV in vaccine carriers with or with-

out ice packs. Vaccine integrity was assured through monitoring VVM status. Health workers were provided with a special VVM scale showing progression of the darkening with 10% increments.

VVM classification grading color scale provided for the study



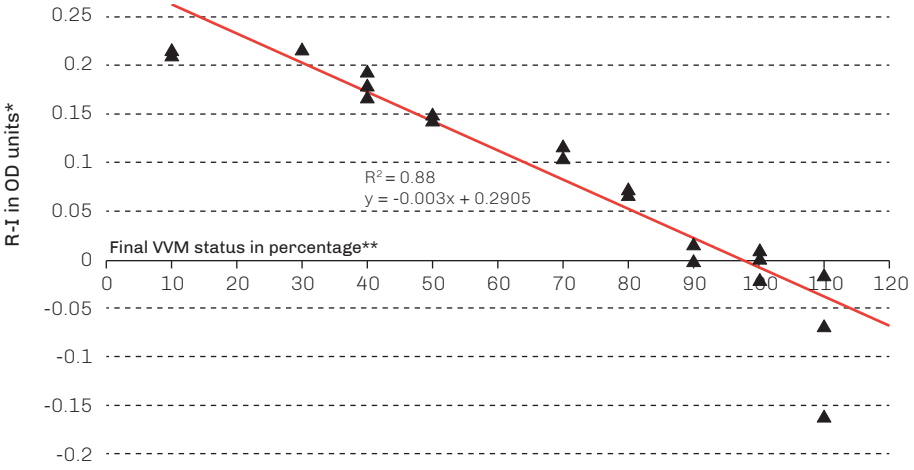
All OPV vials used in the study area, in total 956, were monitored during the study. Most health areas chose to restrict themselves to percentage increments of 20% (0, 20, 40, 60, 80, and 100%) to ease VVM classification. None of the vials used in this NID campaign reached the stage of VVM endpoint at the time of administration. Therefore, no child was given OPV with a VVM that had reached the discard-point. Consequently, there was no loss of vaccine (wastage) due to the vaccine no longer being safe to administer, as measured by the VVM having exceeded the acceptable stage and reached its endpoint. As expected, the VVM progressed through its stages slightly faster during OCC days, which is due to the cumulative higher temperature exposure under those conditions. However, despite this, at the time the last dose was administered, no VVM had surpassed the VVM stage of 60%. Over 90% of vaccinators and supervisors preferred conducting NIDs without ice packs. In addition, using OPV out of the cold chain reduced vaccine wastage resulting from melting ice packs causing labels to detach from the vial. The study also concluded that it is essential that using vaccines outside of the cold chain can only be considered if the vaccine has VVM and if adequate training of the vaccinators precedes the introduction of OCC practices.

Zipursky S, Boulam L, Cheikh DO, et al. (2011) Assessing the potency of oral polio vaccine kept outside of the cold chain during a national immunization campaign in Chad. Vaccine. 29:5652-5656

This study is the first systematic documentation of the potency of monovalent oral polio vaccine type 3 (mOPV3) kept at ambient temperatures during a polio immunization campaign in Chad. During the study test vials were exposed to temperatures of up to 47.1°C, and kept outside of the 2–8°C range for a maximum of 86.9 hours. Post-campaign laboratory testing confirmed that the test vials were still potent, and in conformity with the defined release specifications. Further, the VVMs performed as expected, giving an early warning indication of when cumu-

lative exposure to heat reached levels that may have negatively affected the vaccine's potency.

At the start of the study, the VVM status of all test vials was checked and recorded at the central store in N'djamena. At the end of the first day of vaccination activities, only one of the twenty test vials had a VVM that had reached its end-point. By the end of second day a further five vials had VVMs that had reached their end-point. These readings were conducted visually, based on the percentage scale validated in Mali. Readings conducted in the field by vaccinators were verified upon return to the health care centre, and again upon deposit at the central store and on arrival at the laboratory in Brussels. The vaccinators surveyed indicated they were comfortable administering OPV that had a valid VVM, even if it had been kept at ambient temperatures.



** Difference between the reflection densitometer reading of the reference ring (R) and active indicator surface (I) in optical density (OD) units*
*** Final VVM status visual reading conducted on arrival at the laboratory in Brussels*

Correlation between visual VVM readings and reflection densitometer readings

There was no change in VVM status between the visual classification conducted at the central cold room in N'djamena and upon arrival at the Laboratory in Brussels. These readings were conducted by the same person, without referencing the previous reading. The reflection densitometer readings of the difference between the reference ring and the active surface (indicator) of the VVM highly cor-

related (R^2 = 0.88) to visual readings performed on arrival at the laboratory in Brussels.

This study provided proof-of-concept evidence that certain types of OPV remain potent and thus can be kept, for limited periods of time, as well as administered at ambient temperatures.

WHO recommendations on taking vaccines beyond the cold chain

In 2000, WHO issued its first recommendation on taking vaccines beyond the cold chain with its *"Making the use of vaccine vial monitors: Flexible vaccine management for polio" (WHO/V&B/00.14)* publication.

In 2007, recommendations were expanded beyond the NIDs with the WHO-UNICEF joint policy statement on the implementation of VVMs – the role of VVMs in improving access to immunization. In this policy statement, WHO and UNICEF recommended that all Member States consider the adoption of policies permitting the use of vaccines beyond the cold chain where warranted for routine immunization activities or on a limited basis under special circumstances, such as:

- *National immunization days;*
- *Hard-to-reach geographical areas;*
- *Immunizations provided in the home – including hepatitis B vaccine birth dose;*
- *Cool seasons;*
- *Storage and transportation of freeze-sensitive vaccines where the risk of freezing is greater than the risk of heat exposure.*

Controlled temperature chain

Some of the most useful practical changes are possible when a product insert states that the vaccines can be stored and used for limited periods of time at temperatures above the 2-8°C recommendations. However, without the presence of a VVM, such information can effectively be meaningless simply because health workers at the last mile do not have any means of checking whether vaccines have been maintained within their stability budgets at the upstream levels of the cold chain. The efforts by WHO to allow certain vaccines to be kept at temperatures outside the traditional +2°C to +8°C cold chain for limited periods of time under monitored and controlled conditions has only been possible with VVM.

The "controlled temperature chain" (CTC) is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold for a limited period of time under monitored and controlled conditions.

A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding +40°C and for a specific time immediately prior to administration.

The WHO has established the following programmatic criteria for a vaccine to be labelled for, and used in, a CTC:

1. *The vaccine should be used in a campaign or special strategy setting. CTC is not currently recommended for immunization through routine delivery.*
2. *The vaccine must be able to tolerate ambient temperatures of at least +40°C for a minimum of three days and should be accompanied by:*
   a. *a VVM on each vial, and*
   b. *a peak threshold indicator in each vaccine carrier.*
3. *The vaccine must be licensed for use in a CTC by the relevant regulatory authorities, with a label that specifies the conditions.*

This innovative approach was developed through a series of consultative meetings. In the 4-5 November 2010 IPAC meeting, Michel Zaffran, Senior Advisor at WHO and Director of Project Optimize, presented issues surrounding the use of vaccines in a CTC. "*It is meant to be used in circumstances where it impossible or difficult to maintain a 2°C to 8°C cold chain in the periphery of services, and only to those vaccines that met a number of pre-determined conditions*" said Zaffran, "*Several licensed and future vaccines that are heat stable, some of which are stable at 40°C for at least one to two months and longer. Thus, it was important to explore CTC in order to reach more people, deliver vaccines to the right groups at the right time, reduce or eliminate the risk of freezing, promote more integrated supply chains, and reduce reliance on costly specialized equipment.*"

WHO was considering three inter-linked streams of work to make progress in the CTC area: Vaccines (regulatory pathway), technologies (threshold indicators, etc.), and guidance to countries on how to operationalize CTC at the country level. Zaffran further underscored the importance of addressing this complex issue by mentioning Vietnam's hesitancy in moving to a national policy with the results of their hepatitis B birth dose pilot study, and the logistics involved around the influenza pandemic.

Following discussions on the regulatory, technological and guidance related issues around the CTC, IPAC unanimously endorsed the CTC draft strategy as a roadmap to move forward, and requested that the gaps and issues raised in the meeting be incorporated and addressed in the CTC strategy.

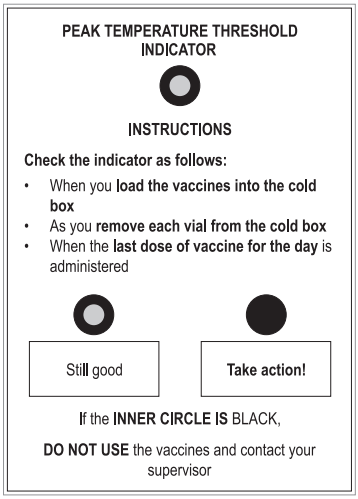
CTC work initially started using hepatitis B vaccine as a pathfinder. However, in-vitro potency data were not entirely predictive of hepatitis B vaccine integrity;

there was no direct correlation with clinical efficacy. It was determined that further data, in addition to in-vitro data, would be needed to demonstrate integrity of the vaccine after high temperature exposure before a license variation could be considered. This resulted in delaying the timing for this work. WHO and Project Optimize estimated that a re-licensed hepatitis B vaccine would not be available before 2014 (by the time of publication of this book, no hepatitis B vaccine has been re-licensed with CTC). In the interim, the meningococcal A vaccine, MenAfriVac™, emerged as a strong candidate for CTC use. As a result, WHO charted the CTC pathway using the meningococcal A vaccine in a campaign setting, while work on hepatitis B vaccine continued.

In the IPAC 2-3 October 2012 meeting, Zaffran reported the groundbreaking progress made with MenAfriVac, to be the first EPI vaccine licensed for use in a CTC. In 2012, the license for Serum Institute of India's Meningitis A vaccine, MenAfriVac, was scheduled for change based on a thorough review of scientific data by regulatory authorities as well as WHO for its use, in a CTC, for a period of up to four days at temperatures of up to 40°C. In addition, after reconstitution, the vaccine would be kept in CTC up to 6 hours, after which it must be discarded. Zaffran expressed his hope that this leap forward would break the cycle of small pilots being used to deliver vaccines out-of-the-cold-chain. This was because, historically, these pilots have not been successful in scaling up due to lack of support from National Regulatory Authorities (NRAs), and subsequently concerns around manufacturer or immunization programme liability. Licensing the use of this vaccine for four days at temperatures up to 40°C set an important precedent for extending the possibility of CTC application to other vaccines.

MenAfriVac received full WHO prequalified and licensed status for use in a CTC in October 2012. Following this, two new products received full licensure and WHO prequalification: pneumococcal conjugate vaccine/PCV (Prevnar 13®, produced by Pfizer, though the labelling has since removed any CTC indications)[36] in early 2015, and human papillomavirus (HPV) vaccine (Gardasil4®, produced by Merck) in mid-2016.

36 Pfizer's Prevnar 13® was approved for use at temperatures up to 40°C for three days. However, this indication was removed in 2016 to allow consistent labelling across Prevnar products (with different presentations/number of doses per vial) and because WHO confirmed that this particular product is not a high priority for CTC, given that it is typically delivered with other vaccines that still require the traditional cold chain.



In addition to VVM, in order to be sure that vaccines have not been exposed to temperatures higher than +40°C, a "peak temperature threshold indicator" must accompany the vaccines at all times when in a CTC to monitor the temperature exposure of the vaccines. This indicator is a card with a sticker which changes color from light grey to black, as soon as the temperature exposure has exceeded +40°C. If this occurs all vaccines in the vaccine carrier concerned have to be discarded, following an appropriate investigation and documentation of the event. Peak temperature threshold indicators do not replace VVMs, as they measure peak exposure, while VVMs measure cumulative exposure to heat. The latter are not capable of indicating short exposures to temperatures higher than accepted by CTC criteria.

Following its prequalification in October 2012, the very first field use of MenAfriVac in a CTC was conducted in December of that year during a campaign in Benin, West Africa allowing the feasibility and acceptability of the practice to be assessed. The CTC was implemented in one selected district, Banikoara (target population of 147,207; 1–29 years of age), across 14 health facilities and 150 villages. The CTC practice was monitored using temperature indicators and daily monitoring sheets. At the end of the campaign a face-to-face survey was conducted to assess vaccinators' and supervisors' experience with CTC.

In the Benin campaign, a mix of strategies were implemented in the field to maximize the benefits from CTC practice, depending on the distance of the population from health centres and the availability of a functioning refrigerator in the health centre. Over the course of the campaign only nine out of approx. 15,000 vials were discarded due to surpassing the 4-day CTC limit and no vial was discarded because of exposure to a temperature higher than 40°C or due to the VVM reaching its endpoint. Overall confidence and perceived usefulness of the CTC approach were very high among vaccinators and supervisors. The study concluded that the vaccinators and supervisors saw clear benefits from the CTC approach in low income settings, especially in hard-to-reach areas and where the cold chain was weak.

In order to track the 4-day CTC of the opened vials, the opened vials were routinely marked with a permanent marker (one line every day) as a visual guide to health workers.

Marked vials of MenAfriVac™ used on day 2 of the CTC implementation

The evaluation of this very first field experience was published in the Vaccine journal.[37] In 2013, WHO published a guideline for immunization programme managers and decision makers to support MenAfriVac in a CTC during campaigns.

A study of the economic benefits of keeping a meningitis A vaccine at or near ambient temperature for up to 4 days during a mass campaign was conducted in Chad. During a 10-day mass vaccination campaign against meningitis A in three regions of Chad in 2011, the costs associated with storage and transport of the vaccine in a traditional cold chain system were evaluated. A mathematical model was used to estimate the savings that could have been achieved if the vaccine had been stored at or near ambient temperature - in a CTC - at the peripheral levels of the supply chain system.

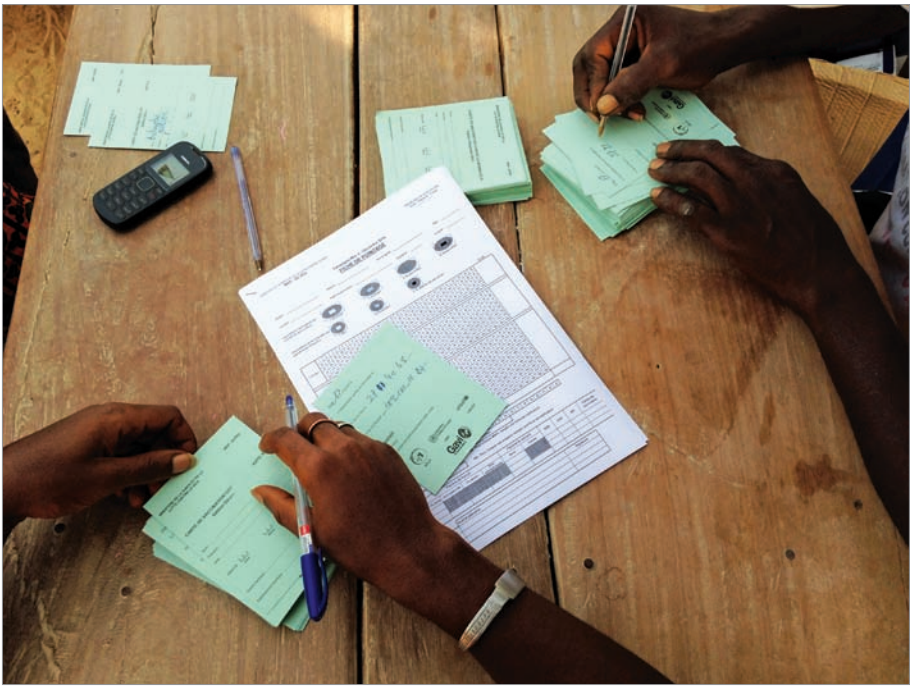
The cost of the cold chain and associated logistics used in the campaign in Chad was $0.24 per person vaccinated. In the modelled scenario for a controlled temperature chain, however, these costs dropped by an estimated 50% to only $0.12 per person vaccinated. The study concluded that the implementation of a "controlled temperature" chain at the most peripheral levels of the supply chain system - assuming no associated loss of vaccine potency, efficacy or safety – could result in major economic benefits and allow vaccine coverage to be extended in low-resource settings.

To supplement the Chad study, during a MenAfriVac campaign, a new study was conducted in Togo to evaluate the economic costs for vaccine logistics when using the CTC approach compared to a full cold chain logistics (CCL) approach.[38] The study was conducted in Togo's Central Region, where two districts used the CTC approach and two relied on a full CCL approach. Data to estimate vaccine logistics costs were obtained from primary data collected using costing questionnaires and from financial cost data from campaign microplans. Average logistics cost per dose was estimated at $0.026±0.032 for facilities using a CTC and

37 Zipursky S, Djingarey MH, Lodjo JC, et al. (2014) benefits of using vaccines out of the cold chin: Delivering Meningitis A vaccine in a controlled temperature chain during the mass immunization campaign in Benin. *Vaccine.* 32:1431-1435

38 Mvundura M, Lydon P, Gueye A, et al. (2017) An economic evaluation of the controlled temperature chain approach for vaccine logistics: evidence from a study conducted during meningitis A vaccine campaign in Togo. *The Pan African Medical Journal* 27 (Supp 3):27

$0.029±0.054 for facilities using the full CCL approach. There was no statistical significance between these two costs. However, if the facilities without refrigerators had not used CTC but had received daily deliveries of vaccines, the average cost per dose would have increased to $0.063 (ranging between $0.007 to $0.33) with larger logistics cost increases occurring for facilities that were in the remoter regions of the district. The study concluded that the CTC approach could reduce logistics costs for remote facilities without a cold chain infrastructure.



Health workers are getting prepared for MenAfriVac campaign in Cote d'Ivoire

The official CTC implementation was scaled up for national campaigns in Mauritania (with knowledge, attitudes and practices study), Côte d'Ivoire, South Sudan and the Democratic Republic of the Congo.

The most comprehensive review of CTC published by Anna-Lea Kahn (WHO), Debbie Kristensen (PATH) and Raja Rao (Bill & Melinda Gates Foundation) summarizes the challenges CTC specifically addresses in the very last miles of the supply chain as follows:[39]

39 Kahn, AL, Kristensen D, Rao R. (2017) Extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines. *Vaccine.* 35:2214-2216

CTC is a risk mitigation strategy

(...)

- Lack of transportation infrastructure, such as navigable roads and sufficiently large vehicles, requiring vaccines to be trans- ported in smaller vaccine carriers and often over arduous terrain by motorcycle, bicycle, or boat, when available, or on foot;
- Lengthy and burdensome preparation of conditioned ice packs to keep vaccines sufficiently cold while also avoiding freezing, which occupies staff time and diverts attention away from routine activities;
- Constraints on time, staff, and equipment that result from maintaining vaccines at appropriate temperatures with ice packs or reliable refrigeration, which incur further staff and transportation costs; and
- New target populations who may not be attuned to the need for immunization or be able to travel to clinical outposts or other vaccine access points.

CTC assumes great importance precisely because of the increased risks the aforementioned challenges pose and the frequency with which they undermine the safe and effective delivery of potent vaccines. Efficiency gains and cost savings also emerge with CTC, in the freeing up of staff time and resources through, for example, the elimination of burdensome journeys to renew ice stocks or condition ice packs - enabling programs to redirect limited resources back to routine immunization services that are often compromised during campaigns. However, CTC is not just an opportunity to alleviate the burdens of health workers at the last mile or a strategy for improving coverage at a reduced cost; CTC is a risk mitigation strategy for filling gaps that cannot fully be addressed with traditional cold chain investments.

The role of CTC in addressing immunization programme needs were summarized in the *"Controlled temperature chain: Strategic roadmap for priority vaccines 2017-2020"* document published by WHO in 2017.

The CTC approach complements supply chain investments and helps overcoming burdens and constraints associated with the last mile of vaccine delivery in a traditional cold

chain. As a result, CTC contributes to increased immunization coverage and equity in low-income countries.

CTC simplifies the logistical requirements and costs for vaccine distribution and extending outreach capabilities by allowing transport and short-term storage of vaccines without ice or refrigeration during the days immediately preceding administration. Since no ice is used, eventually it eliminates the risk of freeze damage for freeze-sensitive vaccines, especially during outreach in vaccine carriers.

A typical vaccine carrier load for a MenAfriVac campaign in Togo

Having no ice in vaccine carriers consequently improves working conditions for vaccinators by reducing weight. Logistics become easier since the need to renew ice packs during long journeys is obviated, and the need to travel to return vaccines into the cold chain after outreach is avoided.

Naturally, CTC raises questions about the use of VVM and the other OCC strategies. Indeed, we may wonder whether WHO continues to recommend the use of vaccines beyond the cold chain under certain circumstances as described in the 2007 WHO-UNICEF policy statement. The answer lays in IPAC's statement on CTC and OCC:

IPAC Statement on Controlled Temperature Chain (CTC) and Out of Cold Chain (OCC) vaccine usage[40]

The WHO Immunization Practices Advisory Committee (IPAC) recommends that countries store, transport and distribute vaccines at temperatures above 8°C only if these products have been licensed for use in a Controlled Temperature Chain (CTC). IPAC further calls for acceleration of vaccine licensing and labelling consistent with CTC usage. The committee recognizes that manufacturers, regulators, national programs and immunization partners consider that on-label indication of temperature storage conditions will enhance communication of correct handling and maintenance of the quality of vaccines above 8°C.

Nevertheless, IPAC recognizes that under special circumstances such as emergency situations, countries may consider delivering certain vaccines out of the cold chain (OCC) for public health benefit especially for otherwise unreachable populations. Should a country choose to use a vaccine OCC, this should only be an interim short-term step while licensure and labelling consistent with CTC is sought for the vaccine. Further, IPAC recommends that countries observe the following five conditions:

- Understand that any associated liability with OCC off-label use must be accepted by the country, irrespective of WHO guidance;
- Apply the OCC strategy only to:
  a) a specific vaccine product, not to a class of vaccine products, where stability data suggest thermostability appropriate to the country's climate. Due caution is necessary with live attenuated vaccines in particular and adequate provision of cold chain management of reconstituted vaccines at the vaccination sites is essential.
  b) a vaccine product fitted with a vaccine vial monitor (VVM);
- Set and monitor explicit time and temperature limitations on the use of the specific product OCC;
- Ensure adequate vaccine handling training of health workers; and
- Use appropriate temperature monitoring tools in addition to VVM, such as peak temperature threshold indicators.

40 https://bit.ly/2RI4vzI

Anna-Lea Kahn in 2014 MenAfriVac campaign in Togo

I discussed one confusing issue with Anna-Lea Kahn (WHO) who is the responsible technical officer for the CTC. Anna-Lea explains that the critical issue in stability data for CTC is the point of assessment. VVM assignment is done based on the stability profile of the vaccine at the release stage. *"As for CTC, we are looking at the end of the shelf life, vaccine has to be tested at the very end when the batch reaches the end life"* says Anna-Lea, *"And the whole basis of premise for VVM is that it is not designed for constant out of cold chain use, it is designed for occasional accidental excursions so throughout the cold chain such excursions are recorded."*

I asked Anna-Lea why CTC had to be implemented in a campaign setting or in special strategies only. *"It is simply because the way CTC brings advantages is that you are taking the vaccine out of the cold chain and delivering out of the cold chain"* says Anna-Lea, *"In routine use, if you deliver something in that bundle of vaccines, where some vaccines require cold chain and others don't then you are not able to take advantage of the thermostable ones in terms of their flexibility. So, then we realized that the scenario where you can really benefit from OCC is either in campaigns or through special strategies, because those thermostable vaccines are often delivered individually."* I also asked about the HPV and whether its implementation is considered as a routine use. Kahn explained that although HPV vaccination is a routine activity, it is akin to outreach programmes because these vaccines are typically delivered in school strategies.

I asked Anna-Lea why no hepatitis B product is re-labelled for CTC to-date. *"In the beginning, we did not know what the sweet spot was in terms of a good duration and reaching 40°C"* says Anna-Lea, *"We thought 40°C was a reasonable request especially based on the experience with MenAfrivac and our initial impressions based on available data through those various studies with hepatitis B. We thought it would not be a major issue, and we could expect a really good duration."* And with the 40°C rule, WHO was not getting the necessary stability data support from the manufacturers. So, it did not bring any programmatic advantages and naturally, if sufficient time cannot be achieved for the CTC to meet country needs, the benefits of using the vaccine in a CTC context are reduced.

The IPAC CTC Working Group started to explore options to increase the CTC duration through either decreasing shelf life, lowering the threshold temperature

2014 MenAfriVac campaign in Cote d'Ivoire

from 40°C to 37°C, or raising the internal minimal release potency limit. But decreasing shelf life is a challenging proposal. The problem is that if a country decides not to use the vaccine in a CTC but starts to receive a decreased shelf life vaccine, they may need more frequent supply, and they may also experience increased vaccine wastage due to early expiration. This proposal also has implications on manufacturers, a decreased shelf life means smaller production runs and more frequent batches leading to increased product costs.

Strategic prioritization

The IPAC CTC Working Group selected HPV vaccine, TT-containing vaccines (TT-CV), oral cholera vaccine (OCV) and HepB-BD as priority vaccines for the CTC based on three criteria: adequate heat stability; a delivery strategy that would benefit from CTC use/expressed country need; and technical feasibility of CTC licensure.

Temperature indicators for CTC

The IPAC CTC Working Group evaluated a lowering of the CTC threshold temperature to 37°C as a "distinct" possibility if it was to result in a much longer duration

than a 40°C threshold temperature. *"This possibility will be explored through dialogue with vaccine manufacturers and review of existing vaccine stability data and temperature exposure data from country studies such as those previously conducted in Uganda and Vietnam. While vaccine wastage due to heat exposure might increase with a lower threshold temperature, it could be offset by reducing wastage due to exceeding the CTC duration once vaccine is placed in a CTC. Advice could also be given to countries to minimize the use of CTC during times of the year where vaccine exposure temperatures are likely to exceed 37°C. If the threshold temperature reduction approach is determined to be favourable, then WHO would need to consider changing the current programmatic definition of CTC. The lower threshold temperature could potentially apply to other vaccines as well."*

The group suggested that the feasibility of raising the antigen content should be explored through dialogue with vaccine manufacturers and regulatory experts.

Currently, CTC requires the inclusion of VVMs on each vaccine primary container. In addition, a separate peak temperature threshold indicator should accompany vaccines in each vaccine carrier to prevent health workers administering vaccines that have been exposed to temperatures exceeding the specified peak temperature. This was required mainly because VVMs are not able to respond to short and high peaks in exposure to elevated temperatures.

In 2012, the Temptime Corporation came up with a novel solution that integrated the peak temperature indicator with the VVM, to provide a unique, simple and clear signal to field workers. For this innovation Temptime received the Grand Challenges Explorations award, an initiative funded by the Bill & Melinda Gates Foundation. The award was announced on 12 November 2012. *"Investments in innovative global health research are already paying off,"* said Chris Wilson, director of Global Health Discovery and Translational Sciences at the Bill & Melinda Gates Foundation, *"We continue to be impressed by the novelty and innovative spirit of Grand Challenges Explorations projects and are enthusiastic about this exciting research. These investments hold real potential to yield new solutions to improve the health of millions of people in the developing world, and ensure that everyone has the chance to live a healthy productive life."*

The dual function VVM-TI or "VVM+" was another revolutionary idea from Temptime. As principle investigator for the Grand Challenge Exploration, Dawn Smith, Temptime's Executive Director for New Product Development, had proposed the idea of developing low-cost individual vaccine vial temperature indicators that provide a unique signal following a defined cumulative heat exposure consistent with WHO PQS specifications for VVM and which could also provide an indication of any brief exposure to high temperatures that could cause vaccines to lose potency and be rendered ineffective. The new dual function heat in-

dicators would be integrated in a single device that features a single visual signal consistent with current VVMs – a square, reactive surface in the center of a circular reference surface that darkens with exposure to heat. *"For more than 20 years, Temptime Corporation has worked with WHO, PATH, and other organizations to develop technology to contribute to the success of global immunization programs that have made such a tremendous impact on saving the lives of people in developing nations,"* said Ted Prusik, PhD, Temptime Senior Vice President and one of the inventors of the original Vaccine Vial Monitor. He continued, *"Temptime is very proud to receive a Grand Challenges Explorations grant and we are fully dedicated to continue our support of global immunization initiatives."*

WHO PQS issued a new product performance specification for a combined VVM and threshold indicator (WHO/PQS/E006/IN06.1) and a corresponding product verification protocol (WHO/PQS/E006/IN06-VP.01) in January 2019. The new specifications required the threshold component of the combined indicator to conform to the performance specification for threshold indicators' (WHO/PQS/E006/IN04.1) mode of operation clause, and the cumulative component to conform to VVM performance specifications (WHO/PQS/E006/IN05.3). On 19 January 2019, PQS also issued an updated version of the VVM specifications to include VVM250. By March 2019, Temptime had already submitted the dossiers for prequalification of VVM250 and separately for the threshold indicator for 40°C. It is expected that VVM+250 will be the first product to be prequalified (designed for Rotasiil™ by Serum Institute of India). VVM+30 has been sent to an independent laboratory which will test the combined device.

With the development of a VVM with an integrated threshold indicator (VVM-TI), the logistics around temperature indicators for CTC will be much easier. There are clear programmatic benefits in using VVM-TI since no training is necessary for its use, on account of the interpretation being identical to that of a regular VVM. Most importantly, countries will not have to purchase, store, and transport separate threshold indicator for CTC. PATH is currently evaluating the potential market for threshold indicators and VVM-TIs for CTC-labelled vaccines as well as an alternative scenario of substituting VVM-TIs for VVMs on all vaccines. The latter scenario could potentially be cost-effective depending on the VVM-TI prices at higher production quantities.

If hepatitis B vaccines become WHO prequalified for CTC use in the near term, threshold indicators will need to be identified and purchased for country use. When WHO-prequalified VVM-TIs become available, then these could be substituted for the current VVM30 used for hepatitis B vaccines.

Removing ice from in-country transport: the "cool" chain

In 2001, Robert Davis from UNICEF raised the question of how to protect the more cold sensitive vaccines from freezing in a TechNet discussion forum, and suggested a return to the 4°C to 8°C recommended refrigeration range of the 1980s. Furthermore, he underlined the importance of low-temperature VVMs to monitor freezing and asked whether PATH could take the project on or whether Gavi were prepared to spend "window-3" money on this. Davis's suggestion of returning back to the old 4°C to 8°C temperature range was discussed at WHO by Julie Milstien, Michel Zaffran, Hans Everts, Philippe Duclos and myself. We came up with a list of reasons why this was not a good idea:

- *A range from 4°C to 8°C is so narrow that it is extremely difficult if not technically impossible to realize. Even if possible, it would raise the price of refrigerators considerably and cheap models would not stand a chance of survival. Besides, these expensive appliances would be primarily used in central levels and places where there is reliable electricity supply.*
- *It could change the cost of appliances such as ice-lined refrigerators (ILRs) with little guarantee that we will actually achieve the required range. ILRs have frozen water in the tubes or icepacks used for the ice lining. Therefore, they suffer from the same limitations: whatever the minimum temperature we require, somehow ice being made of H_2O does not comply and stays at 0°C. We could improve the separation between the ice lining and the storage compartment, but for the latter to be at 4°C, we did not think there would be much volume left to store vaccine. Eventually, unless fresh 'warm' vaccine is added, the temperatures in the whole appliance will stabilize around the temperature of the ice lining.*
- *However, whatever the temperature range we recommend, it is the health worker who sets the thermostat of his appliance and he is not aware of the recommended thermostat setting during the tests. The options are: automatic temperature regulation in the appliance (electronic thermostat); testing on basis of a truly worst-case scenario (this would require a change in test procedures). In contrast to the situation of some years ago, negative temperatures are no longer accepted in test reports of appliances and all manufacturers have been requested to deal with negative temperatures in their appliances.*
- *It will have no influence on the range of storage temperatures in places where most freezing occurs because these places do not go by what is written in specs but do their best with the environment and energy supply available.*
- *Freezing also occurs during transportation. Icepacks start to melt at freezing point but may spend many hours below freezing if used fresh from the freezer - around 10% of the liquid vaccine in a good cold box will be frozen this way. That*

does not change unless we put eutectic products in the icepacks, which creates another set of problems.

- *Avoiding freezing in the periphery may mean separating refrigerators from freezers - hence another substantial increase in price.*
- *As a conclusion three major points can be underlined as priority in addressing the prevention of vaccine freezing: 1) What can be done easily with the existing equipment to prevent freezing? There are a number of simple (wrapping of freeze sensitive vaccines, packs with water, etc.) and not so simple (eutectic products) options. We have to alert health workers and storekeepers to the freezing risk, particularly for HepB vaccine, and warn them of risky practices. 2) How can we make sure appliances do not freeze (specifications and test procedures)? The study Soren Spanner did in India in 1997-1998 showed that in ILRs, over a period of two years, the temperature was below -0.5°C more than 50% of the time! 3) How do we move to take vaccines out of the cold chain, at which levels and what are the repercussions? It may mean that we only need to find solutions for primary and intermediate level storage and can leave the cheaper and smaller peripheral models as they are.*

Low temperature VVMs, and their feasibility from a technological perspective continued to be at big focus. But even were they to have been redeveloped and found a place in the programme, they would not have had any direct impact on the prevention of freezing. Such an indicator would only have told us that "it had happened". Actually, what would have happened is not necessarily the "freezing" but rather an exposure to freezing temperatures, meaning that we could not even be certain if freezing had actually taken place. The only tool that could help us in this situation is the shake test. But if we had a vial with a triggered freeze indicator, and it subsequently passed the shake test indicating that it can safely be used, we would have had a problem. We would have had a viable vaccine vial that was perfectly okay to be used, but with an indicator telling us it was "not good". If it was possible to take the final (to use or not use) decision with the freeze VVM, such an indicator would have worked. But if you needed another tool to verify whether freezing has affected the vaccine, then the freeze indicator would have been more trouble than it's worth. Since those early discussions, freeze VVMs discussions have resurfaced every now and then but it is worth noting that WHO has taken a very clear position on this.

Again in 2001, it was Carib Nelson from PATH who believed VVMs could be an effective tool to prevent freezing. The trick was to expose vaccines to moderate heat with the help of VVMs where the freezing risk is greater than the risk of heat exposure. Freezing in the cold boxes was a well-documented problem, but the

question was how to change the practices to prevent freezing. WHO was recommending conditioning of the frozen packs to 0°C before transferring them to cold boxes and vaccine carriers, but the practice in the field was not in compliance with these requirements. Patience was lacking and when icepacks started sweating and having water beads on them this was enough for health workers. Although, I am putting the blame on the health workers, I must confess that I never found conditioning practical and realistic. In my entire time at UNICEF and WHO, I never came across proper icepack conditioning in the field. My experience as a health coordinator for the Operation Lifeline Sudan (OLS) in 2000 made me think about the possibility of ice-free in-country vaccine transportation. On some days, I had to prepare 5-6 boxes of RCW25 cold boxes fully loaded with vaccines, and bring them next to planes on the airstrip in Lokichogio, Kenya for transportation to war zone locations in the south. That makes for a lot of icepacks to condition. And the conditioning took forever. Following my joining WHO headquarters, I participated from 4-7 December 2001 in the 9th Task Force on Immunization and the 8th African Regional Inter-Agency Coordination Committee (ARICC) meeting, held in Addis Ababa, Ethiopia. I discussed the conditioning of icepacks with every single immunization manager attending these meetings. All EPI managers said that conditioning icepacks was not well practiced and none believed that "waiting for longer hours for full conditioning" would ever work.

On my return back to Geneva, I talked to Paul Tollet from GSK to delve into the details of DTP-HepB international vaccine shipments. In order to protect the product from freezing, the thermal load of the shipping cartons was simply cold-water packs (at 2°C to 8°C). WHO international packaging and shipping guidelines required that the warmest point in the shipping box did not rise above 30°C in a continuous outside temperature of 43°C for a period of at least 48 hours. Why can we not duplicate this practice for in-country vaccine transport, I asked myself. Although we did not have VVMs on all presentations, I thought designing a field study to document the use of cold-water packs could be the answer to vaccine freezing during transport and would also help to prove the case for the VVM. With great enthusiasm, I posted these thoughts in the TechNet forum.

The first reaction I received was a thermodynamics lesson by Ian Wyllie of the University of Southampton. *"The references to cold water packs are indefensible."* said Ian, *"They will not work. The reason that icepacks work in cooling is because the ice requires an enormous amount of energy to change from ice to water. This energy has to be supplied from the environment. It is known as latent (hidden) heat, because no change in temperature is observed while the ice is changing from ice to water. If the environment is the interior of the cool box, then this latent heat is supplied to the ice from the interior of the cool box. This (with the numbers of icepacks specified by EPI) reduces the tempera-*

ture of the interior of the cool box until it is equal to that of the melting icepack. (0°C). Cold water however heats up linearly, and therefore has a minimal cold life." I had no problem with this lesson, of course I knew the thermodynamics of a cold box. But, my question was, if it worked for international shipments, why would it not work for in-country transport?

Carib Nelson took the discussion one step further by suggesting a two-track cold chain; one track would be the existing cold chain for freeze-tolerant vaccines (OPV, measles, and BCG) and a second one, a cool-chain for handling heat-tolerant vaccines with the help of VVM. Carib based his arguments on PATH's studies in Indonesia that resulted hepatitis B vaccine being stored in air-conditioned rooms and transported from the national to province level at ambient temperatures. *"So far this experiment is working well without any vaccine spoilage due to heat exposure and reduced costs for vaccine transport and storage."* said Nelson, *"Again, VVMs provide the ultimate in easy-to-access information about the vaccines' heat exposure at any point in this cool chain. Taking these heat-tolerant vaccines partially or completely out of the current cold chain would increase cold chain capacity, reduce distribution costs, and reduce freeze damage. Significant potential advantages!"*

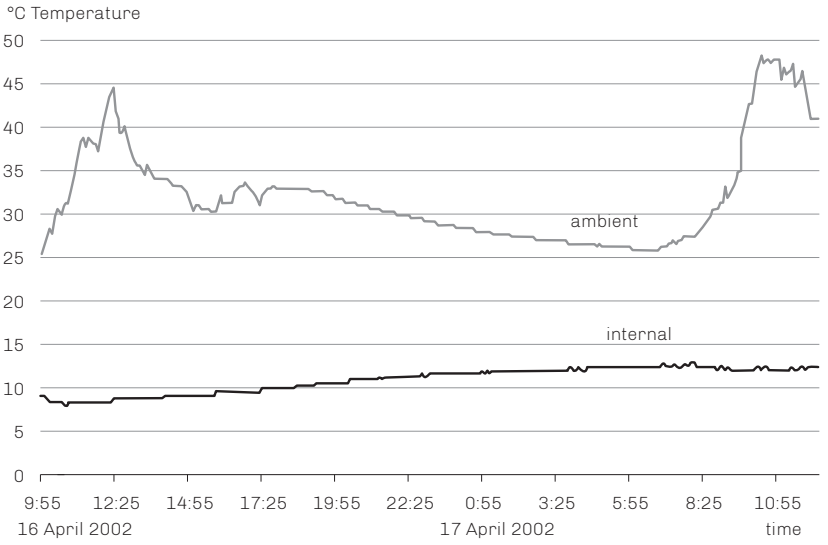
Controlled environment laboratory study and field studies started in 2002 in Nepal, Myanmar, Turkey and Zimbabwe. The objective was to find out the impact of the use of cool water packs (water packs refrigerated at 2 to 8 °C) on the cold life of vaccine transport boxes and the shelf life of the vaccines. 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 were illustrated through degrees of color changes of VVMs. 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°C to 39.8°C over the 98 h 15 min test period.

Temperature recordings and VVM readings in RCW25/CF and RCW2/CF during 48 hours exposure to 43°C and 32°C ambient temperature at CSIR (in °C)

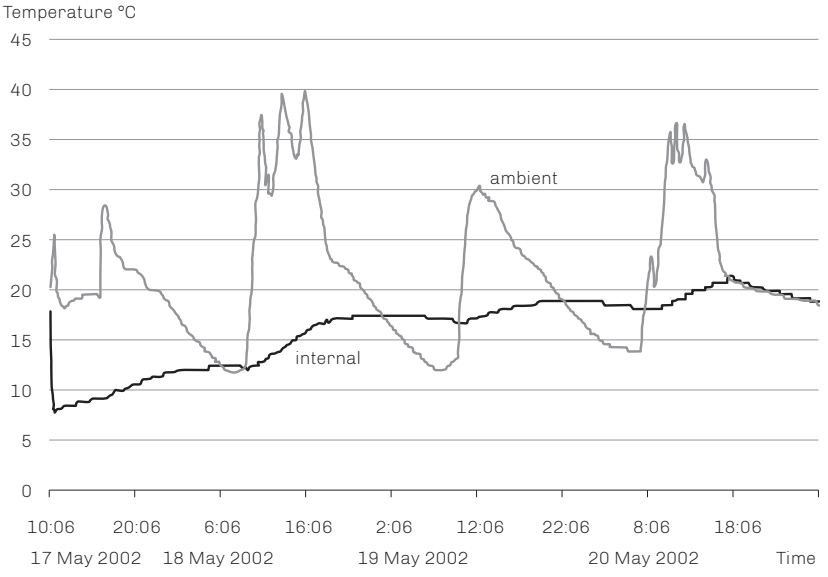
Box type	Ambient temperature	Initial water packs temperature	Temperature of the cold box / vaccine carrier[a]			VVM readings at the end of the test[b]			
			Average	Min	Max	VVM2	VVM7	VVM14	VVM30
Large RCW25/CF	43.0±0.5	2±0.5	11.5	2.5	20.0				
	43.0±0.5	8±0.5	16.3	8.2	23.6				
	43.0±0.5	No packs	33.5	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				

[a] Figures taken from the thermocouple recording the highest temperature.
[b] All VVMs were at their start-point at the beginning of the tests.

Temperature exposure during the longest journey,
Nepal (584 km in 26 hours and 30 minutes)



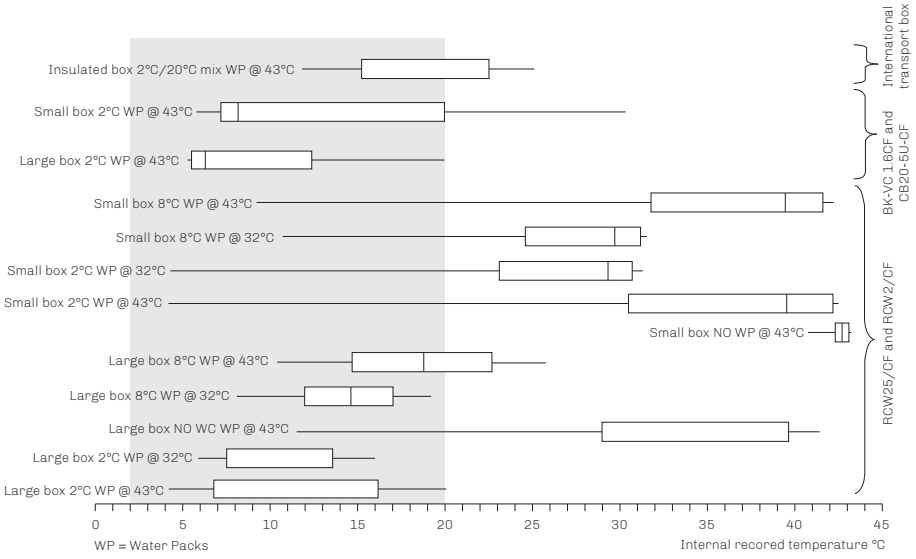
Temperature exposure during simulation,
Zimbabwe (583 km in 98 hours and 15 minutes)



These study results showed that with large vaccine carriers at extreme ambient temperature of 43°C, temperatures inside the cold box rose slightly above 20°C, but did not substantially compromise the shelf lives of vaccines with VVM7, VVM14, and VVM30; all vaccines except the OPV fall under these categories. This series of tests and field trials were naturally leading to the definition of a new concept: the "cool life" of a vaccine container where the vaccines are absolutely free from any risk of freezing.

The cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the vaccine storage compartment first reaches 20°C, at a constant ambient temperature of 43°C.

Box and whisker plot of recorded temperatures at all laboratory tests



The above plot displays minimum, maximum, median, 25th and 75th percentiles of recorded temperatures at the laboratory tests. The shaded area in the background indicates the newly defined cool life. Although temperatures were recorded in the polyurethane (PUR) insulated box of PT BioFarma, VVM life loss was calculated between 0.6% to 2.7% in all vaccines but OPV.

Naturally, small-volume boxes perform less optimal compared to large-volume boxes. The freezing risk was dependent also on the amount of insulation in the boxes. The boxes with better insulation were likely to be riskier if used with

frozen ice packs (the long-life boxes having the highest risk). In general, large cold boxes were used for vaccine transportation from one store to another at the country level. Vaccine carriers were mainly used for bringing vaccines to the health centre as well as for outreach activities. Bringing vaccines to the health centre from the lowest level of storage facility was usually within hours and did not represent any risk to vaccines especially when used together with VVMs. Outreach transport might take extended periods of time (up to 48 h) and, most importantly, health workers needed to have ice at the point of destination to keep reconstituted vaccines cold during the session. If cool water packs were used, there would not be "enough cold" for reconstituted vaccines. Therefore, the use of cool water packs only applied to vaccine transport in between storage facilities and down to a fixed immunization point.

In a typical cold chain distribution system, vaccines travel from the primary vaccine store to intermediate level(s) down to the service level facilities. In most countries, there is only one intermediate level. Some large countries, however, can have up to three intermediate levels of vaccine stores (regional, provincial, and district) with vaccines making up to four trips to reach health facilities. The simulation below was drawn based on such a distribution system using temperature data generated at the laboratory tests above. The assumptions in the simulation were as follows:

- 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 hours

Repeated temperature exposure was applied to used and remaining VVM life calculation through the Arrhenius equation.

Repeated temperature exposure impact on the VVM life (four times of transport at ambient temperature of 43°C for 48 hours each)

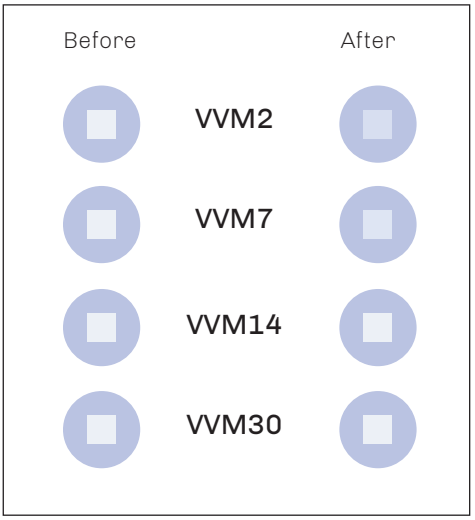
VVM type and (end-point days)	VVM life used (%)	Remaining VVM life if kept at 37°C (days)
RCW 25/CF (Dometic)		
VVM2 (1.75)	25.2	1.3
VVM7 (6.125)	7.2	5.7
VVM14 (12.25)	3.6	11.8
VVM30 (26.25)	1.6	25.8
CB20-50-CF (Blowkings)		
VVM2 (1.75)	2.8	1.7
VVM7 (6.125)	0.8	6.1
VVM14 (12.25)	0.4	12.2
VVM30 (26.25)	0.4	26.1
PUR 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

In spite of the low impact calculated when the Blowkings cold box is used, the VVM2 (OPV) lost 25% of its life with RCW25/CF and 36% of its life with a PUR insulated box. In order not to complicate the transport arrangements, the removal of ice from the in-country transport could have been recommended for all vaccines including the OPV, but the research team decided not to include OPV to be on the conservative side.

The calculated highest impact on VVM readings in a scenario (PUR insulated box in the above table where the transport is repeated four times for 48 hours at +43°C ambient, and an insulated box being used at all levels of vaccine distribution) is presented here for visual reference.

As seen in the figure on page 242, it is not possible to visually detect any change in VVM14 and VVM 30. The change in the VVM7, although small, can be seen. Change can easily be seen with the VVM2; although the VVM has not reached the discard-point (the vaccine remains usable) and lost only 36% of its shelf life.

The study helped us to demonstrate how VVM could significantly contribute to the reduction of vaccine freezing. VVM makes it possible to detect and avoid excessive heat exposure to vaccines when methods are employed to store and trans-



Temperature impact on VVM readings

port vaccines without ice and equipment that is a known source of freeze damage. Availability of VVMs are critical for the introduction of cool water packs for in-country vaccine transportation systems to constitute a more flexible cold chain. This simulation was generated based on laboratory results, since there would be no case of continuous +43°C ambient temperature for 48 hours in real life. If real life examples were applied to a similar scenario, for example, the Zimbabwe simulation of 98 hours 15 minutes transport was repeated four times with the same ambient temperature exposure, the highest loss would be found only as low as 18% in the VVM2 category (OPV).

It took another year to bring together a big group of key players from various organizations and regional offices to draft a policy to remove ice from in-country transport to prevent the freezing of vaccines. The group welcomed the proposed draft policy, but when it started to circulate the policy within the department for clearance purposes, a couple of staff who participated in the meeting and had not raised any objection, started to come up with reservations. We never managed to resolve the problems, and the policy was put on hold by the senior management. This was quite a shock for me. When I decided to publish the results in a peer review journal, I had to obtain clearance from the same department. This process took literally four additional years and finally the study was published in the *PDA Journal of Pharmaceutical Science and Technology* in 2009.

RESEARCH

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

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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.

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Following the submission/acceptance of this article, on 8 December 2008 the WHO/PQS programme has published new performance specifications and verification protocols for insulated containers. As suggested by the research team of the study, in these documents the concept of "cool life"

was introduced. Cool life was defined as *"the empty container is stabilized at 43°C and loaded with cool-packs which have been stabilized at 5°C for a minimum of 24 hours. Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the vaccine storage compartment first reaches 20°C, at a constant ambient temperature of 43°C."* No standard has been set for the cool life, but the performance data was required to be permanently displayed inside the lid.[41]

Vaccine distribution guidelines explained by the PQS Catalogue is as follows:

Vaccine distribution guidelines

Frozen water-packs

WHO recommends that OPV and the single antigen freeze-dried (lyophilized) vaccines should be distributed in cold boxes or vaccine carriers, lined with frozen icepacks.

Conditioned ice-packs

Field studies continue to show that vaccine freezing during transport remains one of the principal causes of damage to freeze-sensitive liquid vaccines in the cold chain. The use of 'conditioned' ice-packs has previously been recommended as the way to avoid this risk; however, ice-pack conditioning is a time-consuming process and recent cold chain surveys have shown that the practice is difficult to enforce and is widely ignored. Note that the use of cardboard, newspaper or similar material to isolate freeze-sensitive vaccines from fully frozen ice-packs is completely ineffective as a means for preventing vaccine freezing.

Cool water-packs

The only way to eliminate the freezing risk entirely is to transport liquid vaccines, other than OPV, in cold boxes lined with cool water-packs which have been pre- cooled in a refrigerator to a temperature of +2°C to +8°C. Where it is essential to transport OPV, liquid and freeze-dried vaccines in a single carrier, experiments have shown that cool water-packs may safely be used provided the cool life of the carrier is not exceeded. For current guidance on the performance and use of cool water- packs refer to Kartoglu U, Ganivet S, Guichard S, Aiyer V, Bollens P, Maire D, Altay B. *Use of cool water-packs to prevent freezing during vaccine transportation at the country level*. PDA Journal of Pharmaceutical Science and Technology, Vol. 63, No. 1, January–February 2009, 11-26.

41 http://bit.ly/2kaKoxT

Changing over to the use of cool water-packs involves significant changes in practice. In addition, there are equipment implications because additional refrigerators will be needed at primary and sub-national level to cool the water-packs in bulk. Consequently, it is strongly recommended that the introduction of this method should be preceded by a formal cold chain study based on WHO/IVB/05.01: *WHO Study Protocol for Temperature Monitoring in the Vaccine Cold Chain.* The study design should aim to establish the extent of current problems and also the logistical and financial implications of the changeover to the use of cool water-packs.

Warm water-packs

Field experience in cold climates has shown that it is necessary to protect freeze- sensitive vaccines from exposure to ambient temperatures below 0°C during transport. Unfrozen ice packs, stabilized at a room temperature between 10°C to 24°C, can be used for the transport of freeze-sensitive vaccines for a period not exceeding 8 hours. These vaccines are generally very heat stable and the short time (typically less than 8 hours) that they are subjected to these temperatures will not harm them. For fuller guidance refer to Figure 1.5.4.A of WHO/IVB/04.18. *EVSM Module 2: Model Quality Plan.*

Today, all cold boxes and vaccine carriers prequalified by the WHO/PQS are tested for their cool life and this information is displayed on the lid. And countries like Albania, Moldova, Zimbabwe, Malawi and Indonesia manage in-country transport of vaccines with cool-water packs. This change, would have not been possible without the VVM.

VVM based vaccine management

There is no temperature monitoring device that has changed vaccine management practices as profoundly as VVM. This was a process of change that started even before VVMs became available commercially. Back at the 1993 TechNet consultation, the industry had just started discussing the possibilities of relaxing the cold chain and managing stocks more effectively with the help of VVM. Today, VVM is an important tool in vaccine management, starting with the international shipment of vaccines to the immunization sessions at the health centre level and in outreach situations.

International shipments

WHO guidelines on the international packaging and shipping of vaccines demand the inclusion of temperature monitoring devices in each and every carton of vaccines. CCM cards are only used for international shipments of OPV packed with dry ice. All other international shipments packed with coolants, other than dry ice, include electronic shipping indicators meeting the specifications described in WHO/PQS/E006/TR07.3. Today, the WHO PQS prequalification list has a total of seven electronic devices, some with a USB interphase for download. All these devices come in two different types, Type 1 for freeze-sensitive, and type 2 for OPV and lyophilized vaccines. There are two more types with different alarm settings specifically designed for Prevnar® and Rotateq® vaccines due to their stability profile.

WHO PQS prequalified electronic shipping indicators			
PQS code	**Manufacturer**	**Manufacturer's reference**	**USB interface**
E006/002	Berlinger & Co. AG	Q-tag® 2 plus	No
E006/010	Sensitech Inc.	VaxAlert™	No
E006/014	Berlinger & Co. AG	Q-tag® Clm	No
E006/016	Berlinger & Co. AG	Q-tag® Clm doc	Yes
E006/021	LogTag® Recorders Ltd.	TIC20	No*
E006/029	Sensitec Inc.	VaxAlert™ USB	Yes
E006/014	Berlinger & Co. AG	Q-tag® CLm doc L	Yes

**TIC20 data can be downloaded via optional LogTag interphase that is sold separately*

All recipient countries (through UN agencies) are required to fill in a vaccine arrival report (VAR) to document the status of arrival and report back to the procurement agency within three days. VAR includes a special section covering temperature monitoring devices (status of shipping indicators) and UNICEF developed a mobile application of VAR in 2014.

The decision to accept or reject a shipment is based on the readings of the electronic temperature recorder. Additional information sources are used to support this decision with the status of coolants and VVMs considered as additional streams. Electronic shipping indicators are designed to monitor temperatures during transit since VVM is not designed for this purpose. Accordingly, VVM is not used in principle to evaluate the temperature exposure during an international shipment. However, VVM status should always be checked and recorded upon shipment arrival.

The relation of electronic shipping indicator readings with VVM

All possible readings from an electronic shipping indicator are explained from a VVM perspective below:

- If there are no alarms, VVM cannot have a status change at all. Even if no change in the status in VVM is expected, VVMs still need to be checked to record the findings in the VAR.
- In the case of <= -0.5°C alarm, there cannot be any VVM status change. VVM does not change color in negative temperatures.
- The alarm of >= 10°C is important for the OPV. In the case of >= 10°C, if the vaccines are other than OPV, the shipment should be accepted, and visible VVM status change is not possible with any of the vaccines with this alarm for the duration of the shipment.

- In the case of the >= 30°C alarm, shipment may be rejected, subject to confirmation by UNICEF and/or WHO HQ. In most of these cases, the VVM status will not be compromised. However, depending on the number and severity of the higher temperature alarms, the VVM status change may be evident by visual inspection.
- In the case of the >= 45°C alarm, shipment should be rejected. Depending on the number and severity of the violation, the VVM status change may be evident by visual inspection.

In principle, when there is no alarm, it is very unlikely that you will see any VVM beyond its start-point. If this is the case, there could only be three scenarios to explain this:

- **Electronic shipping indicator faulty** – In such cases, you need to analyze the transit time, connections, and coolant status on arrival.
- **Mishandling of VVMs before attaching to vaccines at the manufacturer's facility** – Such a case has not been observed since the introduction of VVM in 1996; however, it is a theoretical possibility. If it were ever to happen, it could be established by a simple investigation. Requesting retained samples, release reports, and acceptance reports of the VVM batch in question from Temptime and the vaccine manufacturer in order to make a direct comparison of the results would help to determine whether this is the case. Such investigations could be conducted by WHO.
- **Vaccines being stored for longer periods of time before shipment at the manufacturer's facility** – If the labelled vaccines (with VVMs) are kept for long periods of time at the manufacturers storage facilities they will be affected by time and temperature (even when maintained at 5°C at all times). However, this may also result in the distribution of vaccines with short expiry dates which may be another ground for rejecting the shipment. This could also be established through a WHO HQ investigation.

While I was active with WHO, I was also dealing with complaints relating to the international shipments between countries. I remember several cases where a country claimed that VVMs had reached stage 2 (50% of the reference color) during a shipment. However, WHO did not identify any quality-related issues with these complaints, and the conclusion was that the VVM reading at the country level was inaccurate (staff were assuming that the VVM start color is white and claiming stage 2 if there was any coloring apparent in the square). The table below dis-

plays the time and temperature required for a VVM to reach 50% of its start color based on the maximum time to end-point at 37°C in the VVM specification.

Time required for a VVM to develop 50% of reference ring color at different constant temperatures

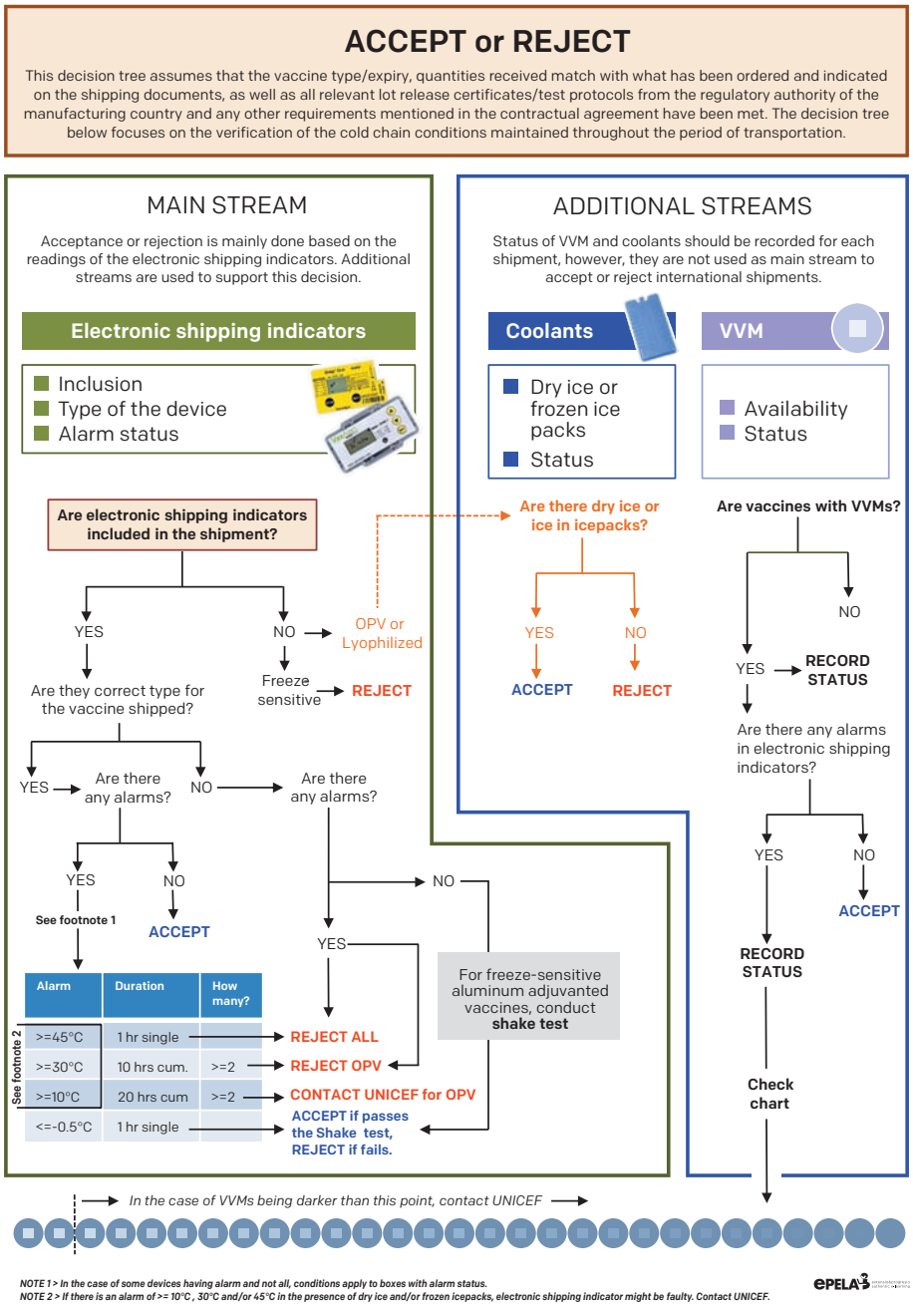
Constant temperature	VVM type	Duration of exposure required (in days)
5°C	VVM2	110
	VVM7	550
	VVM14	1,100
	VVM30	2,400
15°C	VVM2	23
	VVM7	100
	VVM14	200
	VVM30	430
25°C	VVM2	5
	VVM7	21
	VVM14	41
	VVM30	88
37°C	VVM2	1
	VVM7	3.5
	VVM14	7
	VVM30	15

As seen in the above table, VVM2 is the most reactive VVM. It is used only on OPV. It takes one full day at 37°C exposure for VVM2 to reach 50% of the reference color. Of course, such an exposure could occur, but this would also result in the triggering of both the >= 10°C and >= 30°C alarms.

A VVM square not being white is not due to dust during the packaging process, to moisture or to condensation. It is simply the way it is printed. In general, the square of the VVM is about 5-10% tint of the reference ring. In other words, there is no such thing as a "snow white" VVM and any such belief belongs in fairy tales.

The following "Accept or Reject" decision tree was developed as a side product in an authentic task on international vaccine shipments in an e-VVM based vaccine

management course offered by WHO/EPELA. Three factors (alarm status in electronic shipping indicator, coolant status and VVM readings) that affect our decision are used in this decision support tool.

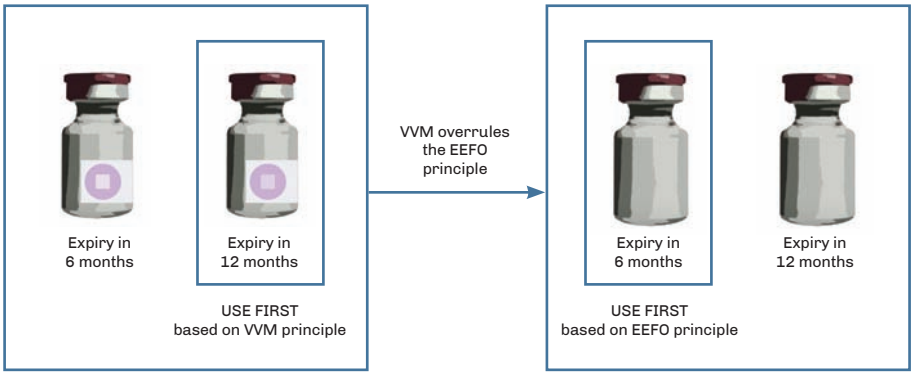


Stock management

Stock management is the practice of ordering, storing, tracking, and controlling inventory. In order to maintain the quality of vaccines throughout the cold chain it is essential to keep complete and accurate records of all stock transactions. In a typical supply chain, a stock control system comprises three levels each of which must be performed regularly, accurately and completely. These steps are arrival, storage and dispatch. All details of vaccine shipments, consignments and vaccines during the storage phase must be checked and recorded. In addition, good warehousing practices should be adopted and physical stock counts should take place in order to verify stock records.

Smart expiry date

Vaccines and diluents have expiry dates after which they must not be used. So, the stock management system must be arranged in a way that allows enough time for vaccines to pass all the way through the supply chain down to the periphery, so they can be used on time. Previously, the "first-in-first-out" (FIFO) principle of inventory management was almost universally applied, meaning that your oldest stock (first-in) gets out first (first-out), not your newest stock. But these days things are a lot more complicated. There is a high possibility that a more recent arrival of a particular type of a vaccine could have a shorter expiry date than a shipment that was delivered earlier. Therefore, instead of a FIFO approach, an approach that takes the expiry date as the dispatch determinant i.e. "earliest-expiry-first-out" (EEFO) should be practiced. But here VVM brings an exception to the EEFO principle. Let's assume we have two different batches of the same type of vaccine, one expiring in 12 months and the other expiring in 6 months. If you apply the EEFO principle, you should dispatch or use the one that expires in 6 months. But, if the VVM on the vial expiring in 12 months is darker than the VVM on the vial that will expire in 6 months, VVM will overrule the expiry date – you



are expected to dispatch or use the vial with a darker VVM first regardless of the expiry date. This is why I call VVM a "smart expiry date".

During the storage period the integrity of stocks must be checked by reviewing the status of VVM for each batch. Any significant color change in VVMs may indicate a weakness in the cold chain which may require introducing corrective actions such as maintenance and/or replacement of the equipment. Such VVM indications may also indicate that the average temperature in the store is skewed toward the higher end of the recommended range. In this case, even when temperatures are within the recommended range, changes especially in VVM7 would be more visible. WHO and UNICEF have received a series of complaints from countries that the VVM on Quinvaxem® (by Berna Biotech Korea Corp.) is changing color fast despite it being kept within the recommended 2°C-8°C temperature range. Until the 2006 prequalification of Quinvaxem®, all vaccines stored in the +2°C to +8°C cold chain had been assigned either VVM14 or VVM30. All products with VVM2 (OPV) and VVM7 (some freeze-dried products) were stored in the freezer rooms at the primary vaccine stores. Quinvaxem® was the first product with VVM7 that was kept in +2°C to +8°C cold rooms at a national level. As a result of this, immunization staff in the field experienced VVMs changing color faster than "expected", mainly because their experience was limited to VVM14 and VVM30 reaction rates.

Since the reaction time on VVM7 is rather fast, small differences in the temperatures have higher impact on VVM7 than on VVM14 and/or VVM30. In order to demonstrate the different impact temperature variations will have on VVM7 vs. VVM30 when stored in the recommended 2°C to 8°C, let's examine an actual example from the field:

In this case a vaccine was received by the country involved on 18 April 2008. The country was concerned that VVM on Quinvaxem® was changing color faster than all the other vaccines in the cold room.

Different vaccine types have different VVM categories, and therefore the reaction rate of these VVMs would not be the same even if they are exposed to the same temperatures. If Quinvaxem® with a VVM7 is kept at all times at 5°C, the VVM would lose 35% of its life. On the contrary, a VVM30 would lose only 8% of its life. Even within the recommended 2°C to 8°C temperature range, if the average temperature is closer to 8°C, the VVM reaction rate would be faster and naturally result in darker VVMs. The table below provides additional information on the percentage of days lost within the recommended temperature range for a VVM7 product stored for 343 days:

VVM7 reaction rates to various temperatures for 343 days

Temperature (constant)	VVM7 days lost (in percent)	VVM7
Start-point	n/a	
5°C*	35%	
6°C	42%	
7°C	50%	
8°C	60%	

** Even it is kept at 5°C at all times, in 343 days (almost a year) VVM would lose 35% of its days. This is "normal" and corresponds to 3-year shelf life of Quinvaxem® at recommended storage temperature*

Continuous temperature monitoring records from the primary vaccine store in the country indicated that the temperature was between 6°C and 7°C with short spikes up to 11°C throughout the Quinvaxem's storage period of 343 days. This information was in line with what is explained above in terms of temperature impact on the VVM7 reaction rate. Therefore, the changes in VVM over the 343 days were around 25% to 40% (variation from different batches produced on different dates) and is an "expected" outcome of such temperature exposure. It is clear that skewed temperatures towards 8°C accelerate the reaction rate of VVM7, therefore it is critical that the set-point for the temperature regulation in the cold rooms should be set to 5°C.

VVMs go through a very thorough quality control process before they are affixed to the vials or ampoules. Each VVM lot produced by Temptime Corp. is released following a series of tests, and similar tests are conducted by the vaccine manufacturers once they receive the VVMs. VVM is a reliable and predictable tool, and when a VVM starts darkening in storage and/or during transport, this should be taken as a sign of a problem in the vaccine cold chain, and not the VVM itself. VVMs simply do what they are supposed to do: pinpoint cold chain problems. Even when the average temperature is set to 5°C in a cold room, it is always advisable to keep vaccines incorporating VVM7 in the coldest part of the cold room. If temperature mapping of the cold room has not been conducted, this should be seen as a priority and completed as soon as possible.

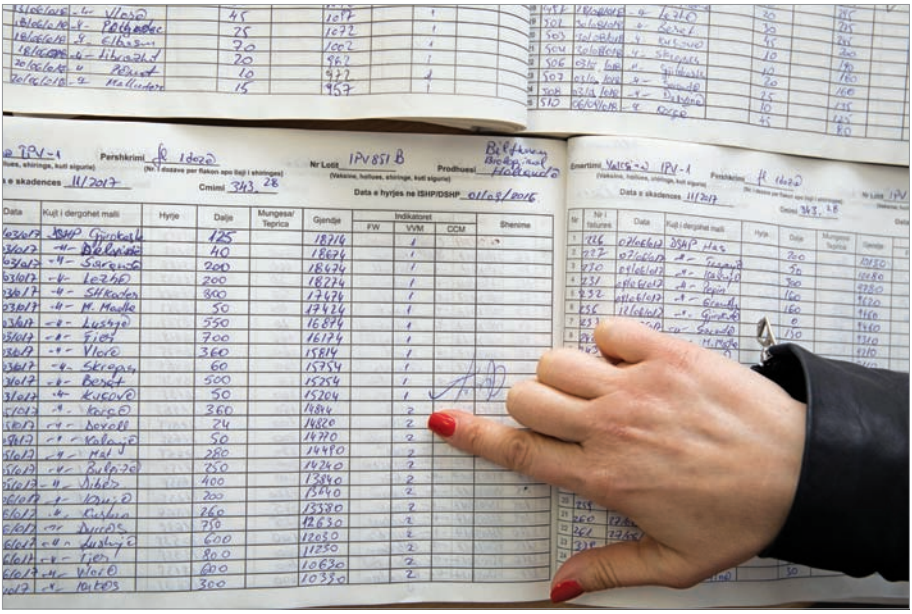
In 2008, the manufacturer submitted additional stability data to WHO in support of VVM14 for Quinvaxem. On 23 February 2009, WHO notified the UNICEF Supply Division of the change of the VVM category for Quinvaxem from VVM7 to VVM14.

Today countries are facing similar challenges with the VVM7 attached on IPV.

Temptime has also recently adjusted the formulation of VVM7 to increase the time to reach end-point at 5°C while keeping the required specification of 7 days at 37°C. The fact remains the same that VVM7 containing vaccines should be kept in the coldest part of the refrigerator unit.

Rotating stocks with the help of VVM

All forms, electronic or manual, that are used in stock management must have a section to record the status of VVM.



Vaccine stock ledger of the primary vaccine store, Albania

Albania has introduced an online immunization information system (IIS) to manage orders, stocks and dispatches as well as monitor children and their vaccination records. The system has different levels of user (health centre, district, national) and Institute of Public Health (IPH) administrative staff. The system is currently being revised and is at pilot phase in the Shkoder district (the remaining districts are continuing to use paper system). The VVM status appears in all rele-

vant sections of the online system. The most important feature of the system is that when VVM status is recorded as stage 2 with a particular vaccine batch, the batch is automatically transferred to the top of that particular vaccine batch signaling that it must be dispatched and/or used first.

VVMs ruling the dispatches

During the dispatch, in addition to all necessary data (e.g. type of vaccine, diluent, expiry date, batch numbers, and number of vaccines dispatched) VVM status should also be recorded. In principle, five levels of controls are suggested in deciding what to dispatch:

- VVM availability
- Batches
- VVM status + expiry
- Supply period + expiry
- Quantity

The following decision tree has been constructed with the use of IF/THEN statements. Each branch of the tree is created until all options under the question are exhausted. Let's follow the statement below in the decision tree:

If there is VVM, *and* **there are more than one batch,** *and* **batches have different VVM color,** *and* **the expiry of the batch with darker VVM is shorter than the next dispatch date,** *and* **you have enough quantity to dispatch,** *then* **dispatch clarker ones.**

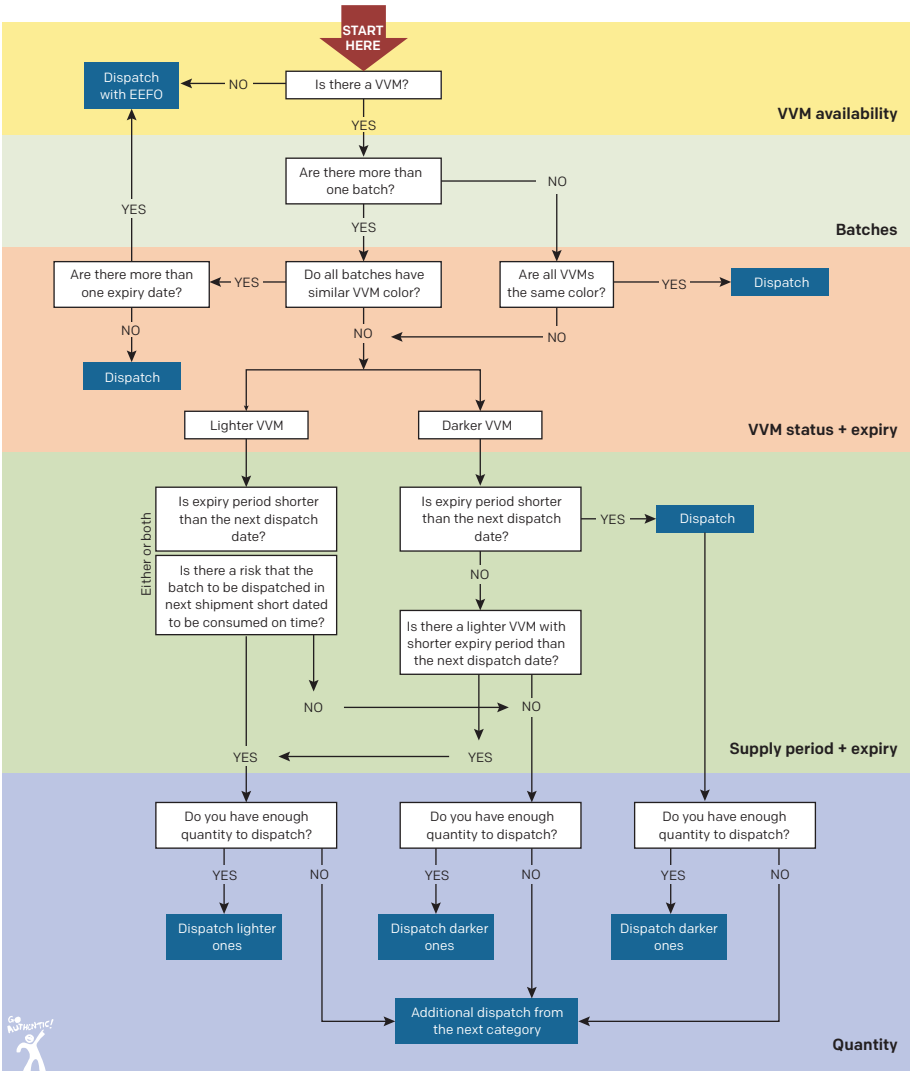
In this flow of logic, at the end, a batch with darker VVM and with shorter expiry date than the next dispatch date would be dispatched. For example, if they did not have enough quantity for dispatch in that particular batch with darker VVM, then they will need to add from the next batch.

Let's explain the logic with another statement:

If there is VVM, *and* **there are more than one batch,** *and* **batches have similar VVM color,** *and* **batches have different expiry dates,** *then* **dispatch with EEFO.**

EEFO dispatch would also be applied when there is no VVM.

Using VVMs to dispatch vaccines (Kartoglu, 2014)



VVMs pinpointing cold chain problems

Although there are purpose-made temperature monitoring devices for the monitoring of storage facilities and transport, VVMs can actively help in pinpointing cold chain problems. The VVM7 reaction when the average temperature of a cold room is skewed to the higher end of the temperature range, as explained above, is

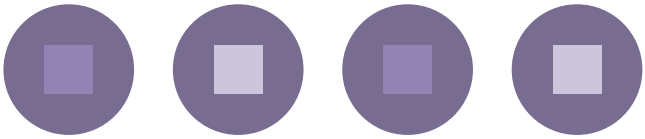
a perfect example of this. In principle, since the temperature is within the recommended range, one may think that there is no problem. This is correct, and the temperature monitoring system of the cold room would not raise any flag. But if your vaccines with VVM7 (e.g. IPV) are changing color faster than you are expecting, then you should check whether you are keeping these vaccines in the coldest part of the room.

On 14 February 2008, India received one million doses of Japanese encephalitis (JE) vaccine. This shipment was received in Delhi, where it was split-up and vaccines sent to Karnal Medical Store (450,000 doses) and Chennai Medical Store (550,000 doses) on the day of receipt. The Lucknow Directorate of Medical Health and Family Welfare received 50,000 doses of JE on 23 September 2008. Following an inspection of the received JE vaccines, the responsible staff were not prepared to accept the vaccines on the basis that the VVM status was not deemed acceptable. Although the VVMs were still at a usable stage, they were quite dark in color. This rejection was broadcast in several print and online publications. The Health Commissioner invited LisaLine (Lifescience Technologies Pvt Ltd) to assist with the spectrodensitometer readings of the VVMs in both stores. The investigation revealed the following information:

- *Both stores received the vaccines on the same day.*
- *There were no irregularities in transport of vaccines to both stores.*
- *Both stores accepted vaccine with the VVM in very good condition.*
- *In Karnal, 43 batches of JE vaccines from this shipment were found, kept at two different stores. In the first store, densitometer readings indicated that one batch had VVM at the end-point (unusable), and the remainder had only 30% shelf life left. VVM readings showed 80% shelf life remaining in the second store. In Chennai, only 7 batches were found. The VVM readings showed a remaining shelf life of 90% including the batches that were found in Karnal.*
- *A relatively recent EVSM assessment report was found covering the Karnal store. From this it was established that none of the stores had any continuous temperature recording system and only manual records were available. These showed no anomalies. At the time of assessment, since the store did not feel cold, the investigation team compared readings of the temperature device with a reference one. The comparison revealed that when device in use showed 8°C, the reference thermometer indicated 12°C! If this was the average temperature of the first store, the coloration of the VVM7 could be easily explained after a continuous exposure to such a high temperature for 7 months.*

Here, it was actually VVM that triggered the investigation by raising a flag. Indeed, VVM directly pinpointed the cold chain problem. Even without any densitometer reading, and with only a visual inspection, the following comparison would tell us instantly where the cold chain problem took place.

Visual and densitometer readings of VVMs



Luknow	**Chennai Store**	**Karnal Store #1**	**Karnal Store #2**
35% shelf life remaining	80% shelf life remaining	30% shelf life remaining	80% shelf life remaining

Following this investigation, the programme introduced corrective actions in all stores.

Keeping vaccines in order

When you go to a supermarket and want to buy some milk, the bottles that are in front and closer to your reach are almost always those with the shortest expiry date. This is normally the result of 'rear loading' the shelves. As with EEFO, the earliest expiry dates are in front, the latest dates at the back. Even although the staff loads the products standing in front of the shelves, the new, fresher products are always placed to the back. Many customers pick products from the front row but if you want the freshest perishables, those with the longest expiry possible, then you've got to reach to the back rows.

Organizing a vaccine store or a refrigerator would be much easier if you only had one condition to check: the expiry date. But in a typical health centre refrigerator, there are other conditions you need to check in order to organize it so that the correct items are in front. In addition to the expiry dates (and therefore batches), you have different types of vaccines (liquid and lyophilized). You have unopened vaccine vials, and because of the MDVP, you may also have opened multidose vaccine vials. You can also have vaccines with or without VVMs. And when

you have VVM, you may have different color VVMs on different vials. Some vaccine vials (lyophilized products) will also have their specific diluents and these are not interchangeable.

As in the case with distribution, VVM also rules here. Let's try to demonstrate this with an example. In order to be as authentic as possible, the simulation below will contain all the potential challenges that one might face when arranging products in good order in a health centre refrigerator. When you are analyzing the situation, you should keep in mind that you are doing this on 2 February 2019, so you must think and act accordingly when it comes to expiry dates.

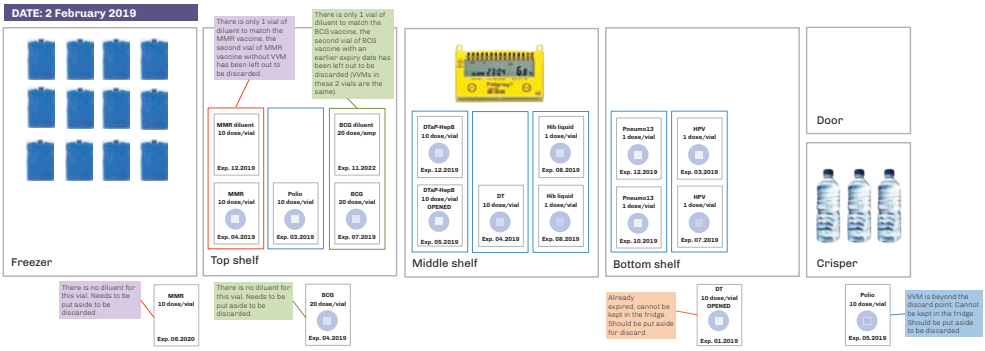
Here are the vaccines:

DTaP-HepB 10 dose/vial OPENED Exp. 05.2019	DTaP-HepB 10 dose/vial Exp. 12.2019	MMR diluent 10 dose/vial Exp. 12.2019	MMR 10 dose/vial Exp. 04.2019	MMR 10 dose/vial Exp. 06.2020	BCG diluent 20 dose/vial Exp. 11.2022	BCG 20 dose/vial Exp. 04.2019	BCG 20 dose/vial Exp. 07.2019	Hib liquid 1 dose/vial Exp. 08.2019
Hib liquid 1 dose/vial Exp. 08.2019	Pneumo13 1 dose/vial Exp. 12.2019	Pneumo13 1 dose/vial Exp. 10.2019	HPV 1 dose/vial Exp. 03.2019	HPV 1 dose/vial Exp. 07.2019	DT 10 dose/vial Exp. 04.2019	DT 20 dose/vial OPENED Exp. 01.2019	Polio 10 dose/vial Exp. 03.2019	Polio 10 dose/vial Exp. 05.2019

In addition to the vaccines, you have the following items to place in the refrigerator:

The refrigerator has the following compartments: freezer, top shelf, middle shelf, bottom shelf, crisper, and door.

First, I would like to share my final arrangement and explain the reasoning step by step. Here is how I would organize my refrigerator:



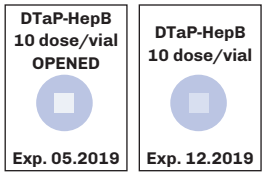
But before getting into the reasoning behind this arrangement, let's summarize the problems we were facing:

- BCG vaccine and BCG diluents were not in matching quantity
- MMR vaccine and MMR diluents were not in matching quantity
- One of the OPV vials had a VVM that was beyond the end-point
- The opened DT vial has already been expired

Though not a problem, there were vials with no VVMs, with different VVM shades and expiry dates as well as some opened vials.

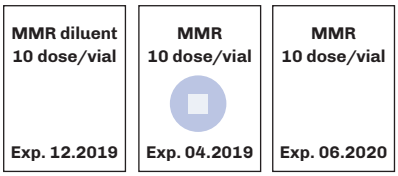
Let's go from left to right of the vaccine set:

The first set of vaccines is **DTaP-HepB** in 10 dose/vial presentation with two different expiry dates, one expiring in 05.2019 with a lighter VVM and the other with 12.2019 expiry with a darker VVM. However, the very first one is also an OPEN vial.



First of all, DTaP-HepB is a freeze-sensitive vaccine and should be stored either in the middle shelf or at the bottom shelf. In the shelf, the vial(s) that need to be used first must be arranged in a way that they can be readily accessed. The opened vial must be used prior to any unopened vial regardless of the VVM status and/or remaining shelf life. In our case, the opened vial must be placed in the middle shelf and the unopened one behind it.

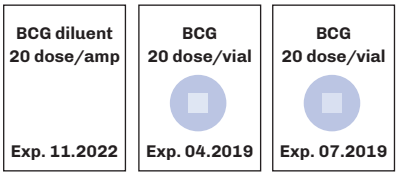
The second group of vaccines is **MMR**. MMR is a lyophilized vaccine and comes with a diluent. Here, we have a problem of mismatching quantities of vaccine and the diluent. In addition, one of the MMR vials does not have any VVM (could be from another manufacturer). The one with VVM expires in 04.2019 while the one without VVM expires in 06.2020.



Based on good stock management practices, all lyophilized vaccines must have matching quantities of diluents. In the case of mismatch, the orphan one should be taken off the stock records by discarding it. Since lyophilized vaccines come with a matching quantity of diluents, there is no way you can purchase diluents separately. As you know, diluents are not interchangeable; only the diluent that comes with a particular vaccine can be used to reconstitute that particular vaccine. In this regard, we need to decide, which MMR vial to take out of the fridge to discard. We can keep the one with longer shelf life; however, this particular vaccine does not have any VVM. The one with VVM has just 2 months shorter expiry but with VVM. Here, I would prefer to keep the one with the VVM and discard the other one.

When we say "discard", of course we need to inform our supervisor and follow the routine discard procedures of the MOH. It is not simply taking it out of the fridge and throwing it away. If discarded, this vaccine will be recorded as "missing inventory".[42]

The next set of vaccines is **BCG**, with a similar mismatch problem. Here, the 2 BCG vials have different expiry dates but similar VVM status.

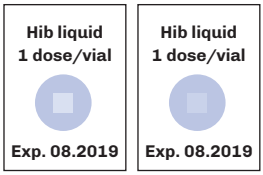


Here, I would prefer to keep the longer expiry date one and discard the one that expires in 04.2019.

42 For details of such cases, please refer to the *Vaccine stock management: Guidelines on stock records for immunization programme and vaccine stock managers,* by A Afsar and U Kartoglu, WHO/IVB/06.12.

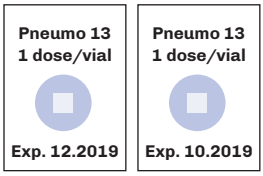
Both MMR and BCG vaccines should be placed on the top shelf. The diluents must be kept together with the vaccine. It is recommended to place the vaccine in front and its diluent just behind. If possible, using trays and/or carton boxes will help keeping vaccines and corresponding diluents together.

Next set of vaccines is **Hib liquid** in 1 dose vial, both vials with the same expiry date but with different VVMs.



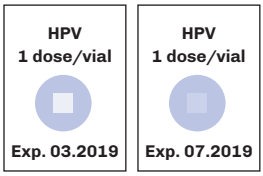
Hib liquid is freeze-sensitive and must be placed either in the middle or bottom shelf. To be used first, the one with darker VVM must be placed in front of the one with lighter VVM.

The next set of vaccines is **Pneumo13** in single-dose vials with different expiry dates but with similar VVM status.



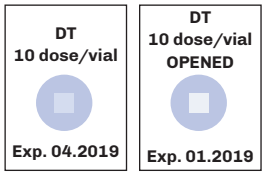
Pneumo13 is freeze-sensitive as well and must be stored either in the middle or in the bottom shelf in a front opening refrigerator. Since the VVMs exhibit a similar status, the one with shorter expiry should be placed in front for priority use.

The next set of vaccines is **HPV** in single-dose vials with two different expiry dates and VVM status.



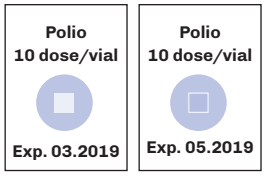
HPV vaccine is also freeze-sensitive and must be stored either in the middle or bottom shelf of a front opening refrigerator. Here the vaccine with quite dark VVM should be in front and the one expiring in 03.2019 behind it.

The next group of vaccines is **DT** in 10-dose vials with different expiry dates, VVM status and one being opened.



In principle, the opened vial must be used first, however this particular one is already expired (remember 'today' is 2 February, and this particular vial has expired on 31 January). This vaccine must not be kept in the fridge and should be put aside to be discarded according to approved discard procedures. Since we have only one vial of DT with an expiry date of 04.2019, we place this vaccine either in the middle or bottom shelf.

The last set of vaccines is **OPV** in 10-dose/vials with different expiry dates and VVM status.

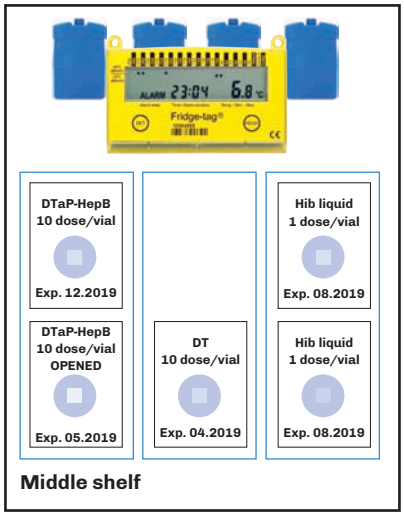


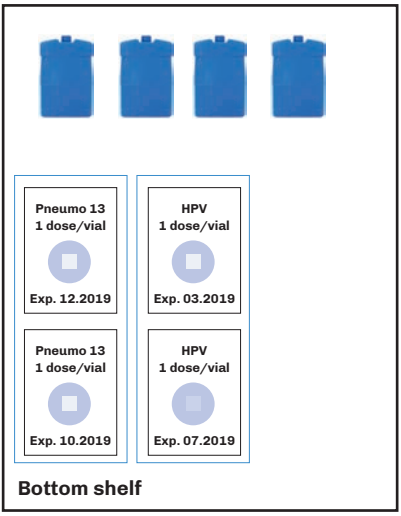
The one that expires in 05.2019 has a VVM that is beyond its discard-point and should not be used. This vial must be removed from the fridge and put aside to be discarded according to approved discard procedures. The only remaining vial of OPV should be placed in the top shelf. Although OPV can be kept in the freezer, WHO does not recommend OPV to be kept in freezer at the health centre level.

The temperature monitoring device is recommended to be kept with the freeze-sensitive vaccines. In front-opening refrigerators, it is best to keep temperature monitoring devices in the middle shelf.

The crisper should be taken out of the fridge and its place filled with **water bottles**. This will add thermal mass to the fridge, which will be critical in delaying the temperature rise in the case of power loss. Labels and non-toxic colorants can be added to these water bottles to dissuade people from drinking them.

Water packs are usually kept in the freezer compartment for having ice available for outreach sessions. It is also possible to put water packs to the back side of all shelves to add a buffer zone to prevent vaccines being exposed to cold temperatures coming from the back panel. This is a good practice.

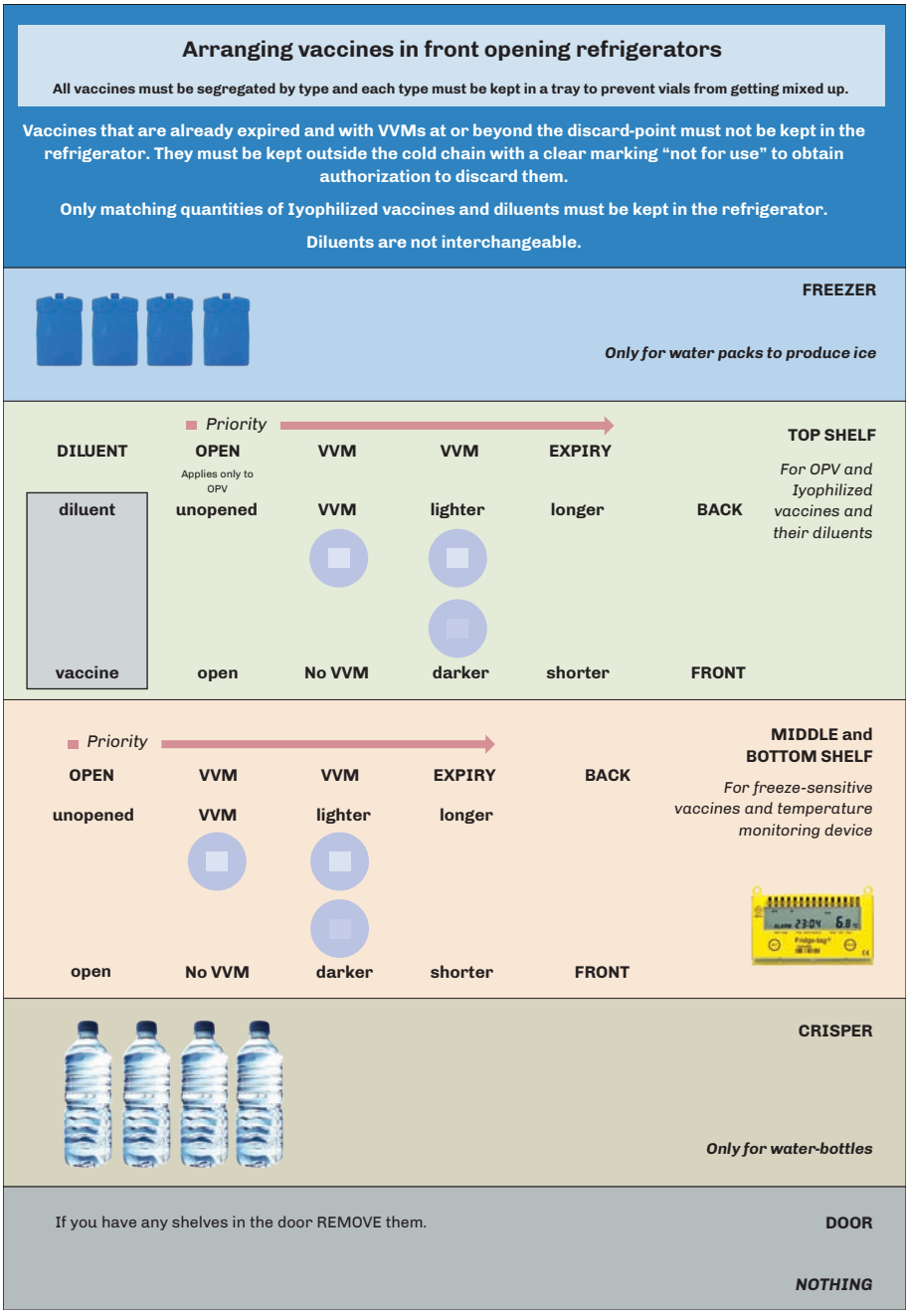




No vaccine should be stored on the inside of the **door**.

Now, let's put all this reasoning in a decision tree format. In this decision tree, I have added a 'priority' scale which takes vaccines that are opened and kept for subsequent immunization sessions first, then vaccines without VVMs, then vaccines with VVMs, and the expiry period.

Decision tree for arranging vaccines in front opening refrigerators



In refrigerators, all vaccines of the same type should be kept in trays and labelled. This will help health workers to easily find what they are looking for. Trays should also be organized to indicate vaccines that have priority in use (VVM indication, opened vials, expiry). When VVMs show different shades, then within the trays, separating the vaccines to signpost which ones must be used first is a good practice.

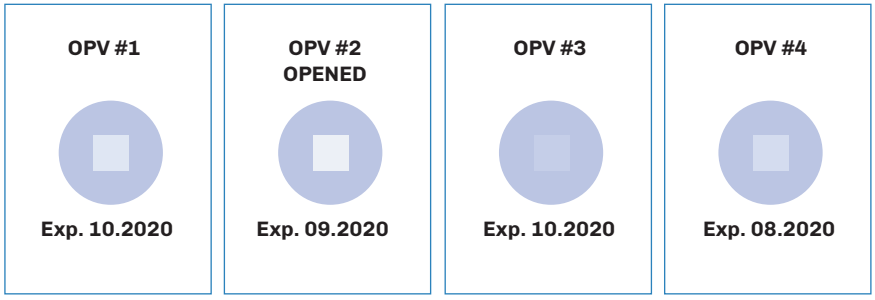
When I was in Oman for the EVSM assessment, I was impressed with the way health centre staff organized OPV tubes in a tray, clearly indicating the ones to be used first.

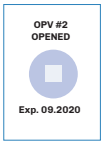
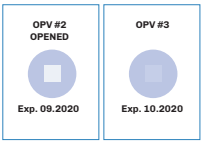
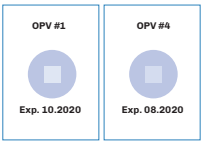
Signposting priority use vaccines in a tray based on VVM indication, Oman

Which vial to use first?

VVMs can help in deciding which vials are to be dispatched first from storage facilities. Similarly, VVMs help health workers to decide which ones to use first for different types of activities. Vaccines can be safely used when the inner square of VVM is lighter than the outer circle (reference). When there are different shades of inner square of VVM (still lighter than the outer circle), in principle the darker one should be used first. However, there are cases where lighter VVMs should be picked up and not the darker ones. Let's review different situations and reasons for using light or dark VVMs.

Let's assume that on day 12 May 2020, we have the following OPV vials in the health centre refrigerator. For the three scenarios given below, let's determine which OPV vial we would select to use.



Scenario	Vaccine to be used	Reason
Fixed immunization session at the health centre		Opened vials must be used first for fixed immunization sessions. If an open vial is finished in the session and you still have children to be immunized, next choice would be the darkest VVM with OPV#3.
Short outreach – Departing from the health centre, conducting the outreach session and come back is within 4 hours		In principle, open vials must be used first. However, in order to reduce the contamination risk, they should be used with caution for outreach. Depending on how many doses are remaining in the opened vial, the next choice would be the darkest VVM with OPV #3.
Long outreach - Departing from the health centre, conducting the outreach session and come back is 48 hours		It is not wise to risk VVMs reaching their discard-point in long outreach activities. This is why we do not recommend vaccines with the darkest VVMs to be used in these cases. Best is to pick a VVM that still has quite a safety margin – a lighter one. Here in our example, we have 2 VVMs that are lighter than the OPV #3, one with expiry date 08.2020 with a darker one, and the other much lighter with 10.2020 expiry. Depending on the climatic conditions, picking any of these two would be correct.

When there is an alarm

WHO recommends the use of 30-day electronic refrigerator logger for health centre refrigerators. Currently, there are three devices prequalified by the WHO PQS.

WHO PQS prequalified 30-day electronic temperature loggers*			
PQS code	**Manufacturer**	**Manufacturer's reference**	**USB interface**
E006/013	LogTag® Recorders Ltd.	LogTag VaxTag	No**
E006/020	Berlinger & Co. AG	Fridge-tag 2	Yes
E006/014	Berlinger & Co. AG	Fridge -tag 2E	Yes

(*) Although a 30-day electronic temperature logger, HETL-01 by Qingdao Haier Biomedical Co., Ltd (PQS code E006/042), is listed I would not consider this device as actually belonging in this category since it does not meet all PQS product specifications.

(**) VaxTag data can be downloaded via optional LogTag interphase that is sold separately

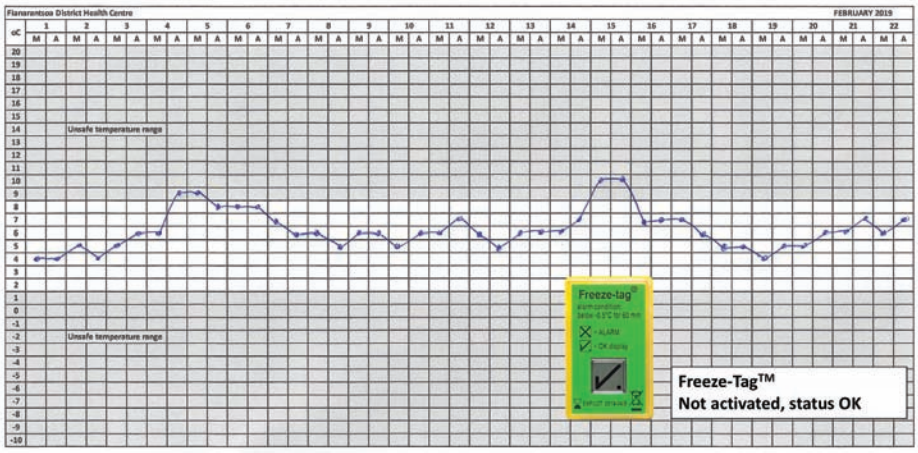
In addition to these devices there are also remote temperature monitoring devices that can be used in health centre refrigerators which send SMS alarms to registered users. These are costly compared to 30-day electronic temperature loggers.

Some refrigerators may have electronic freeze indicators (and no 30-day electronic temperature logger). These threshold indicators trigger an alarm when there is an exposure to a single temperature event of -0.5°C or below for a minimum of 60 minutes.

Alarm settings for these devices are factory programmed. Low Alarm triggers when an exposure to a single temperature event of -0.5°C or below occurs for a minimum of 60 minutes. High Alarm triggers where there is an exposure to a single temperature event of +8°C or above for 10 hours. Here the question is what action to take when such alarms trigger. As for the High Alarm, the answer lies with the VVM. If there are no VVMs, in any such cases of High Alarm, all vaccines must be discarded. This demonstrates how VVMs can reduce vaccine wastage and save money.

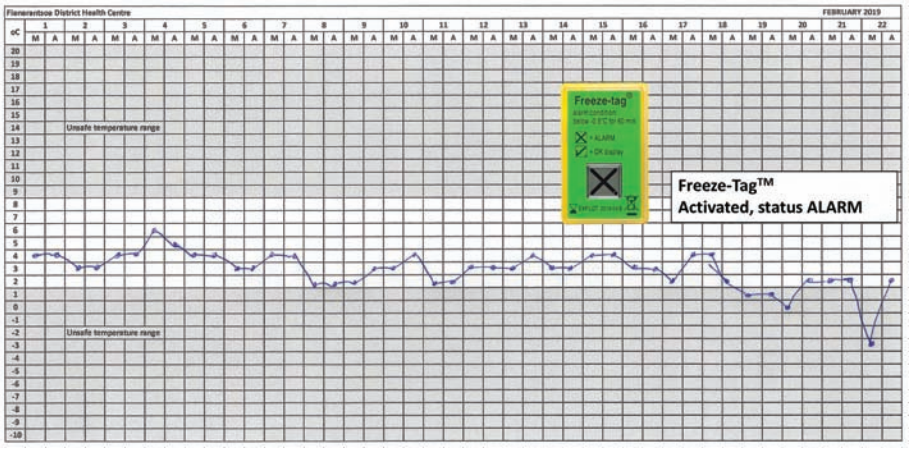
Let's illustrate this with two different scenarios. Here, I will present two scenarios along with a series of vaccines. Then we will discuss each vaccine as to whether it can be used based on the temperature scenarios. You should note that today is 23 February 2019 when evaluating.

SCENARIO 1



Vaccine	Status	Use	Don't use
TT (VVM on label) **Exp. 02.2019**	**Opened** 3 days ago	Expiry date has not been passed (expiring at the end of the month). Although it is open, VVM is on the label and in good condition. Vaccine can be used.	
OPV (VVM on label) **Exp. 06.2019**	**Opened** 7 days ago	Expiry date has not been passed. Although it is open, VVM is on the label and in good condition. Vaccine can be used.	
HPV (VVM on the cap) **Exp. 05.2020**	**Unopened**	Vaccine can be used. Expiry date has not been passed.	
MMR (VVM on the cap) Exp. 03.2019	Unopened		Expiry date has not been passed. However, VVM is beyond the end-point. It should not be used. The vial must be taken out of the fridge for approved disposal.
BCG (VVM on the neck of the ampoule) Exp. 06.2019	Unopened	Expiry date has not been passed. VVM is in good condition. Once opened, it must be discarded within 6 hours or at the end of the session, whichever comes first.	
No label	Unopened		Vaccines with no labels should not be used and must be taken out of the fridge for approved disposal.
MMR (no VVM) Exp. 10.2019	Unopened		Although expiry date is good, since there is no VVM, vaccine should not be used and must be taken out of the fridge for approved disposal.
HepB (VVM on label) Exp. 12.2019	Unopened	Expiry date has not been passed. Although VVM is quite dark, it is still usable. Vaccine can be used with high priority.	

SCENARIO 2



Vaccine	Status	Use	Don't use
TT (VVM on label) **Exp. 02.2019**	**Opened** 3 days ago		Vaccine is Al adjuvanted, therefore freeze-sensitive. Since it is open, it is recommended not to conduct any shake test and to discard it in accordance with authorized procedures.
OPV (VVM on label) **Exp. 06.2019**	**Opened** 7 days ago	OPV is not affected by negative temperature excursions. Although VVM is quite dark, it is still usable. Vaccine can be used.	
HPV (VVM on the cap) **Exp. 05.2020**	**Unopened**	Vaccine is a liquid presentation and Al adjuvanted. Shake test must be conducted. It can be used if it passes the shake test.	Vaccine is a liquid presentation and Al adjuvanted. Shake test must be conducted. It must be discarded in accordance with authorized procedures if it fails the shake test.

MMR (VVM on the cap) Exp. 03.2019	Unopened		MMR is a lyophilized vaccine and is not affected by negative temperatures. However, VVM is beyond its end-point. Vaccine cannot be used and must be taken out of the fridge to be discarded in accordance with authorized procedures.
BCG (VVM on the neck of the ampoule) Exp. 06.2019	Unopened	BCG is a lyophilized vaccine and is not affected by negative temperatures. VVM is in good condition. Once opened, it must be discarded within 6 hours or at the end of the session, whichever comes first.	
No label	Unopened		Vaccines with no labels should not be used and must be taken out of the fridge and disposed of in accordance with authorized procedures.
MMR (no VVM) Exp. 10.2019	Unopened	MMR is a lyophilized vaccine and is not affected by negative temperatures. Since there is no VVM, vaccine should be used with higher priority.	
HepB (VVM on label) Exp. 12.2019	Unopened	Although VVM is quite dark, it is still usable. Vaccine is Al adjuvanted. Shake test must be conducted. It can be used if it passes the shake test.	Although VVM is quite dark, it is still usable. Vaccine is Al adjuvanted. Shake test must be conducted. It must be disposed of in accordance with authorized procedures if it fails the shake test.

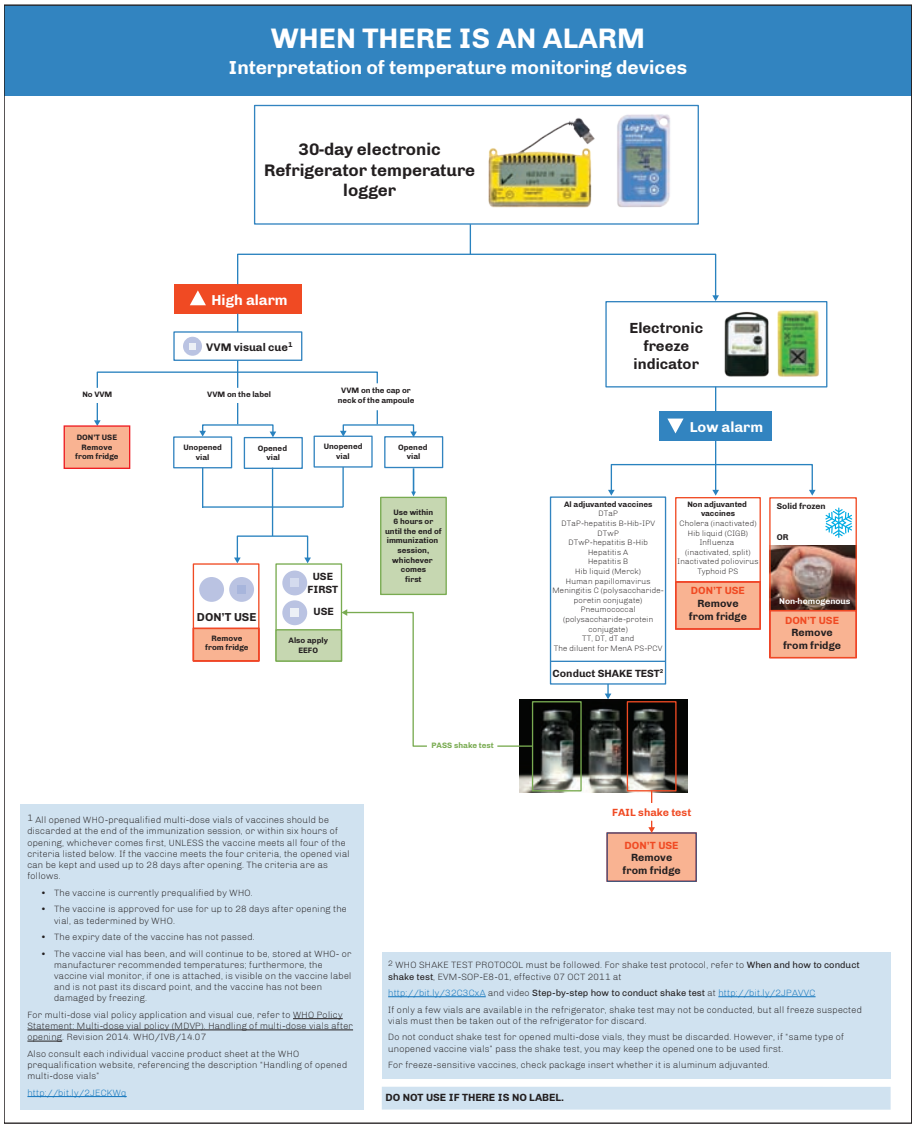
Based on these discussions, we understand that there are two tracks – High Alarm and Low Alarm. In the case of Low Alarm (-0.5°C for 1 hour), a shake test should be conducted for all Al adjuvanted freeze sensitive vaccines. As for the High Alarm, we refer to VVM as the visual cue.

The most critical principle is that any vaccine that is unfit for use has no place in the cold chain. Such products should not be kept in the refrigerator even with

clear markings. Such vaccines (expired, heat damaged and freeze damaged vaccines) must always be removed from the refrigerator and the approved local discard procedures followed.

We can now apply all these arguments into a decision tree.

Interpretation of temperature monitoring devices when there is an alarm



VVMs constitute an important reference in deciding whether or not to use the vaccines in the case of High Alarms. Without VVMs, in all High Alarm situations, all vaccines, regardless of their presentation (liquid or lyophilized), should automatically be discarded. Even though the high temperature excursion may not be excessive, without VVM no one can take the risk of assuming that these vaccines were handled within the recommended temperature range before they reached the health centre.

Look my friend, your VVM is as good as mine

The supervisor of a number of vaccination teams is waiting for vaccine carriers and icepacks in order to start immunization against polio in the region for which he is responsible. He received the vaccines, but to his astonishment, he hears over the radio that the vaccine carriers were delivered to the wrong place, and that he is expected to manage by whatever means he can think of.

The local population tells him about what they call. “the local fridges” containing gourds filled with water and charcoal, that allow the contents to be kept cool. The supervisor decides to ask the population for a number of gourds. First there is some resistance, because the people are afraid that their precious gourds might get broken, but when the supervisor asks whether they prefer

polio or broken gourds, the argument is settled. The supervisor puts a "kick Polio out of Africa" t-shirt on top of the water and charcoal container and places the vaccines wrapped in "kick Polio out of Africa" caps, on top. He then sets off for the cattle camp, where he starts immunizing after arrival.

However, another team, with vaccine carriers and ice, had also decided to immunize in the same camp. The supervisor of this team accuses the 'gourds' team of using non-potent vaccines, because of improper storage, and advises people to bring their children to his vaccination team. The supervisor of the gourds team of course cannot accept this insult to his professional pride and very clearly expresses his opinion in front of the VC supervisor. This nearly develops into a fight, until the village elders decide to interfere. They ask the VC supervisor why he thinks his vaccine carriers are any better than their gourds. On his guard, and realizing how delicate the question is, the VC supervisor challenges the gourd supervisor by accusing him of using non-patent vaccine.

The latter takes two vials of OPV, one out of the gourd, and one out of the vaccine carrier and says proudly:

"Look my friend, your VVM is as good as mine."

Hans Everts, Technical Officer, WHO

Use of vaccine vial monitors to manage vaccines after the recent earthquake in Jogjakarta, Indonesia

Indonesia has applied vaccine vial monitors to all its EPI vaccines except for BCG vaccines (due to economic reasons). VVM is used for Measles, OPV, DTP and DTP-HB, HB, TT and DT vaccines. The example that follows illustrates the "Earliest Expiry First Out" (EEFO) system and how it improves the confidence of the health workers at all service levels regarding the "quality" of the vaccine to be delivered.

During the May 2006 earthquake centered in Yogyakarta (on the island of Java in Indonesia), much of the infrastructure was damaged including the cold store facilities at the district and health centers. Electricity supply was out for some days and generators were not functioning or used. By observing the VVM condition on the vaccines, health workers were able to decide which vaccines were still viable for use and which needed to be discarded. In the disaster areas, VVMs on the OPV vials were already reaching the usage limit, giving visual indications to health workers that vaccines needed to be discarded and re-supplied. The other vaccines with VVMs still showing good condition were not discarded and could still be used to reduce wastage. As for the BCG, the MOH decided to discard all BCG vaccines because there was no indicator to show the

heat exposure effect in a non-functioning cold chain condition. In total, vaccine in 5 districts and more than 50 health centers (an estimate of up to 50,000 doses) was saved from being wasted due to the presence of VVM on the vials. The practicability of VVM as an indicator that can be read visually without any accessory devices is a great advantage.

This is one example how the use of VVM is able to reduce vaccine wastage and improve health workers' confidence in vaccine quality before administration.

Anton Widjaya and Vanda Moniaga
PATH Indonesia Immunization Team

The PAHO controversy

Although PAHO serves as the Americas Regional Office for WHO, it differs in many ways from other WHO regional offices. PAHO wears another institutional hat; it is the specialized health agency of the Inter-American System; a body founded many years before the formation of WHO.

In fact, PAHO's history goes back to 1902, making it the oldest international public health agency. The Second International Conference of American States (Mexico, January 1902) recommended that "a general convention of representatives of the health organizations of the different American republics" be convened.

Myron E. Wegman describes the lack of significant progress at the international sanitary conferences as being the main drive thrust of the second meeting of the International Conference of American States in 1902. He further describes that there was major concern with expediting the conveyance of perishable cargoes and overcoming the crazy quilt of quarantine, inspection, and exclusion regulations which were seriously impeding the transport of goods.[43] "Another timely point was the, at the time, very recent proof of the theory of Carlos Finlay, the great Cuban physician, about the transmission of yellow fever by Aedes aegyfiti. The demonstration of this theory in Havana by Reed, Lazear, and Agramonte highlighted the possibilities of international cooperation."

43 Myron E. Wegman. (1977) A salute to the Pan American Health Organization. *PAHO Bulletin.* 11(4):297-302

Signing of the agreement between the WHO and Pan American Sanitary organization by Dr. Brock Chisholm, Director-General, WHO, and Dr. Fred L. Soper, Director, Pan American Sanitary Bureau, on May 24, 1949 (United Nations photo)

The conference was held in Washington, D.C., on 2-4 December 1902 and established a permanent directing council: The International Sanitary Bureau, which was the predecessor of the current PAHO. In 1923, the 5th International Conference of American States, meeting in Santiago, Chile, changed the name to the Pan American Sanitary Bureau. In 1924, the Pan American Sanitary Code, signed in Havana and ratified by the governments of the twenty-one American republics, assigned broader functions and responsibilities to the Bureau as the central coordinating agency for international health activities in the Americas. The 12th Pan American Sanitary Conference (Caracas, 1947) adopted a reorganization plan whereby the Bureau became the executive agency of the Pan American Sanitary Organization, whose Constitution was officially approved by the Directing Council at its first meeting in Buenos Aires later that year.

After the creation of WHO in 1948, an agreement was signed with the Pan American Sanitary Bureau recognizing it as WHO's Regional Office for the Americas (1949).

The following year, an agreement was signed with the Organization of American States (OAS) recognizing the Pan American Sanitary Organization as a fully autonomous and specialized inter-American organization. Thus, the Organization became a component of both the United Nations and the inter-American systems. The 15th Pan American Sanitary Conference (San Juan, Puerto Rico, 1958) changed

the name of the Pan American Sanitary Organization to the Pan American Health Organization, but the name of the Pan American Sanitary Bureau remained unchanged.

Even by the time the Pan American Sanitary Bureau became the WHO Regional Office for the Americas, PAHO had many achievements under its belt. This continued to be the pattern with PAHO always seeming to be one step ahead of WHO. During its more than 100 years of existence, PAHO has been the catalyst for many initiatives that have resulted in remarkable public health achievements. Life expectancy in the region has gained 30 years on average since 1902. In 1991, the last case of polio was reported in Latin America and the Caribbean. In 1994, the Region was certified as being polio free of the indigenous wild poliovirus. It was going to take six more years for the next Region (Western Pacific) to eradicate polio. In 2002, the Region met its goal of eliminating the circulation of the endemic measles virus and in 2015, an International Expert Committee determined that the region had interrupted the endemic transmission of rubella. In 2016, during the 55th Directing Council of the PAHO/WHO, the Region was declared free of measles.


EPI Newsletter
Expanded Program on Immunization in the Americas
Volume XVI, Number 4 IMMUNIZE AND PROTECT YOUR CHILDREN September 29, 1994
The Americas conquer Polio!
On August 23, 1991, Luis Fermín Tenorio was the last person to suffer from poliomyelitis in the Americas when at the age of two he was infected by the wild polio virus in his town Pedregal, Peru.
In this issue:

PAHO EPI Newsletter announcing the Americas conquering polio (1994)

The problem with the PTS technology

PAHO is the only WHO Region not requiring VVM on any vaccines, and although PAHO officials never showed any negativity towards VVM in international platforms, they somehow managed to drag their feet for years with a range of arguments.

In the early 1980s, validation field studies of measles VVM based on PTS technology were being conducted in Argentina, Brazil and Peru. These validation field studies were co-sponsored by the PAHO/EPI and PAHO's Programme for Health Technology Development. Field study reports indicated that health workers had a positive reaction to the indicator, and the workers were unanimously in the view that the indicator provided the security of knowing they were administering an effective vaccine. They felt the indicator was valid for its designed purpose, and there were no problems with color interpretation.

Peter Carrasco (PAHO) recalls that PAHO was always supportive of VVM, and only started to harbor reservations when they discovered that information on the

PTS technology was not being communicated openly to all parties, especially to PAHO. This was a specific reference to a toxicity issue that had emerged with the PTS technology. *"We did not believe, with their knowing about the toxicity problem, that PATH would carry on with the field validation studies."* But Peter did not remember exactly when and how the toxicity issue was discovered by PAHO. Following this claim, I talked to Ray Baughman, as to whether the toxicity issue was known at the time they handed over the product dossier to PATH for licensing purposes. Ray says that the toxicity issue came up in 1984 when the field validation studies had all been completed. Vivien Tsu, who was the responsible officer in PATH of the early field validation studies confirms this. Although the PTS technology had limitations to be expanded to vaccines other than measles, this negative development was a great disappointment to everyone.

"For the 31 years that I worked for this company during which it had the various names Allied Chemical, Allied, Allied Signal, and eventually Honeywell, the company culture fostered the highest standard of ethics." says Baughman, *"I did not personally see any example of an instance where this high standard was not upheld. In fact, the absence of appropriate disclosure during negotiations would have likely led to the firing of the offending person concerned, so that no more damage could be done by the individual."*

Ray pointed out that research and licensing are kept as two separate activities. *"I have a strong memory of the event where I learned about the Ames test result (likely no more than a week after the tests were conducted by others who were not in my team), since it was at a reception prior to a board meeting, where I was briefly presenting the time-temperature indicators."* An Ames test is a biological assay to assess the mutagenic potential of chemical compounds. It utilizes bacteria to test whether a given chemical can cause mutations in the DNA of the test organism. A sample's mutagenic potential is assessed by exposing amino acid-requiring organisms to varying concentrations of chemical and selecting for the reversion event. Media lacking the specific amino acid are used for this selection which allow only those cells that have undergone the reversion to histidine/tryptophan prototrophy to survive and grow. If the test sample causes this reversion, it is a mutagen.

During that time, Allied conducted a series of 12 studies. These studies and the review of a consultant toxicologist, concluded that the solid PTS chemical in the quantity deposited on the label (3 mg), has insignificant oral toxicity and low potential for mutagenicity in humans. This is thought to be largely explained by the extremely low solubility of the chemical (10^{-6M}). However, the chemical in its monomer form, when the indicator is colored red, was a significant dermal sensitizer and eye irritant. It had caused a general rash in a human subject working with the raw chemical (recorded under Toxic Substances Control

Authority – TSCA registration) and caused permanent eye damage in test rabbits. The presentation of the indicator and the protection from the active chemical was therefore of great importance in order to reduce the risk of contact to negligible levels. Exposure of the discarded red indicators to high temperatures causes them to polymerize and renders them harmless. The active chemical was registered accordingly with the U.S. EPA under the TSCA and would be manufactured according to the requirements of the United States regarding hazards to employees during volume manufacture.

In the view of this potential danger of the active chemical to the eyes and skin, the protective encapsulation of the indicator was inadequate and the printing paper being used was unable to offer such protection. The problem was mainly a risk at the production stage, rather than for the users of the technology. Nevertheless, despite the extremely low risk, PATH concluded that the PTS technology was not promising for its application onto other vaccines in view of the associated constraints. These included a reaction rate that was too slow for use on the most heat sensitive e vaccine OPV, dermal toxicity issues, and printing difficulties.

In the following years, two other PAHO countries were involved with VVM design studies, Mexico and Bolivia.

A public health hero Dr. Ciro de Quatros and VVMs

Following the emergence of today's VVM technology with LifeLines, on 15 October 1991, Peter Carrasco signed a memo, addressed to PATH, requesting VVM samples for internal use and evaluation, indicating that they needed to decide on the introduction of VVM before September 1992. In the 1994 TechNet Consultation in Washington, D.C., Peter Carrasco presented the regional working plan that included VVMs. In this action plan, with the objective of assuring that opened vials of vaccines were discarded before the vaccine loses potency, Peter indicated that PAHO would implement a strategy to introduce VVMs on TT, DPT and DT vaccines for 1994-1996. In this regard, he indicated three major activities relating to VVMs:

- *Circulate samples of VVMs with costs and instructions on use to AMRO countries*
- *Request that 1995 EPI Revolving Fund tenders include VVMs for EPI vaccines*
- *Survey all countries to determine quantities of vaccine/number of sites where EPI vaccines will be taken out of cold chain.*

The TechNet Consultation endorsed a plan of action for the Regional Office for Americas, as well as the Regional Offices for Africa (and separately for Ethiopia

Dr. Ciro de Quadros

and Tanzania), Western Pacific (and separately Papua New Guinea) and GVP/EPI Geneva with specific highlights on the VVM. In forthcoming consultations with TechNet, PAHO did not report back on these issues nor was it questioned by any TechNet members.

That was the time when big preparations were underway to get the VVMs onto OPV vials. But, an important public health achievement by PAHO was going to be used as a case against the VVM shortly afterwards. Just three months after Peter Carrasco produced PAHO's action plan for 1994-1996, the Americas Region was certified as being polio free of the indigenous wild poliovirus by The International Commission for the Certification of Poliomyelitis Eradication (ICCPE) in Washington, D.D., during its third meeting from 24-25 August 1994.

It was Dr. Ciro de Quadros, EPI Programme Coordinator for the Americas, a Brazilian epidemiologist, who was the central figure in the eradication of polio from Latin America and the Caribbean. In the late 1970s, Ciro founded the EPI at PAHO, encouraging and supporting the countries of Latin America and the Caribbean in making vaccines available. He began advocating for the eradication of polio from the Americas in the early 1980s, and successfully mobilized support from immunization experts, organizations and health authorities in PAHO Member States. In 1979, De Quadros was behind the creation of the PAHO Revolving Fund for Vaccine Procurement, to pool the demand for vaccines and immunization supplies. This led to achieving economies through purchasing vaccines at lower prices.

Dr. Ciro de Quadros, center, in Ethiopia in 1971

Dr. Donald A. Henderson (WHO) says that De Quadros was a fearless and inspirational leader and *"It is difficult to grasp the magnitude of Ciro's achievement."*[44] Dr. Henderson, recruited Ciro to help organize smallpox eradication in Ethiopia. De Quadros served as WHO's Chief Epidemiologist for the Smallpox Eradication Programme in Ethiopia from 1970 to 1979. His work in Ethiopia brought him the fame as a leader in the development of surveillance and containment strategies that were used in the eradication of smallpox worldwide.

44 https://nyti.ms/31VEjGt

It is difficult to understand why a public health paragon closed the doors to a technology that was realizing great savings for immunization programmes, as well as facilitating a considerable number of vaccine management strategies. Could this perhaps be explained by professional hubris?

PAHO's main argument was that they had managed to eradicate polio, using the most heat sensitive vaccine, without the help of VVM so why would they need it for much more heat-stable vaccines. One other argument PAHO used was that the cold chain in its Member States was good. Gordon Perkin explains that it was not until after the work with VVM was advanced that the naysayers had emerged. *"I hate to use names but the leader of this was Ciro de Quadros in PAHO,"* says Perkin, *"He said that if we tried to bring this into Latin America, it would be over his dead body. And unfortunately, that turned out to be the case. He said they had spent thousands of dollars indoctrinating health workers with the credo that 'if a vial of vaccine sits out you throw it out'. Here you are coming along with a technology that makes us look like we are liars, so we are going to fight you every step of the way to keep this out of Latin America."* Perkin continues: *"And then there was Peter Carrasco in PAHO who said what if someone eats the markers – apparently the PTS was associated with some skin irritation – and it proves to be toxic what is the liability and what's going to happen?"*

In fact, Ciro's concern relating to VVM implied that vaccines are not necessarily spoiled when they are temporarily removed from the cold chain and this, of course, was correct. But in all field studies, health workers were very hesitant to accept that a vaccine could be used based solely on the VVM indication since they have been emphatically drilled to discard the vaccines under such circumstances. This was the reality at that time simply because there was no proven means of differentiating a heat damaged vaccine from the others since such a damage was not visible. Only VVM made this possible.

De Quadros's legacy continued after he left PAHO and joined the Sabin Vaccine Institute as Vice President in 2003.

Nonetheless, despite the very strong stance at PAHO, there were numerous attempts to break through the PAHO barrier.

Consider a region-wide policy to include VVMs on all vaccines

At a Geneva VVM technical review meeting in 2002, Dr. Otavio de Oliva, Regional Advisor for AMRO (PAHO), stated that they had not accepted VVMs at that point because they were available only for OPV and polio had already been eradicated in Americas. He went on to say that they were revisiting this position, and before they took a decision, they would need to check with the regulatory authorities in the Americas. Dr. de Oliva also added that PAHO's delay was due to their

preference for all vaccines to have VVMs. On the surface this was a reasonable excuse. He said that following the provision of all technical information on the use and interpretation of VVMs to Member States, and their agreement to the added expenditures, and after consideration of all training needs considered, PAHO would probably accept vaccines with VVMs. But, PAHO never came back with any position of the regulatory agencies from Latin America and the Caribbean nor with any argument on the costs involved. Basically, the reasons for PAHO's rejection did not go much beyond its 'eradication of polio' argument.

As new vaccines were introduced into EPI programmes, the financial investment in vaccines increased significantly. The existing cold chain was naturally limiting vaccine availability and effectiveness. In response to this dilemma, UNICEF's The Americas and Caribbean Regional Office (TACRO) and PATH convened a regional workshop to foster a practical discussion on cold chain management issues. PAHO had representatives participating but was not involved in the organization of this. EPI managers, cold chain managers and MOH representatives from 14 Member States along with UNICEF, PAHO and PATH representatives met in Panama City in central America from 31 May to 2 June 2006. Despite PAHO occasionally mentioning that information on VVMs would be distributed to countries amidst their claim that PAHO countries did not have any cold chain problems, the meeting served to expose the whole of the iceberg and establish that the reverse was true. Here are some highlights from the meeting report (Some sections underlined for emphasis):

"Peru is working hard to improve its cold chain and immunization programs. Advocacy has brought cold chain issues to the attention of the Minister of Health. An inventory of equipment was conducted which showed 134 different types of cold chain equipment in use, much of it obsolete and not WHO-approved. Increased awareness is necessary to prioritize a large investment in equipment replacement."

"Many country representatives expressed interest in learning more about the science and application of the VVM technology."

"Freeze indicators are needed at all levels to know whether vaccines have been damaged due to freezing."

"Participants were interested in using VVMs and out-of-cold-chain strategies to reach inaccessible populations with immunization services. Several countries cited examples of where such approaches would help them reach remote populations."

"Some countries access difficult-to-reach populations, but with high wastage of vaccine–– out-of-cold-chain strategies would reduce wastage and extend immunization services further into hard-to-reach populations."

"VVMs are an important tool for reducing vaccine wastage: vaccines that have been exposed to heat during cold chain breaks may not need to be discarded if VVMs are available."

"Advocacy for new/improved monitoring systems in central stores is an essential component of improving vaccine management practices—these systems, once operational, are low maintenance and highly reliable."

"Better monitoring in smaller health centers is urgently needed."

The problems spelled out by country representatives were exactly like the cold chain and vaccine management problems one would face in any other region. PAHO, despite its claims, was not an exception.

By the time of this meeting, a Bolivia temperature monitoring study had been published by Carib Nelson.[45] This study monitored vaccine cold chain temperatures during routine DTP-HB-Hib vaccine shipments from central stores to 11 communities in 3 provinces of Bolivia. In all 11 monitored shipments, vaccines were exposed to freezing temperatures at one or more points. In each of the shipments, temperatures below 0°C were recorded for 2-50% of the monitoring period. Freezing occurred at almost every level of the cold chain distribution system, especially during district and health center storage and during transport to the province and district levels. Seven of the 11 shipments were exposed to temperatures above 8°C, although none were exposed to excessive heat longer than 1.3% of the total monitoring period. Following the study, Bolivia introduced corrective actions in a systematic way and they have been praised for their dedication to improving the quality of their cold chain. Most importantly, other countries expressed interest in conducting similar studies in their countries.

The meeting concluded with a list of country priorities and solutions. Here, I have created a regional map with priorities and recommended solutions related to VVM. Non-marked countries on the map had listed mainly training, cold chain equipment, and funding related priorities.

The recommendations on the problem of hard-to-reach areas focused on the cold chain constraints as well as the need to improve awareness of the heat stability of the vaccines. The group was in consideration of a region-wide policy to include VVMs on all vaccines. In addition, the identification of situations where an out-of-cold-chain strategy could be implemented to increase coverage in hard-to-reach populations was agreed upon. The group also agreed that such strategies should be introduced in target areas on a phased basis.

Despite Member States representatives being eager to reduce wastage, and increase coverage in hard-to-reach geographical areas with the help of VVM, such a sensible move was not easy to implement at all. The PAHO Revolving Fund for Vaccine Procurement never agreed to include VVMs in their tender documents. Countries were free to procure vaccines with VVM themselves, but not through the fund.

45 C Nelson, P Froes, AM Dyck, et al. (2006) Monitoring temperatures in the vaccine cold chain in Bolivia. *Vaccine*. 25(3):433-437. Epub 2006 Aug 28.

Priorities and recommended solutions related to VVM, Latin America and the Caribbean

In that same year, during a SAGE meeting, I sounded out with the PAHO representative the possibility of an impact study to be conducted in a country (to be decided by PAHO) with the objective of demonstrating how VVM reduces vaccine wastage and improves coverage in hard-to-reach areas. The only thing that was required from PAHO was their agreement to the review and their selection of the country to be studied. The funding would come from the WHO headquarters. For a moment, I thought that there was some light appearing at the end of the tunnel but, in the end this discussion came to nothing.

The blow: 2009 Argentinian cold chain law

On 11 March 2009, Argentina passed a law (see Box on page 285) on the regulation of the cold chain for pharmaceutical products. This decreed that within a 2-year period all the pharmaceutical products for human and veterinary use containing thermo-sensitive active ingredients would have to be supplied in their individual packaging with an indelible, inalterable and irreversible temperature in-

dicator providing verification that the cold chain for the product has not been broken by the time it is received by the consumer. However, at the time of enactment of the law the Argentinean market had absolutely no experience with time and temperature integrators (TTI). The initiative came to nothing and amounted to nothing more than a complete calamity. So, what went wrong?

MEDICAMENTS

Law 26.492

Regulation of cold-chain of the medication

The Senate and Chamber of deputies of the Argentina nation assembled in Congress, etc. they sanction with force of law:

LAW OF REGULATION OF THE CHAIN OF THE MEDICATION

Article 1º – In the term of two (2) years from the date this law is in force, all the pharmaceutical products for human or veterinary use containing thermo-sensitive active ingredients will have to be supplied in their individual package with an indelible, inalterable and irreversible temperature indicator, which allows verifying that the cold chain for the product has not broken by the time it is received by the consumer.

Article 2º – The indicator will have to be introduced by the manufacturer and will have to remain in the pharmaceutical product up to the individual consumer unit.

Article 3o – For multidose units, the indicator will have to remain in the package, so that the consumer can verify that the cold chain of the product that is in his/her possession was not interrupted, having altered or inactivated the original properties of the medicine.

Article 4o – The enforcing authority will promote, either directly and/or through the actors of the cold chain, the greatest knowledge of the population about the implemented system, its characteristics, and the recommendations for its proper and efficacious implementation.

Article 5o – The Executive Branch of Government will appoint the enforcing authority for the application of this Law and will issue its regulations with the purpose of, among others:

a) Determining according to its properties which products should be considered thermo-sensitive and list them in order of priority to apply the temperature indicator;

b) Establishing the maximum and minimum temperatures each product can be exposed to without losing its essence and the estimated shelf life from the moment the cold chain has broken;
c) Defining rules with the characteristics that the indicator must have, as per the contents of Article 1° herein and establish the inspection procedures according to them;
d) Establishing the plan to be executed with each medicinal product for implementing the introduction of the indicator;
e) Determining the responsibility of the actors in every stage of the cold chain and the way in which their compliance will be recorded;
f) Establishing the procedure for the destruction of the unit;
g) Establishing the sanctions that correspond to the infringement of each responsibility

Article 6o – In exceptional cases and with the express and proper foundation, the enforcement authority may extend to twelve (12) months at the latest, the term of two (2) years established by the Article 1° of this Law.

Article 7o – To be notified to the Executive Branch of the Government. GIVEN IN ARGENTINE CONGRESS SESSION ROOM IN BUENOS AIRES, ELEVEN DAYS OF THE MONTH OF MARCH OF THE YEAR TWO THOUSAND AND NINE.

- REGISTERED UNDER NO. 26.492 - JULIO C. C. COBOS. - EDWARD A. FELLNER. - Enrique Hidalgo. - John H. Estrada

Unofficially translated from its original source
https://bit.ly/2NlzyD2

First of all, there was no preparatory work done with any of the partners that would be affected by the law. It appears that the law was put forward by two senators from some northern provinces where the ambient temperatures are usually quite high. But it is not known who drove their decision to initiate the law and how it passed through the legislature in the first place. And during the drafting of the law, there was no coordination between the lawmakers and the technical departments. To a grave extent, this lack of coordination continued once the law was in force. The reasoning for the law, the real motive, was never established. No scientific or technical information on the magnitude of any cold chain problems nor the necessity to introduce detective measures, were shared with anybody. As a result, the debate on the need for the law, its importance and legitimacy, didn't take place until after it had entered the statute books rather than during its development.

Meanwhile, the Pharma industry in Argentina at the time was having a WIIFM[46] (what's in it for me) moment, because they did not see any benefits in this initiative. Lawmakers and/or technical departments did not think of communicating these benefits to the pharma manufacturing sector. In addition, no technical solutions were being offered to the pharma industry. This was mainly due to the state technical departments not being aware of the availability of possible solutions such as TTIs. This absence of communication was taken advantage of by the pharma industry who were able to raise a flag to the effect that no technical solutions were available for them to comply with the law.

As a result, the pharma industry expressed their considerable resistance. They joined together and put up a very strong fight against the law, including lobbying the President for its veto/abolishment. As well as asserting that there were no technically feasible solutions they also claimed that there was no other example of such a law anywhere else in the world.

Of course, the industry protesters never revealed their true unease: a fear that such an implementation might reveal a scale of cold chain breaches for which the pharma industry might be, at least partly, responsible. This could have had serious cost and liability repercussions. For example, when it came to determining the correct matching of product with TTIs the lack of stability data on products might have been apparent. More importantly, there could have been concerns about levels of product recalls and returns that might be triggered. Of course, none of these underlying matters were cited as concerns at the time.

In Argentina the pharma sector is politically very strong. There are even instances of the pharma industry having been powerful enough to force the resignation of some high-level officials in ANMAT (National Drug, Food and Medical Technology Agency - equivalent to FDA).

As for the failure of the initiative, there were other factors as well. Many of the pharma products were being imported in finished form. Naturally, this added complexity mainly because the manufacturers had to apply the indicators at the fill finish locations.

It was also evident that the law was too broad in scope to obtain acceptance. It applied to all human and veterinary cold chain products without any prioritization. Although there was some support from the FDA for biologics and blood products this was not far reaching. No support was forthcoming from the medical community, trade unions (the Argentina Medical Association is organized in trade union/syndicate form) or patient groups. Some of these groups were not even aware that the law had been passed.

46 A question that may be asked about a new idea or method where the benefits are not obvious.

As a result, following the law entering statute, none of the industry made any effort to comply. Because of all the unfortunate and, often, baffling mistakes, this became a lost case; a bitter blow, and a missed opportunity that could have been otherwise if it had been more wisely planned.

PAHO Immunization Project Working Group on VVM with no VVM expertise

The Member States in PAHO continued to request information on VVMs. At one point in 2011, the PAHO Immunization Project requested that the PAHO Technical Advisory Group (TAG) provide a recommendation on the possible benefits provided by VVM were they to be introduced. Consequently, PAHO's Immunization Project convened a Working Group on VVMs which met in Washington, D.C., from March 3 to March 4, 2011.

The Working Group had three primary objectives for the meeting:

- hear and discuss a series of presentations on VVMs;
- review and assess the evidence on the performance of VVMs; and
- discuss the possible programmatic implications of introducing VVMs in the Region of the Americas.

The plan was to present the final report of the working group to the PAHO 19th TAG on Vaccine Preventable Diseases in preparation for a meeting on 6-8 July 2011 in Argentina.

One would have expected that this working group would have consisted of professionals with a vast knowledge and experience of VVMs either from a technical or an operational perspective. One would also have expected that a significant volume of reference documents would be shared amongst the participants as background documents. However, this was not the case at all. From the following list of participants, only a few had any direct experience with VVM, mostly as ordinary users, rather than as technical experts (except Ted Labuza). The majority of the group had no experience at all. It was like an all-men panel discussing women's rights.

List of the PAHO VVM Working Group Members

Lic. Analía Aquino, Ministry of Health – Argentina*

Dr. Bruce Weniger, MD, MPH. Associate Editor, Vaccine (Elsevier), PAHO temporal Advisor

Mrs. Catarina Schubert, Cold Chain Manager – Brazil

Dr. Carlos Castillo, PAHO Measles/Rubella Regional Advisor

Dr. Cuauhtémoc Ruiz, PAHO Principal Advisor Immunization Program

Mr. Daniel Rodríguez, PAHO Revolving Fund Regional Advisor

Dr. Ida Berenice Molina, EPI Manager – Honduras

Mrs. Jennifer Sanwogou, PAHO New Vaccines Introduction

Dr. Mohamed Ben Ghorbal, EPI Manager. Ministry of Health – Tunisia*

Ms. Mónica Pereira, PAHO Revolving Fund

Ms. Nora Lucía Rodríguez, PAHO Regional Coordinator Cold Chain Operations

Mr. Souleymane Kone, WHO Technical Officer, Geneva Department of Immunizations, Vaccines and Biologicals

Professor Theodore P. Labuza, Ph.D, Department of Food Science & Nutrition, University of Minnesota, PAHO temporal Advisor

Eng. Víctor Gómez Serna, PAHO Cold Chain Consultant Eng. Víctor Gómez Bravo, PAHO Cold Chain Consultant

** Participated via teleconference*

The reference materials that were circulated did not include any of the VVM impact studies. There was no reference to any of the out-of-cold chain studies that had been published in peer-review journals. Interestingly, however, all three WHO Technologies and Logistics Advisory Committee (TLAC) reports were among the reference materials. This selective information disclosure leads us to Dr. Bruce Weniger from the participants, who in 2008 and 2009 led a movement against VVM in the TLAC as committee chairman. Although WHO continued to require VVMs, Weniger brought his personal agenda to the 2011 PAHO Working Group where the participants essentially had no technical expertise to reply or challenge him (except Ted Labuza). He basically led the show in the working group.

In its first meeting on 3-4 September 2008, the TLAC was asked to advise on OCC and MDVP revisions. Given the key role of VVMs in OCC and MDVP policy, Bruce insisted that TLAC should review the scientific data relating to the efficacy, validity, and regulatory status of VVM technology and the underlying fundamental research methods and results. Following this review, TLAC requested the following information on VVMs:

- *For the existing VVM2, VVM7, VVM14, and VVM30 versions, copies of documentation illustrating the individual data points and frequencies for each replicate in VVM validation studies for the exact temperatures studied and the exact days when the replicate VVM labels were deemed to change color to indicate their endpoints.*
- *Data on the effect on VVM performance when the VVM label is frozen, wetted, or otherwise stressed or abused.*
- *A definitive briefing on the regulatory history and status of any licensure/registration from recognized and respected NRAs of VVMs since medical devices applied to vaccine vials are duly regulated as a "combination" medical device/biological product.*

During the MDVP discussions, Weniger also opposed the function of VVM as a visual cue. He argued that neither WHO nor UNICEF appeared to control the potential use and placement of VVMs on private sector vaccines that might enter a health centre's vaccine formulary side-by-side with WHO prequalified vaccines. He further argued that VVMs were not designed to indicate whether bacterial contamination and overgrowth have rendered a vaccine unsafe, nor for how long an opened vial could be used safely. Trying to add such additional purpose to the location of the VVM on vaccine vials would lead to confusion, particularly for newer combination vaccines shipped with components in separate vials for mixing by the end-user before administration.

None of these issues were valid. If you refer to the efforts of WHO IPAC (a committee that replaced TLAC following the Weniger case) to develop a visual cue to be printed on labels, the whole idea was to separate vaccines that can be kept for subsequent immunization sessions once opened. The meaning of such a printed visual cue was not to indicate that the vial was free of bacterial contamination.

The PAHO working group considered that vaccines might be classified into three thermostability categories: (1) vaccines that are damaged by freezing but relatively heat-stable (such as hepatitis B vaccine), (2) vaccines that are also freeze-sensitive, but with lower tolerance for heat exposure (e.g., diphtheria-tetanus-pertussis [DTP]), and (3) vaccines that are freeze-tolerant but very heat-sensitive and should be stored frozen or very cold (e.g., oral polio vaccine). But this classification was incompatible with the four VVM categories classifying vaccines based on their heat stability.

The final report is full of claims, accusations, disagreements, and denunciations. Here we consider its argument, that if VVM is not being used in industrialized countries, it cannot be of value:

"All existing reports and experience with VVMs come from developing countries that purchase them for use in public immunization programs. Nothing is reported or published on their use, if any, in the private sector in industrialized or developing countries. Many countries - both industrialized and those with emerging-economies - do not use VVMs, including those in Europe, North America, South America, Australia, China, Japan, Malaysia, and Singapore, among others."

As for the benefits of VVMs, the final report pointedly used the term "theoretical" as if the benefits had never been physically observed anywhere at any point:

"VVMs have a number of theoretical advantages for immunization programmes around the world."

It was also mentioned that China and India produce high quantities of vaccines for their domestic markets without VVMs. At the time of the meeting, the information on China was correct, but not the India example.[47] In fact, China and VVMs is another story. Shanghai CDC was actually the first to require VVM on HepA, then Pneumo for seniors in 2012 followed by Beijing on influenza vaccines in 2014.[48] Following the 2016 Shandong province disaster, 12 provinces in China now require VVMs on vaccines. After this huge vaccine scandal VVM was seen as a measure to be implemented to prevent such cases in the future. This was a clear example of reversed risk management because the essence of risk management is to anticipate and evaluate the risks together, and then identify the procedures to avoid or minimize their impact. In this sense, risk management is an anticipatory approach where you do not wait for a fire to happen before introducing smoke detectors, sprinkler systems and/or fire extinguishers. VVM has also helped with improving parental confidence in the vaccines being used in China.

The classic PAHO argument of 'we eradicated polio, why do we need VVMs' was brought up by Ms. Nora Rodriguez. She stated that in the Region of the Americas the Member States have highly developed immunization programmes, with very high vaccine coverage levels, highly trained health workers, and a good cold chain. These 'no problem' and 'a good cold chain' claims were at the opposite side of the facts articulated by Member States in the Panama City 2006 UNICEF-TACRO/PATH meeting. This indicated a gross disconnect with anything indicating problems such as cold chain, vaccine wastage, and hard-to-reach populations. Ms. Rodriguez continued listing down the public health achievements of PAHO: that in 1994, polio was certified as having been eradicated in the Americas, and that in 2002 that same goal was achieved for measles. The elimination of rubella virus was now underway in the Region she concluded before adding the killer punch:

47 As of March 2007, there is a VVM policy for all EPI vaccines supplied to the Indian immunization programme.

48 http://bit.ly/2ydY26w

"All this has been achieved without the use of VVMs. Taken together, all these accomplishments provide a context for considering what additional benefits might come from using VVMs in the Americas."

Ms. Rodriguez also mentioned that Argentina had recently approved legislation calling for the wider use of temperature monitoring devices for pharmaceutical products, but she failed to provide an evaluation of its effectiveness or relevance (at the time of this meeting, it was evident that the Argentinean law had already failed).

The working group concluded that stronger, more-scientific evidence was lacking for the claimed benefits of VVM such as the reduction in wastage, increased flexibility in the cold chain, and assurance of the quality of the vaccines that are administered. One may ask how could this be concluded despite all the experience and evidence that was available. In this respect, the working group was doing nothing more than playing the three monkeys, embodying the proverbial principle 'see no evil, hear no evil, speak no evil'.

The three wise monkeys at the Tōshō-gū shrine in Nikkō, Japan

It was also pointed out that information from reports and other sources indicated that health workers were continuing to have difficulty in accurately interpreting the color changes that occur with VVMs. It was not clear to which reports and other sources the group was referring to here. There were no documents among the reference list provided to the working group that relates to perception test and VVM. The only two references from India that were distributed to partic-

ipants had many design-related flaws.[49] Jain and colleagues concluded that despite a good correlation found between VVM and potency, there was a substantial risk that when VVM expires slowly a sub-potent vaccine is administered and when VVM expires quickly there is a problem of vaccine wastage. These arguments are simply incorrect, because there is actually no slow or quick VVM expiry, this is dictated by the combination of time and temperature and all reactions are entirely predictable. What the authors probably meant was that when VVM reached its end-point, vaccines were found to have potency and therefore this was considered as wastage.

This would only be correct if VVM was actually a dipstick potency indicator. VVM always reaches its end-point with a safety margin. Halm's study using OPV beyond the cold chain in Mali and Zipursky's study again using OPV outside the cold chain in Chad also found similar results, but these authors rightly did not consider this as "wastage" (these published studies with an excellent research design were not included in the package for the PAHO working group). It was simply interpreted that VVM was doing what it was designed for. In fact it is somewhat problematic to analyze Kamlesh's study on the knowledge and practice of OPV VVM among health personnel in India since the study is constructed on health personnel experimentations involving boiling the VVM, exposing it to the direct sunlight and keeping it in the pocket. The study concluded that such tests were prompted by a failure of the anticipated change in VVM color when they had the evidence of a breakdown of the cold chain, but no details of such breakdowns were given. For whatever the reason, these health professionals assigned to VVM seemed to judge the quality of it by their gut feelings. As a result, word-of-mouth stories started to circulate that VVMs are defective and they don't change color. Just like the old Quinvaxem and new IPV VVM7 complaints. Although the study had inadequacies from a design perspective, in the end Kamlesh and colleagues recommended that WHO, UNICEF and the Ministry of Health India should provide further clarification and guidelines so that the unnecessary confusion could be removed.

The PATH/WHO study on the VVM availability and use in the African, Eastern Mediterranean, Southeast Asian, and Western Pacific Regions (2010) as referred to in the PAHO working group meeting was selectively chosen so that the results showed a clear lack of evidence on the use and benefits derived from using VVM. In fact, this study had three aspects: the total proportion of vaccines with VVMs in the regions with detailed information by country, in-depth information on pol-

49 R. Jain, A. K. Sahu, S. Tewari, et al. (2003) Cold chain monitoring of OPV at transit levels in India: correlation of VVM and potency status. *Biologicals*, 31:237-244 and J. Kamlesh, JS Thakur, A. Singh. (2007) Knowledge and practice of oral polio vaccine-vaccine vial monitor among health personnel in India. *Indian Journal of Community Medicine*. 32(4):283-285

icies and practices, and knowledge and attitudes in a selected sample of countries. The issue of staff having difficulty in accurately interpreting the color changes that occur with VVMs appear only in this report under the focus groups conducted in the Philippines. The staff there having mentioned the difficulty of distinguishing between stage 1 and different levels of stage 2. Since VVM color progression is a continuous process and stage 2 literally corresponds to the 50th percentile between the start-point and end-point, it is practically impossible to successfully distinguish between say 48% (which is stage 1) and 52% (which is stage 2). See Box on Staging and interpretation of shades of VVMs.

Staging and interpretation of shades of VVMs

VVM color change is a **continuous** process. The combined effects of time and temperature cause the inner square (active surface) of the VVM to darken gradually and irreversibly. The rate of color change increases with temperature. The inner square is initially lighter in color than the outer circle (but the inner square is never white). It remains so until the temperature and/or the duration of heat reaches a level that is likely to degrade the vaccine beyond the acceptable limit. The inner square continues to darken as heat exposure continues, until it is much darker than the outer circle. If the inner square becomes as dark as or darker than the outer circle the vial must be discarded. Therefore, the whole interpretation of whether to use the vaccine depends on whether the inner square is lighter than the outer circle.

Since VVM color change is a continuous process, all stages that are referred to are fully **arbitrary**. In reality, there are millions of hues between the start-point of the inner square and the end-point.

The current *PQS vaccine vial monitor product specification (WHO/PQS/E06/IN05.1 dated 15 May 2018)* defines only two stages in VVM color: **start-point** and **end-point**.

At the start-point, the optical density of the active surface must be lower than the optical density of the reference surface by a difference of at least 0.23. The end-point is reached when the difference in the average optical density obtained from readings at two different points on the reference surface and the optical density of two different points of the active surface is 0.00. The end-point is exceeded when the OD of the active surface is higher than the OD of the reference surface.

The VVM inner square start-point color is approximately 10% of the outer reference circle color. With heat exposure over time, this percentage increases to reach 100% of the outer circle color (match-point) which represents the discard or end-point. As you can imagine, there are 10%, 10.1%, 10.2%, 10.3%,

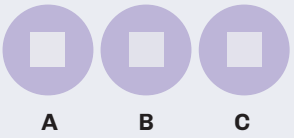
..., 20.6%, 20.7%, ... and many more values between 10% and 100%. We can even make these percentages in smaller fractions such as 10.001% and so on. This is why we say there are an almost infinite number of hues between the start and end-point. The figure below includes a total of 16 VVMs from the start-point color to the end-point color. This scale can also be filled with 160 VVMs as well as 1,600 VVMs (and even much more) between the start and end points.

Let's try to explain this **stage** issue differently. There are three types of data: nominal, ordinal and numerical. Nominal data have a dichotomous character, like yes/no, healthy/not healthy, male/female, or positive/negative. If we apply a nominal approach to VVM color change, we can group VVMs as only **usable** and **non-usable**. Usable ones will have VVMs with the inner square lighter than the outer circle color, while non-usable ones will have VVMs with inner square equal or darker than the outer circle color.

Ordinal data are categorical data where there is a logical ordering to the categories. A good example is the Likert scale that you see on many surveys: 1=Strongly disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly agree. This ordinal approach CANNOT be applied to VVM color change since by their nature differences between values in an ordinal scale are not important - which is not the case with VVM color change.

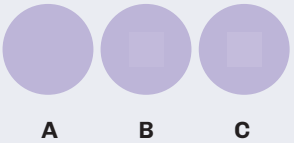
The third type of data is numerical (some schools also further divide numerical data into two: interval and ratio). Numerical data is measured or identified in a numerical scale. As for VVM color change, the OD difference between the inner square and the outer circle color is measured numerically. Within this scale, you can always measure the median (50th percentile) which corresponds to the second stage as mentioned by many colleagues.

However, we must recognize that VVM interpretation in the field is always done visually. When it comes to validation of VVMs, both makers Temptime and the implementing vaccine manufacturers use a special densitometer that reads the color density optically. In visual interpretations, however, we have to accept a variance between different people (interobserver variation). It is very difficult for people to look at a VVM inner square with a 52% hue of the outer circle color and say that it is 52%. It is very difficult to see small changes in hues unless one has very trained eyes in color receptivity. Let's try to illustrate this with an example. Below you will see three VVMs. Examine them carefully and decide whether the squares are the same color (take your time and do not scroll down the page to find the answer).



Of course, this is a difficult case. Each of the three squares are different. The lightest one - which also represents start-point - is the A. Square in C is 2.4% more darker than the square in A, and B is 5.2% darker than the square A. With this example, it is obvious how difficult it can be to determine the difference visually even when there is a 5% difference which is not too small for colors. But, is it really so important to be able to differentiate between such small fractions of color shades? If you picked C instead of B as the darkest one, what could be impact on the programme? In fact, in real life, health workers are faced with bigger difference in shades and are not actually challenged to this extent.

In reality it is always possible to make a comparison of a VVM inner square color against the outer circle color and decide whether it is lighter or darker. See the example below:



Even if the percentage associations of these squares are similar in terms of differences, it is much easier to indicate B and C have lighter squares compared to the reference circle, and in A the square and reference circle colors match. In this example, the overwhelming majority will agree on the classification that A is non-usable and B and C usable VVMs. However, if a health worker were to decide that all had reached their end-point, that would not be a problem.

When it comes to recording VVM status in documents and forms at the country level, in order to use this information usable/not-usable information would be of little value, and this is why countries use staging of 1-2-3-4. As explained in the Albania case (page 192), this helps to give priority to vaccines with darker (stage 2) VVM compared to lighter ones (stage 1) in use and distribution.

As a matter of course, scientific evidence on the performance of VVMs was presented by Dr. Weniger, but as expected, there was not a single word of positivity. It was more of an onslaught. Dr. Weniger referred to TLAC VVM discussions

in which he maintained that the actual technical and field performance of VVM and their correlation with specific vaccines were questioned. He listed five points covering issues that 'his committee' (as he referred to TLAC) were unclear about or were awaiting on information. This included requested publications or documents that describe the intended VVM function, performance, and tradeoffs in their design and development that would satisfy current FDA, ICH, EMEA, or similar regulatory guidance standards for new medical devices.

1. *nonexistent or undisclosed "pivotal" licensure-grade studies, if any, of VVM "bench" performance,*
2. *unpublished and undisclosed shelf-life plots correlating VVM conversion with potency loss of specific vaccines using them,*
3. *increasingly difficult to understand specifications for VVM performance standards to guide lot release and quality control,*
4. *nonexistent or undisclosed "human-factors" studies for how well health workers interpret VVMs when nearing conversion, and*
5. *lack of any "post-marketing" surveillance of VVM conversion frequency during actual use, among others.*

At the request of TLAC, it was me who provided what was being requested. However, there was no end to Dr. Weniger's further requests each time I submitted what had been required. In TLAC, he even went on to labor this point by introducing specificity and sensitivity arguments relating to false positive and false negatives with VVM. He claimed that when VVM reaches its end-point and a vaccine is discarded when the vaccine is still potent, this would amount to a 'false positive', and therefore a wastage (actually this is a 'false negative' – the VVM is negative/bad/expired/at a point when vaccine is still potent).

False positivity and false negativity of a test in question compared to real condition as determined by the gold standard

		Condition (as determined by GOLD standard)		
		Positive	**Negative**	
Test outcome	**Positive**	True positive	False positive (Type I error)	Positive predictive value
	Negative	False negative (Type II error)	True negative	Negative predictive value
		Sensitivity	Specificity	

Dr. Weniger brought up the same argument in a PAHO working group that VVM conversion would not necessarily accurately predict when the enclosed vaccine has lost, or will imminently lose its potency. Of course, as a scientist he would surely have known that this was not the case, that the validity model can only be applied to models in which a 'golden test' is available. For example, taking the shake test, the specificity and sensitivity of this were checked against the actual status of freezing (solid frozen or not) and phase contrast microscopy of the samples (homogeneous distribution of particles for non-frozen samples and cluttered aggregates for frozen samples). As for the vaccine potency, the expiry date cannot be taken as the golden test because expiry date does not mean that the vaccine is potent before and will not be potent afterwards. Dr. Weniger must also have known perfectly well that when a vaccine reaches the end of its expiry period, its potency properties do not immediately go down to zero. Take the example of fresh milk. If you drink a pint of milk today that expired just yesterday, you are very unlikely to be poisoned. But if you were, the manufacturer would not be liable since there was a clear warning that it should not be used. Expiry dates are added to products as a cut-off point up to which the producer accepts liability. For whatever time-period is on the label, the manufacturer must provide the supporting data to the appropriate regulatory authorities for approval. In many cases, stability studies are continued well beyond the 'official' expiry periods although this is not information found in the public domain. Only the part of the data corresponding to the expiry period is generally provided to regulatory agencies. Therefore, if you were to inadvertently administered a vaccine the day after it technically expired, you would almost certainly still experience the expected seroconversion (although I am not suggesting that vaccines can be safely used beyond their expiry – this is an example for the sake of the discussion).

As a result of this systematic demolishment, the working group members agreed that there was insufficient evidence, data, and analysis to justify adopting VVMs for use in the Americas.

The PAHO 19th TAG on Vaccine Preventable Diseases meeting on 6-8 July 2011 in Argentina did not include anything on VVMs in its agenda.

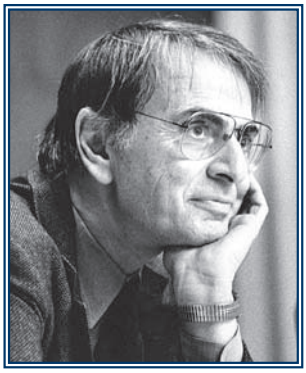
VVMs start make it to Americas, PAHO advises countries to ignore them

For some time, VVMs on OPV and other vaccines had started to enter the Americas without any additional costs for Gavi-eligible countries. Of course, countries naturally approached PAHO seeking advice on using these VVMs, and the response they received was simple and categorical: 'Ignore them'.

Nonetheless Honduras, Nicaragua, Haiti and Colombia decided to develop their own resource materials on the use of VVM without any blessing of PAHO, so as not to waste this opportunity.

Here, we should also note that the price of vaccine with VVM through Gavi (and therefore UNICEF) was cheaper than the price of vaccine without VVM through the PAHO Revolving Fund.

Suppression of uncomfortable ideas



Carl Sagan

"Over the course of the six years I've been here at Temptime, we've been increasingly focused on the Americas, since it is the one region of WHO that has resisted consistently the use of VVMs." says Michael Rush, Executive Director, Global Health Policy at Temptime Corporation, *"An eminent scientist, Carl Sagan who sadly has now passed away, said the suppression of uncomfortable ideas might be common in religion and politics, but it is not the path to knowledge, and it has no place in the endeavor of science. And he went on to say that 'it is the responsibility of scientists never to suppress science, no matter how awkward that knowledge is, no matter how it may bother those in power, we are not smart enough to decide which pieces of knowledge are permissible and which are not'. Yet, despite of that great statement, it's been incredibly disappointing to me to witness throughout the Americas region and here in the country where I live, the United States, the significant efforts of public health officials to suppress knowledge and to prevent the creation of evidence to support the benefit of using VVMs. That's been my reality over the past six years."*

Michael says that it has been tremendously gratifying to find people in countries who tenaciously and fiercely want to create the evidence that supports the use of vial-level temperature monitoring for vaccines. *"Some of the most valuable verification comes from the uncovering of vaccine wastage rates, and the discovery that there are many cold-chain problems that can be solved by using VVMs.*

Michael Rush

"Countries have recently been interested in adopting VVMs in spite of resistance from organizations like PAHO. Countries have been assisted in their efforts by receiving bivalent polio vaccines from Indian manufacturers with VVMs on them. So, countries like Honduras, Nicaragua, Colombia have developed their own VVM resources, they've looked for what's out there, things that have been created by individuals at WHO, and

they've adopted and adapted them, translating them into Spanish and they are using them without the official blessing of international health organizations like PAHO."

Although these are recent developments, in February 2011, Honduras officially embraced VVMs when it issued its technical and operation guideline on pneumococcal conjugate vaccine.

The PAHO working group on VVM claimed that there was no proof of any tangible benefits that VVM brings to an immunization programme. In fact, a powerful example of such evidence actually comes from a country in the Americas: Haiti, just within the last few months. Haiti had received a shipment of 800,000 doses of OPV that sat on the tarmac at the airport because of a strike of airport workers. Not having VVMs the vaccine was considered to be heat damaged, so the decision was taken to destroy the vaccine. *"This story was shared by individuals from PAHO at an international meeting,"* says Michael, *"and it's an important anecdote that emphasizes the huge benefit of having potentially been able to salvage some of that vaccine had the doses come with VVM. So, these countries that I mentioned earlier proactively and without any external approval decided to use VVMs. This was a decision taken at the municipal level, not at the national level. Although the countries are ordering through PAHO's revolving fund, as those doses arrive and are distributed to the rural level, some of these rural health departments are proactively developing their own VVM resources, and using the VVMs. This is a recent development within the last two years."*

PAHO never admitted that wastage was ever a problem in the region. Peter Carrasco says that almost all vaccines come in single dose vials except measles for campaigns and tetanus for mothers. He says that nobody wants them (VVMs) because of the cost implications. *"The matter came up just before I left"* says Peter, *"If the country is using a multi-dose vial policy, then it may make sense to use VVM, otherwise you don't need VVM with single-dose vials."*

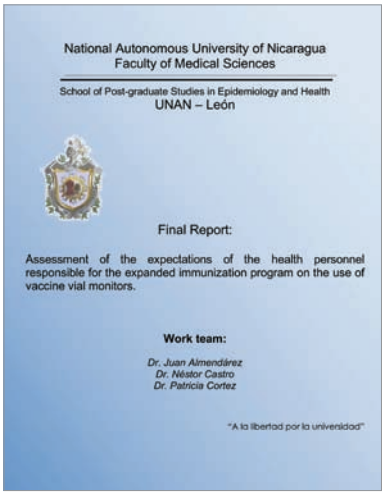
However, single-dose vials are not immune to temperature excursions, since they are in the same supply chain. Whatever the multi-dose problems that exist in a supply chain equally apply to single-dose vials. Naturally, wastage rates are less in mono-dose vials compared to multi-dose vials. But, countries that have been transparent about their high wastage rates and which would like to do something about it recently got involved with studies with the object of providing evidence about the potential of VVMs to reduce wastage. These countries are hoping to make a policy case for national requirements for the use of VVMs and recent additions to this group include Mexico, Argentina, and Brazil.

In Argentina hemorrhagic fever is endemic and there is a very temperature-sensitive vaccine that is manufactured by a national manufacturer – the National Institute of Health. A study that is designed to show the potential benefits of VVMs across distribution routes of that vaccine is about the conclude.

Meanwhile, in Brazil, a very proactive MOH worker decided to conduct a study of vaccine wastage rates on a number of antigens in several states throughout Brazil. The results revealed that in the case of one particular antigen there was as much as 73% vaccine wastage. Michael Rush says that on presenting this data to PAHO and sharing it with some MOH officials, PAHO indicated that they still felt that there was not a problem with wastage in the region or in Brazil. The data was also shared with the Minister of Health who has recognized that this is a resolvable problem with a cost-saving tool and that it is unacceptable in the sphere of public health to continue to allow vaccine wastage rates to remain at these high levels. There is a new political will in Brazil to conduct studies that demonstrate the utility of VVM to support the national needs.

Separately, in Mexico, which does not procure its vaccines through the revolving fund, one of the manufacturers with which they work is SII, and there is great interest on the part of the Secretariat of Health/MOH for Mexico to encourage SII to begin to import doses with VVMs with the object of demonstrating their utility. Mexico is about to conclude a temperature monitoring study, in two very large states which have extremely had high temperatures as well as extremely low winter temperatures. There they have already experienced excursions along their distribution routes in both large and in very rural communities. Now that they have seen the potential benefits of VVMs there is a strong political will in Mexico to have a national VVM policy.

"Those who are resistant to VVMs consistently tried to hold VVM to a different standard than any other technology." says Michael, *"The opponents of VVM are always asking for it to be a potency indicator. And no matter how hard you work to explain that nothing is a potency indicator, there is an unrealistic expectation that VVM should act as a potency indicator. That's a consistent challenge from those who are opposed. They don't expect anything else to be a magic solution, the silver bullet, but they do expect VVM to be all things to all people, which is not fair to VVM. But it is the reality in the Americas region."*


National Autonomous University of Nicaragua
Faculty of Medical Sciences

School of Post-graduate Studies in Epidemiology and Health
UNAN – León

Final Report:

Assessment of the expectations of the health personnel responsible for the expanded immunization program on the use of vaccine vial monitors.

Work team:

Dr. Juan Almendárez
Dr. Néstor Castro
Dr. Patricia Cortez

"A la libertad por la universidad"

In 2010, a group of researchers at the National Autonomous University of Nicaragua, Faculty of Medical Sciences, School of Post-graduate Studies in Epidemiology and Health designed and conducted a study on the use of VVM with the H1N1 vaccine.

It is important to recognize that, despite the fact it required some additional procedures, the study found that field operators did not consider the use of this technology to be an onerous imposition. In the focus groups and in-depth interviews, staff pointed to the need to integrate this technology into most if not all of the vaccines, which demonstrated that they trusted the validity of the indicator, although they were also aware that it would involve an additional cost. They therefore suggested its integration into those least temperature-stable vaccines that were used the most in the national vaccination campaigns, or that are sent to health brigades in the field.

The course of VVMs in Americas will definitely change, but this will require more consolidated efforts and collaboration with those far-sighted countries that are eager to better serve their populations.

Sole-source supplier - To act like one or not: that's the question

Starting in the early 1980s, PATH worked with several potential VVM manufacturers: 3M, LifeLines Technology, Bowater, Rexam, Albert Browne, CCL Label, and Sensitech. However, with the sole exception of LifeLines none of these companies succeeded in developing a VVM that could meet the WHO specifications or at an affordable price. As a result, LifeLines (today Temptime Corp) became the sole supplier.[50] Temptime's sole supplier position was raised on many occasions and a number of different parties expressed their discomfort with this situation. Sole source products are invariably very unique products, which explains the absence of competition. It is the case when innovations make it to the market, depending on the product and levels of demand, competitors will tend to naturally appear over time. An example is when Gavi/UNICEF had to use a sole supplier when the combination HepB vaccine appeared on the market and was WHO prequalified. It took several years for other competitors to come to the market but they inevitably appeared.

In VVM, this normal course of events did not happen. It did not happen simply because, despite intensive efforts by many companies, they were unable to create

50 Sole-source procurement refers to those purchases where there's only one supplier that provides the product. Usually these are unique products that you cannot find anywhere but only through one supplier/manufacturer.

a product that met the WHO requirements. Some other companies that did manage to meet the specification did not succeed in coming up with a competitive price and in the end, development efforts were ceased by the senior management of these companies.

Of course, there can be risks associated with using sole source companies and it is important to distinguish between single-sourcing and sole-sourcing. So why do many believe that single-sourcing is a good strategy and in what ways does sole-sourcing differ from single-sourcing?

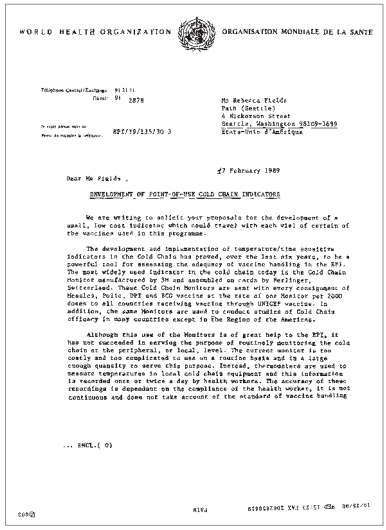
The biggest difference between single-sourcing and sole-sourcing is that single-source purchasing refers to purchases from one selected supplier, even though there are other suppliers that provide similar products, which is not the case for sole-supplier. With single-sourcing there can be many advantages, such as administrative efficiency, lower inventory costs, and improved product quality. Temptime Corporation is an example of a sole-supplier bringing all these single-source advantages to their customers (vaccine manufacturers) as they were single-sourcing.

However, the fact that LifeLines was a sole supplier was one of the reasons many vaccine manufacturers were dragging their feet in complying with VVM integration. This matter had come up on several fronts during the 2002 VVM technical consultation in Geneva. And it wasn't only vaccine manufacturers that was concerned, but UNICEF SD as well: *"We have to have symmetrical commercial relationships since UNICEF is asking manufacturers to deal with a single commercial entity. For example, in the case of minimum ordering quantities, if LifeLines said the order was too small, then UNICEF cannot ask for such a small quantity from the vaccine supplier."* The minimum order quantity was certainly an issue with VVM (it was set at 500,000 units for the full label). However, LifeLines offered a range of VVM options corresponding to a vaccine manufacturer's needs. For example, for quantities below 500,000 units, LifeLines offered a dot solution for attached to the full label by vaccine manufacturers. Since dot VVM could be kept as inventory, lead times were able to be kept to a minimum.

Being a sole-source supplier vs. acting like a sole-source supplier

The issue of being a sole-source supplier and acting like a sole-source supplier are two different things. Since its involvement with VVMs, Lifelines had always kept VVM prices at a minimum and price increases were never more than fractions of cents, always keeping the market price much lower than the target price. When the VVM project originally started, WHO set the target price so as not to exceed

10% of a 10-dose OPV vial cost, which was 5.2 U.S. cents in 1989. This was communicated to PATH by John Lloyd (WHO) on 17 February 1989. In his letter, John explained the target price among the minimum requirements of an OPV VVM:



WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

Ms Rebecca Fields
Path (Seattle)
4 Nickerson Street
Seattle, Washington 98109-3499
Etats-Unis d'Amérique

EPI/19/135/30 3

17 February 1989

Dear Ms Fields ,

DEVELOPMENT OF POINT-OF-USE COLD CHAIN INDICATORS

We are writing to solicit your proposals for the development of a small, low cost indicator which could travel with each vial of certain of the vaccines used in this programme.

The development and implementation of temperature/time sensitive indicators in the Cold Chain has proved, over the last six years, to be a powerful tool for assessing the adequacy of vaccine handling in the EPI. The most widely used indicator in the cold chain today is the Cold Chain Monitor manufactured by 3M and assembled on cards by Berlinger, Switzerland. These Cold Chain Monitors are sent with every consignment of Measles, Polio, DPT and BCG vaccine at the rate of one Monitor per 1000 doses to all countries receiving vaccine through UNICEF vaccine. In addition, the same Monitors are used to conduct studies of Cold Chain efficacy in many countries except in The Region of the Americas.

Although this use of the Monitors is of great help to the EPI, it has not succeeded in serving the purpose of routinely monitoring the cold chain at the peripheral, or local, level. The current monitor is too costly and too complicated to use on a routine basis and in a large enough quantity to serve this purpose. Instead, thermometers are used to measure temperatures in local cold chain equipment and this information is recorded once or twice a day by health workers. The accuracy of these recordings is dependant on the compliance of the health worker, it is not continuous and does not take account of the standard of vaccine handling

... ENCL.(0)

"The minimum requirements of such time and temperature sensitive indicator which travels with each vial of oral polio vaccine is proposed as follows:

Clear and positive color change when exposed to:

24 hours at +37°C (equivalent to a Log drop in potency of 0.15)

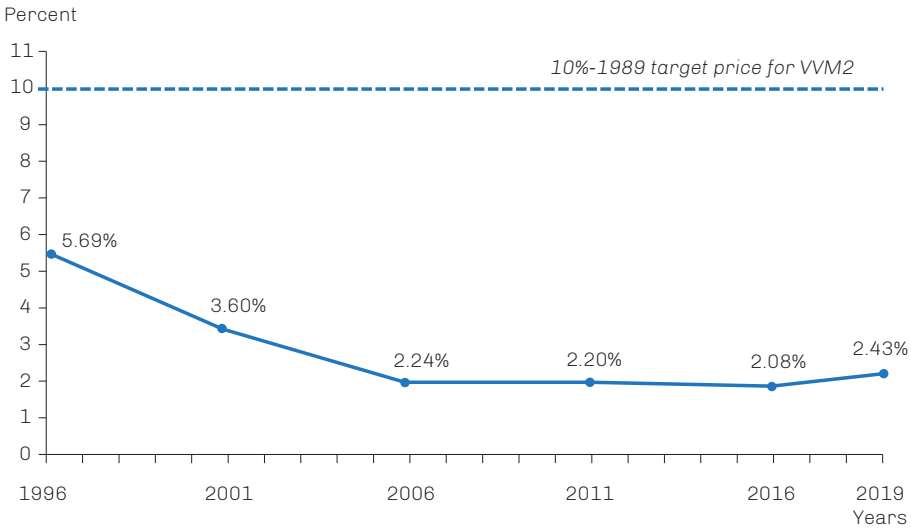
or...

26 weeks at 8C (6 months at refrigerated temperatures)

Cost limited to less than 10% of the cost of the vaccine in ten dose vials. (A typical 10 dose vial of oral polio costs $0.52 today)."

When we look at the relative price development of OPV VVM since they first appeared on vials in 1996, we can actually see a downward trend. In 1996, VVM cost was 5.69% of the cost of a 10-dose OPV vial. Today a VVM dot for OPV costs 4.0 cents and is only 2.43% of the cost of a 10-dose OPV vial.

Percent of VVM dot price of one dose of OPV in 10 dose vials

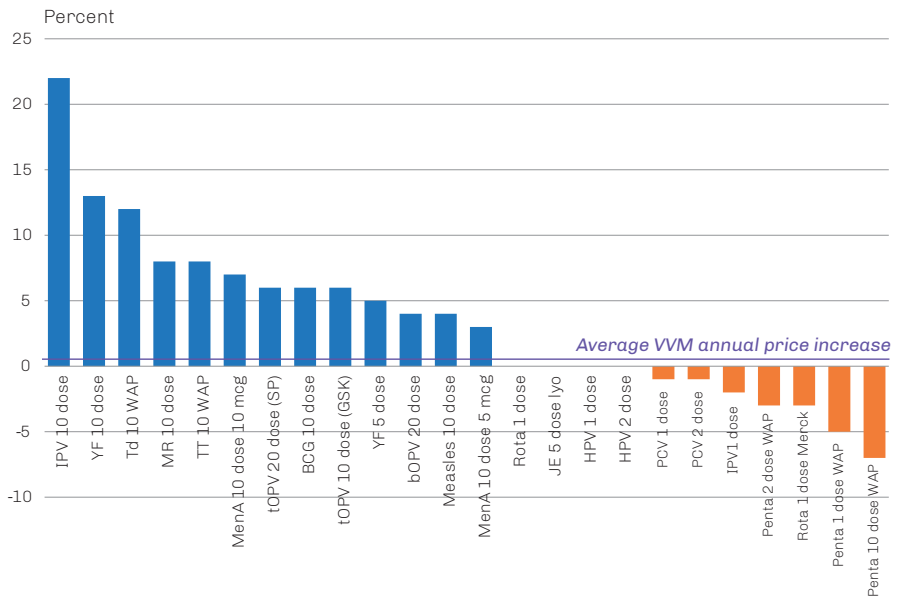


Jean-Paul Martin in his study with artefacts from his father's pharmacy, Zermatt, Switzerland, April 2019

For many years there was no price increase at all for VVMs. The very first price increase was initiated by the President and CEO, Jean-Paul Martin in 2001. Jean-Paul Martin tells me about this difficult but necessary decision: *"We were losing money. Expecting that the volume would increase and result in reaching the break point to turn positive was the general anticipation in the company. My interpretation was different. The business had to be profitable if we had to survive. We were selling the VVM with negative margin. And with this you cannot succeed even when there is an increase in sales. It was time to increase the price. We had to explain this decision first to PATH, UNICEF and WHO. It was a matter of survival, not the case of a sole-source supplier increasing the price. Everything was transparent, and from this point onwards we started to issue 'pricing guide' on a yearly basis."*

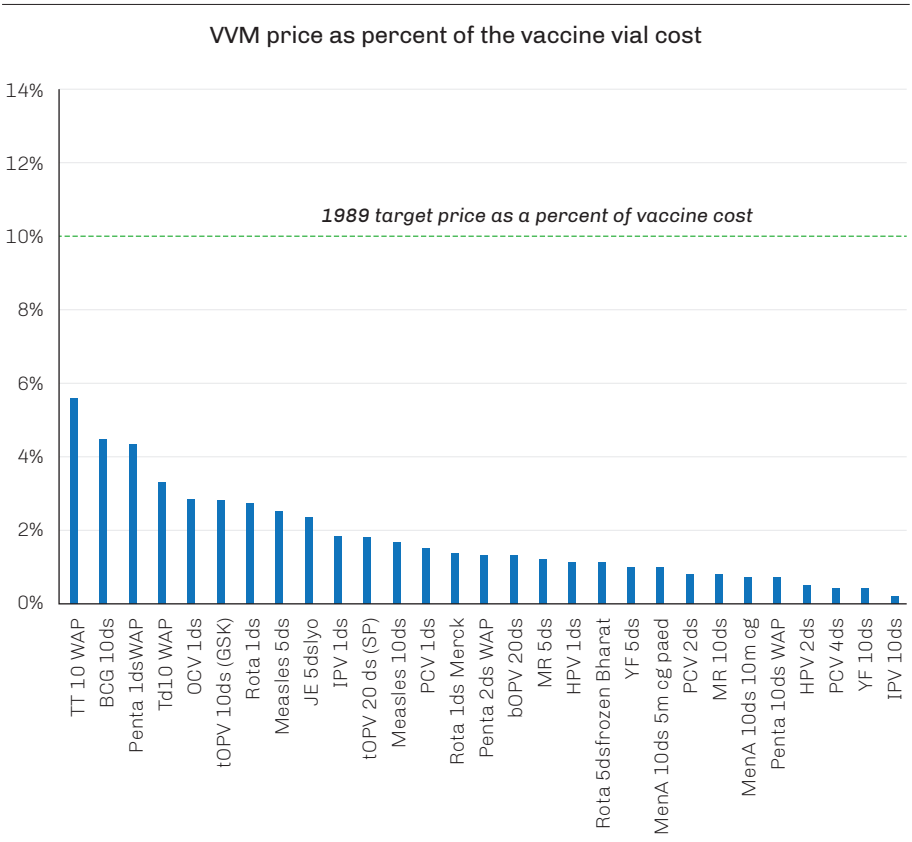
Without checking the full facts, some people complain that vaccine prices are decreasing while VVM prices go up. This was spelled out in 2002 at the VVM Technical Consultation meeting in Geneva where Steve Jarret from UNICEF SD confirmed that vaccine prices were not going down.

Average annual price increases/decreases in vaccines and VVM



Let's look at the picture today. The majority of vaccine prices are increasing; the average annual price increase has been estimated at somewhere between 3% to 22%. In four vaccines there has been no price increase, and with seven vaccines a decrease was observed of between 1% to 7% annually. The VVM average annual price increase has been kept at a minimum, approximately 1.2%.

More interestingly, when analyzed against different vaccines, for the majority of the vaccines, the VVM price is found to be less than 2% of the vial cost.



"A sole-supplier situation is not by design." says Renaat Van den Hooff (President and CEO, Temptime Corporation), *"Other companies have tried to come up with a VVM to compete, and because Temptime continued to perfect its manufacturing processes, we were able to generate the productivity gains that have allowed us to keep our price increases to a minimum level for the VVM. And on the other side we've tried to build another business, a private market business, for unit level and shipment monitor-*

ing solutions for biologics, for specialty pharmacy shipments, for medical devices and other applications, that has allowed us to grow another business, another leg on the stool, that is more profitable than the business of VVM for humanitarian causes."

"When such arguments came up, I was always saying that we are not in a monopoly situation" says Jean-Paul Martin, *"We were the only company able to succeed in developing a product and sell it at the price of 3 cents while there were other technologies where this was not possible. You can't blame us for being successful when others failed."*

Renaat Van den Hooff explains that in 1989, WHO established the target price for the VVM, and this target price was calculated as the cost on one dose of oral polio vaccine in a 10-dose presentation. That worked out to about 5 cents. Today in 2018, Temptime still has dots that sell at around the 5 cents level. *"We have a commitment at Temptime, a time-honored leadership commitment, that we will always do our utmost to act responsibly. We are in a sole supplier situation, we try desperately not to act like a sole supplier, because there is a big difference between being a sole supplier and acting like a sole supplier. The concern of UNICEF, which was very understandable, was that we could just unilaterally triple the price. And of course, we could have done this. But that would amount us to behaving like a sole-supplier when in fact, we always act like we are in a normal competitive environment. Actually, even more so, we try and keep our price increases for humanitarian markets lower than those in our mainstream commercial markets. It is part of a deep-rooted culture of integrity within the company.*

Renaat Van den Hooff and Ted Prusik in Geneva, Palais de Nation, 2018

"Temptime over the past 30 years has undergone different types of ownership and different types of leadership, but we've been successful in maintaining this fundamental level of decency and fairness. It's a baton that gets passed on.

"To be honest, the fact that someone like Ted Prusik is still with the company is a big factor, because obviously Ted invented the VVM, he was there at the outset, and he continues to be an inspiration for everybody in this organization. Ted will be with the company as long as he wants and as long as he can be, but the spirit of the founders of Temptime stays with the company forever. For me that's very important, as a leader of this company I consider myself as the guardian of this culture, and whether you like it or not, I often try to downplay my role, because I am only part of the team. I realize that as the leader of an organization I have a big responsibility for the future of the company. There is a mission, there is a culture, there are values and whatever happens my job is to assure that the baton gets handed to the right level of people moving forward."

Going out of business is the biggest risk for sole-suppliers. *"When you are a 40-million-dollar company, and you want to stay in business, you have to make some profit,"* says Renaat Van den Hooff, *"and you have to make some profit with a bit of a margin because if we are making a profit margin that is too thin and anything bad happens we could go out of business. So, I have the responsibility for the VVM and Temptime, including all image, reputation and humanitarian aspects. I also have the responsibility to look after the families that are employed by this company and to make sure that Temptime exists next year and for many years to come. With very low or non-existent margins it becomes impossible to meet employee expectations in terms of keeping pace with the rate of inflation, rewarding effort and, of course, keeping and attracting the best talent. We cannot afford to lose our best people to other companies. Making VVMs is a complex process and we need a stable workforce to ensure business continuity. So, we have no option other than to run the company on commercial lines. Of course, this does not stop the vaccine manufacturers waving their arms around at even a hint of a price increase so I think this is an area that we need to study so that we can get our message over better. A strong, stable business is in everyone's best interest."*

Strengthening the culture

"The culture of the company was very positive." says Jean-Paul Martin, *"We had high-level scientists like Ted (Prusik) and Fred (Grabiner) for whom honesty was the very essence of our core values and principles. I initiated monthly 'all staff' meetings which encouraged inner transparency."*

Each time I visited Temptime, I always got the opportunity to interact with the workers, especially during lunch. I took such visits as an opportunity to bring the realities of the field to all staff; to motivate them and get them to better under-

stand the important contribution they were making towards vital health programs around the world. *"They like these types of meetings,"* says Renaat Van den Hooff, *"because it gives them some connection with what they are making every day. The executives and myself as the leadership of the company, like to maximize these opportunities, because we know it is a unique opportunity for creating that connection. As executives, we travel all over the world, as do our sales staff, but it is important that the people on the shop-floor, in the office, in the warehouse and everywhere else get a little bit of exposure to the real world. Sometimes we can do this with pictures and videos but there is nothing like someone like yourself, or someone from PATH coming and telling us about the life-saving work that you do. The direct message comes across with a completely different degree of candor and sincerity. So, we are looking for every opportunity for the staff to be able to associate what they do as individuals with the life-changing outcomes of successful vaccination programs in remote parts of the world."*

Following a lunch with Temptime staff in December 2018, I took a short tour of the facility, met the staff in action and asked them what they felt about being part of the VVM story.

"I am responsible for the inks" said Azard Ali, Senior Leader Process Analyst, *"I had no idea of the uniqueness of this product when I started. But now, I know the significance of what we produce. I come from a poor country where I have seen polio outcomes, and I am proud of being part of this team to help eradicate and eliminate diseases, and help the children of the world."*

Azard Ali

Fatima Hamdan

Mohannad Abdo

Noah Smith

Tim Carrollo

Zofia Kolenski

"We are actually helping others to make sure that vaccines are in good shape," said Fatima Hamdan from the quality department, *"and it makes me feel good."*

"I wake up every morning and always enjoy coming to work," said Jennifer Porada, QA specialist, *"I never had a Monday syndrome. I like helping people, and this is what we do here."*

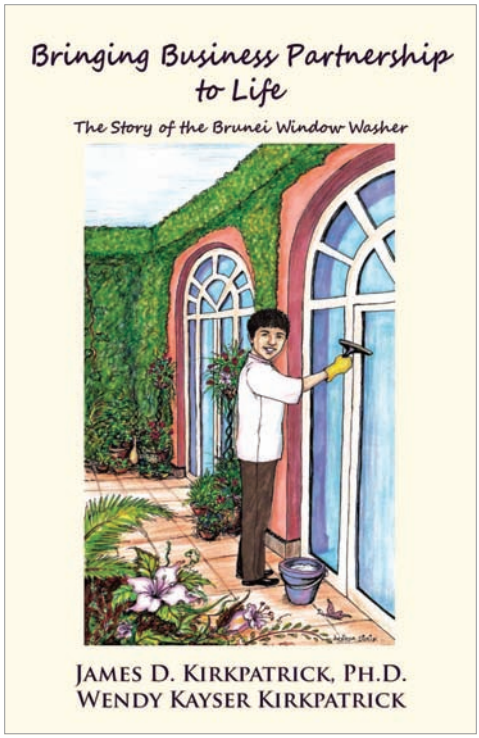
"I had a very nice job in an upstream innovation cosmetic company before," said Mohannad Abdo, from the R&D department, *"I joined Temptime four years ago. I am also involved in innovation which I like a lot, but there is a bigger purpose than simply coming up with a new product. This what I like being in Temptime. I really feel that I am making a difference."*

"The labels we make save lives," said Noah Smith, machine operator, *"it's a big deal, and a good opportunity to be part of this incredible work."*

"It blows my mind to know how many of these labels we ship around the world," says Tim Carrollo, from the packaging and shipping and receiving department, *"I take great care of the product when packing, and I perfectly know that I am an important gear in this whole business, and I feel good about it."*

"It is important to do the work right," said Zofia Kolenski, machine operator, responsible of the slitting the VVM rolls, *"and I know how and where these VVMs are used, this makes me feel so important here."*

After his retirement, I asked Fred (Grabiner) to reflect on his feelings for being part of this long journey, and the moments he would cherish. *"The actual beginning,"* said Fred, *"being able to make a VVM for OPV that worked and was acceptable and saved so many lives."* Steve Fields, co-founder and first President of LifeLines says that he is proud of being part of this and of "the real human impact of the product". *"The very positive human benefit"* says Steve, *"is very satisfying."*



These reflections remind me of *The Brunei Window Washer* by James and Wendy Kirkpatrick, which tells the delightful story of Chai, the Brunei window washer. Through Chai's experiences, you learn the secrets of developing a team that cares about their customers and the overall mission of the business. Chai embodies the qualities that employers want to see in every member of their

team. He gets his work done well while providing memorable customer service that really makes a connection with resort guests. Jim waiting for his cab to arrive, sees Chai and just for killing the time, he asks Chai what does he does for a living. You would expect Chai to respond that he is a window washer. Instead he proudly exclaims, *"I am part of a team that creates great experiences for our guests!"*

I wonder how many "Chai" work in Temptime!

VVM, the risk buster

In March, 2016, a vaccine scandal in Shandong province, shocked China. Though food and drug crises had been common for years, the Shandong scandal led to the deaths of four children. "According to state media, the prime culprit, a former pharmacist, was caught delivering vaccines to medical facilities on bicycles without approved storage conditions. The Shandong Food and Drug Administration made public a list of 25 problematic vaccines - including polio, mumps, rabies, hepatitis B, encephalitis, and meningococcal vaccines - that had been illegally sold in at least 24 provincial areas since 2011. Those vaccines are worth more than ¥570 million (i.e., $88 million).[51]"

Naturally, the vaccine scandal caused public panic across the country. Jie Qiu and his colleagues reported in The Lancet that although relevant government departments have stressed that improperly stored vaccines are unlikely to cause deaths directly, public confidence in the health department was, nonetheless, hard hit. "There is no doubt that the vaccine management system has a serious vulnerability, which permitted the improperly stored vaccines to be distributed across two-thirds of the country in the past 5 years. The problem of the public health management system has already been recognized since 2008, when the toxic

51 Jie Qiu, Hengjing Hu, Shenghua Zhou, Qiming Liu. (2016) Vaccine scandal and crisis in public confidence in China. *The Lancet*, 387(10036):2382, June 11, 2016 (published as correspondence)

chemical melamine was discovered to have been added to formula milk, causing at least six infants to die. However, no effective reform in the system has been made in the past 5 years, and public health is still under threat.

"The crisis was also fueled by the news media's improper reporting. The key problem of those vaccines is ineffective immunity rather than lethality. Because of these exaggerated reports, the public is now questioning whether their children should be vaccinated, even though most vaccinations are mandatory in China. However, both the public and the media have missed the point: without vaccines, infectious diseases will take away many more lives.

"The Chinese Government should address the shattered public confidence made worse by the vaccine scandal. The health management system should be improved to ensure that vaccines are properly stored and transported, and transparency of supervision should also be enhanced. Moreover, the government needs to ensure that communication to the public is accurate."

Chris Caufield

"In the Shandong province scandal at that time, there were no requirements to have VVM," says Chris Caufield, *"But now they have it, as a direct result of this event. It reached a point where the national CDC actually drafted the legislation, something we became aware of after the fact, that would have mandated VVM for all Chinese vaccines. But, of course, as it went through the political debate process the initial language was altered and ultimately removed. What was left behind is guidance saying that in rural or outreach areas, temperature monitoring devices should be applied to each vial, so that the person receiving it, knows that the vaccines have been handled in the appropriate way. However, rural and outreach was not defined, so that the decisions are open to the interpretation of the people doing it, and we know there is only one on-vial temperature monitoring solution that can be used."*

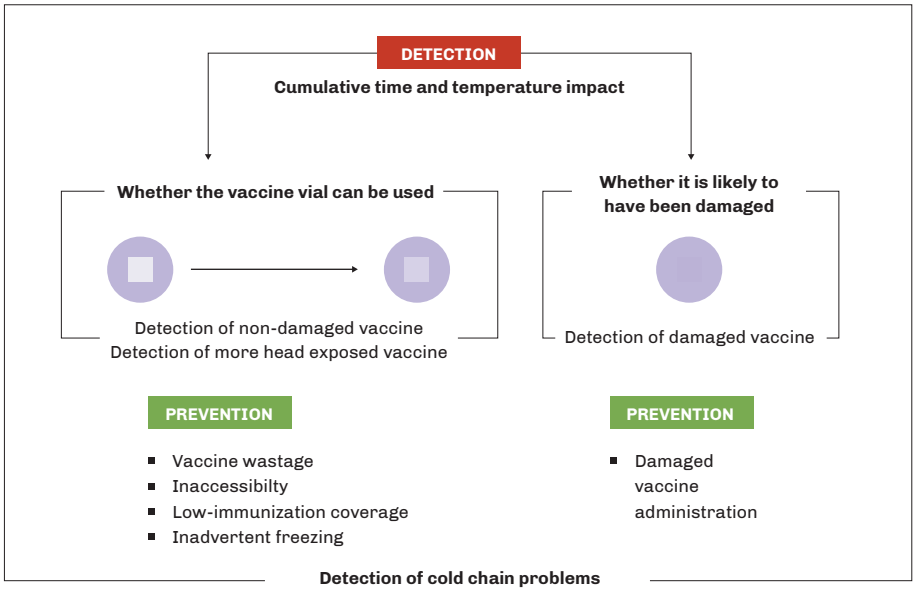
If the vaccines (in the Shandong scandal) had had VVMs, they would have signaled the improper storage conditions. The measures taken by the authorities to prevent such cases in the future are obviously of a "damage control" nature, but it is important that these measures brought VVM into the picture as a control measure.

VVM in many senses is an important and far-reaching risk control tool. As a risk control measure, it addresses more than one hazard within the vaccine supply chain and, in this sense, VVM really is an exceptional risk buster.

In risk management terminology, VVM "detects" the cumulative time and temperature impact on the vial it is attached to. VVM displays the information visually, simply through a chemical reaction in the active square of the VVM. Al-

though VVM is not a dichotomous go/no go indicator, in principle, VVM gives two major signals: firstly, whether the vaccine vial can be used or, secondly, whether it is likely to have been damaged (and should not be used).

VVM signals from risk point of view



"VVM has very direct benefits" says Jim Vesper, risk management expert (Valsource), *"Do we use, or do we not use?"*

When a vaccine is "usable" it may have any shade that is lighter than the outer reference circle. In this sense, we have many possibilities of different shades that are all usable. VVM also tells us the extent of heat exposure over time so that we can compare vials of the same type to detect which ones are more heat exposed. Here comes the trick with the VVM as a control measure.

Progress of VVM from start to end-point by time and temperature

"VVM is a contributor," says Jim, *"a contributor that allows more flexibility around the risks that can be absorbed by the system, because VVM provides greater control."*

According to ISO 31000, risk is defined as the "effect of uncertainty on objectives" and an effect is a positive or negative deviation from what is expected. ISO 31000 recognizes that we all operate in an uncertain world. Whatever we plan to do, every step of it has an element of risk requiring it to be managed and this is why every outcome is uncertain. Depending on the standard of control measures introduced, we may or may not always get the results we expect. Jim maintains that within cold chain operations, VVM reduces uncertainty and can therefore allow more risk to be tolerated by the system to achieve certain goals, such as reaching children in hard-to-reach areas.

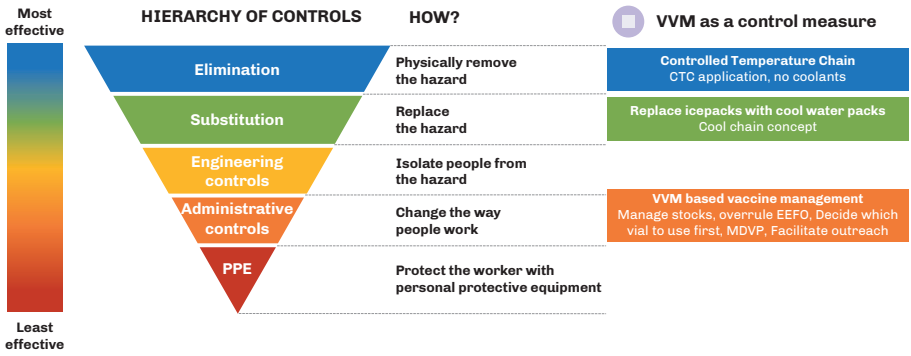
Jim Vesper explaining hazards by an example of banana peel, Pharmaceutical cold chain management on wheels course, Turkey, 2017

Another example of this is the removal of ice and replacing it with cool water packs. Of course, the use of cool water packs dramatically reduces the safe period for vaccines, but this is typically done to prevent inadvertent freezing with the knowledge that mild heat exposure is acceptable but any exposure to freezing temperatures is completely unacceptable. The use of cool water packs is recommended if vaccines are supplied with VVM. In this sense, VVM as a detection control measure facilitates the eradication of ice which is the recognized cause of most vaccine freezing events.

"This is a good example," says Jim, *"VVM is very flexible; it is a risk reducer and a risk preventer and it can enable you to take creative risk-management measures in some situations because you don't have that uncertainty anymore. When you have more certainty, you have less risk."*

In the hierarchy of control measures, VVM offers three levels of control, namely elimination, substitution and administrative controls.

Hierarchy of controls and VVM as a control measure
(Adopted from NIOSH, USA)



The cool chain concept is a perfect example for substitution, where ice, as the main source of freezing hazard is replaced with cool water packs at 2°C-8°C. No ice means no freezing. Although VVM itself does not do it directly, VVM facilitates the application of CTC which removes all coolants from the transport of vaccines within the CTC implementation. In this respect, the physical removal of ice (a recognized source of freezing hazard) not only improves immunization coverage by reducing logistics requirements and increasing access, but also prevents accidental freezing.

The policies induced by VVM, such as overruling EEFO, deciding which vial to be used first, MDVP, facilitating outreach, taking vaccines beyond 8°C are all made possible with the flexibility that VVM brought into the vaccine logistics process. In this sense, VVM greatly supports and improves the way health workers carry out their vital duties.

Future VVMs

Many technologies emerge as revolutionary but, over time, they inevitably lose their revolutionary status and standing to other (and usually better) products. Time passes and eventually they become nothing more than "history".

Take the Freeze Watch™ by 3M. At the time it was incorporated into the EPI programme to detect exposure to temperatures below 0°C, it was a revolution. Then, by the time that electronic threshold indicators started to get PQS prequalified, WHO had changed the product specifications, this time demanding ±0.5°C tolerance for the trigger-point. Freeze Watch™ failed to meet this requirement. As a result, the product was taken off the PQS prequalification list (although the product is still in production by 3M).

The CCM card was also quite revolutionary when it was adopted by the global EPI. The monitor was only relaying that an exposure over 10°C had taken place, with no other details. Although the ABC window revealed some information regarding the duration/severity of the exposure, it was an indication only with no real precision. By the time electronic shipping indicators for long-haul use were developed, and WHO had issued new product specifications as expected, the CCM

card had a very small role to play in international shipments, simply to be used only with dry ice shipments. Another point was that the new electronic devices were able to reveal the nature of the exposure both by temperature and duration. And it was possible to determine exactly when this has happened. Such information was considered important, so the programme agreed to absorb the increased cost – in the end, you are paying for an increased quality of information.

VVM as a chemical indicator had many advantages when it emerged. First of all, it was flexible enough to be adopted to different stability profiles. It was also printable, and affordable.

The combined VVM and threshold indicator

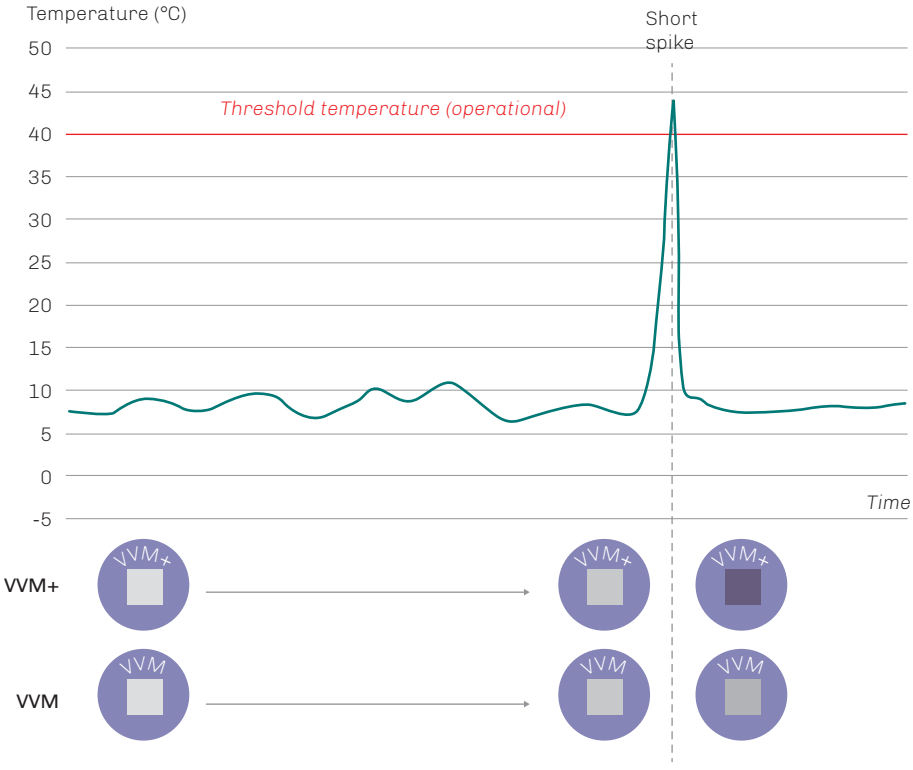
The CTC approach requiring a separate peak temperature indicator alongside the VVM, encouraged Temptime to come up with a novel approach by integrating the peak temperature indicator with the VVM. This solution provided a unique, simple and clear signal to the workers in the field. This innovation received the Grand Challenges Explorations award in 2012, an initiative funded by the Bill & Melinda Gates Foundation.

In January 2019, WHO issued the combined vaccine vial monitor and threshold indicator product performance specifications (WHO/PQS/E006/IN06.1) and verification protocol (WHO/PQS/E006/IN06.VP.1). Since the VVM and the threshold indicator function independently from each other, the PQS specifications require that each component must conform to related specifications: The threshold component of the combined indicator to conform to Clause 4.2.2 of WHO/PQS/E006/IN04.1 and the cumulative component to conform to section 4.1.1 of WHO/PQS/E006/IN05.3. Similarly, as with the tests, the two technologies are required to be tested in accordance with the current version of their own appropriate protocol: PQS Independent type-testing protocol: Vaccine Vial Monitor WHO/PQS/E006/IN05.3-VP.3 and PQS Independent type-testing protocol: Threshold Indicators WHO/PQS/E006/IN04-VP.1. In addition, as for the combined indicator, three tests are required: type examination, effect of VVM transition on TI performance, and water resistance test.

Here, there is a need to explain clearly the function of these two technologies together. VVM+® or VVM-TI is the combination of a VVM and a threshold indicator. Unless the threshold indicator is activated, the combined product looks like a VVM and reacts like a VVM. When the threshold is hit, the threshold indicator is activated and turns dark so that the VVM looks as if it is beyond its end-point and the vaccine must not be used. In this sense, the threshold indicator is more of an

operational tool rather than having a direct linkage to the stability of the product in particular. Although vaccines that are licensed for CTC use are tested at this threshold temperature, this testing is done with products that have reached the end of their shelf life. One may argue that in a majority of cases where a product is used for CTC, it will not be at its end of shelf life, but CTC had to go with the worst-case scenario. Remember, in order to specify the VVM, vaccines are tested at release stage (beginning of their shelf life) at certain temperatures, 37°C being the upper limit.

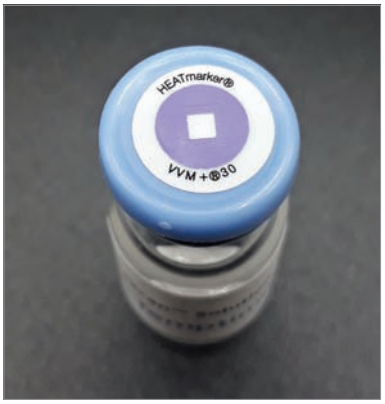
The operational difference VVM+ offers



In summary, CTC with an on label 40°C upper limit at least allows the vaccine to operate in the 2°C to 40°C range. In this sense, the threshold indicator should be considered as more of a compliance component than a "stability" proxy component.

VVM minimizes the risk of a cumulatively heat-damaged vaccine being given to a child provided that the vaccine is not exposed to temperatures above 37°C. This is the normal upper temperature at which stability studies are carried out and VVM is specified. Of course, regarding the VVM component, if studies were undertaken at 45°C and VVM was chosen accordingly there could also be minimized risk up to 45°C or 50°C, but appropriate analysis work studies would need to be carried out.

The very first combined VVM and threshold indicator was PQS-prequalified on 28 March 2019 (E006/059). This combined device brings together VVM250 and threshold indicator 40°C. VVM 250 is designed for very high stability vaccines (e.g., lyophilized Rotasiil from SII).



Prequalified products

When Temptime's HEATmarker® VVMs were prequalified, we had four types of VVM - namely VVM2, VVM7, VVM14 and VVM30. With the need for a better match between the VVM reaction and the stability of IPV products, a new category, VVM11 was suggested. VVM11 was prequalified on 19 June 2018 with WHO/PQS/E006/052 code.

WHO/PQS prequalified VVMs as of April 2019 are as follows:

WHO/PQS prequalified VVMs

Product	PQS prequalification date	PQS code
VVM2	30 September 2007	E006/001
VVM7	8 October 2007	E006/051
VVM11	19 June 2018	E006/052
VVM14	15 June 2018	E006/054
VVM30	24 March 2007	E006/050
VVM250	27 March 2019	E006/058
VVM+250	28 March 2019	E006/059

The very latest product that is prequalified as a combined VVM and threshold indicator the VVM+250, incorporates a 40°C threshold indicator by Temptime (PQS prequalification on 27 March 2019, with WHO/PQS/E006/057 code).

In a digital world

Barcodes have become a ubiquitous element of modern living. Today, the majority of items you buy in the shops, with the exception, perhaps, of some freshly produced ones, feature a universal product barcode (UPC). Barcodes help in identifying and tracking items.

Two-dimensional (2D) barcodes look like squares or rectangles that contain many small, individual dots. A single 2D barcode can hold a significant amount of information and may remain legible even when printed at a small size or etched onto a product. 2D barcodes are used in a wide range of industries, from manufacturing and warehousing to logistics and healthcare.

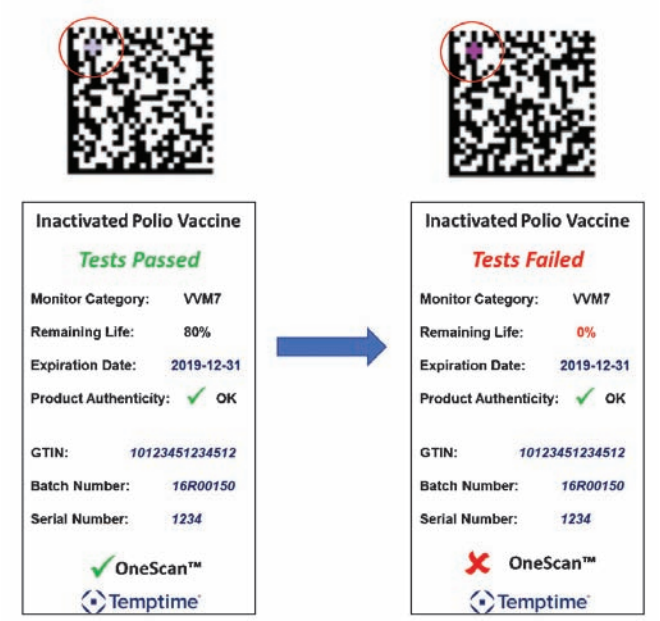
Besides inventory tracking, barcodes in general are useful in logistics and supply chain management by assigning a unique identification number (UID). Barcodes can be applied at individual unit level or to secondary and tertiary packaging. Currently Turkey is the first and only country that has adopted 2D barcode on its all pharmaceutical products including vaccines at the unit level.

In 2017, at the 15th TechNet conference, Ted Prusik presented a pitch on an innovation that meets the need for digital information at the unit (vial) level by integrating VVM with a 2D barcode. In a rapidly digitizing world, Temptime is transforming this elegant analogue indicator into a 21st Century digital solution. This new product, will be capable of capturing the color shade of the VVM along with all product related information.

"This digital vial-level information can then be linked to other electronic data that you have in the system to provide a full temperature history of that particular vial." says Prusik, *"The technology is scalable and it is sustainable."*

This innovation will definitely help to make health care system more effective and efficient. But, how does it work?

A specific area of the GS1 2D data matrix contains the indicator ink (as marked in the image). This could be either a cumulative VVM or a threshold indicator as part of the barcode. The 2D barcode will be readable by either a phone or a scanner and these can be connected to cloud- or web-based databases. In this example, the scanner indicates that this particular vial of IPV has an 80% remaining shelf life by reading the VVM color shade in addition to other static information that is coded into the 2D barcode.

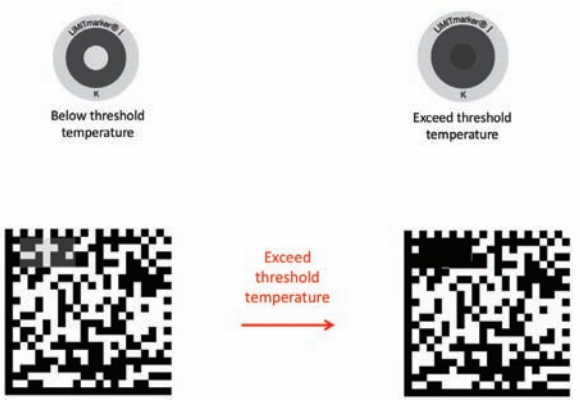


In the second image, VVM has reached its discard-point (or beyond) and this is indicated by 0% remaining shelf life.

Let's see these applications more closely.

GS1 data matrix with time and temperature integrator (VVM)

GS1 data matrix with threshold sensor



Serialized barcodes on individual saleable units provide the enabling technology for global identification and tracking regulations. This significantly enhances product integrity, patient safety, supply security, and temperature compliance from manufacture to point of use. Once commercialized, the integration of VVM with the 2D barcode might also be the entry point for VVM into developed markets. In addition to the advantage of having merged serialization and temperature monitoring in a single scan, the technology could also act as a counterfeit indicator. Although 2D barcodes can be counterfeited, the missing VVM information would alert the parties.

New lives for VVM

Since its development, VVM has been instrumental and influential in the quest for best practice in vaccine handling. Many vaccine management policies have only become possible as a result of VVM. It is the only universal tool helping health workers to reach deprived and distressed children in the most difficult situations, whether it be remote and difficult terrain, conditions of extreme famine, and in times of armed conflict. Although it has been developed as a time and heat integrator, it helps in the prevention of inadvertent freezing simply by allowing vaccines to be kept under control in temperature conditions that do not require the use of ice in proximity to the product. Today, there is no other technology that facilitates overruling the expiry date - making VVM the “smart expiry date”. By its positioning on the vial, VVM also tells whether a multi-dose vial can be used in a subsequent session after opening.

The most recent developments including the reinvention of VVM by combining it with a threshold indicator and further incorporating a 2D barcode shows us just how flexible the technology is. This reminds me about the ancient proverb about cats:

"A cat has nine lives.
For three she plays,
for three she strays,
and for the last three she stays."

I wonder, in this ever-changing world, how VVM will keep up with all the developments in the field of vaccine management.

Long live VVM!

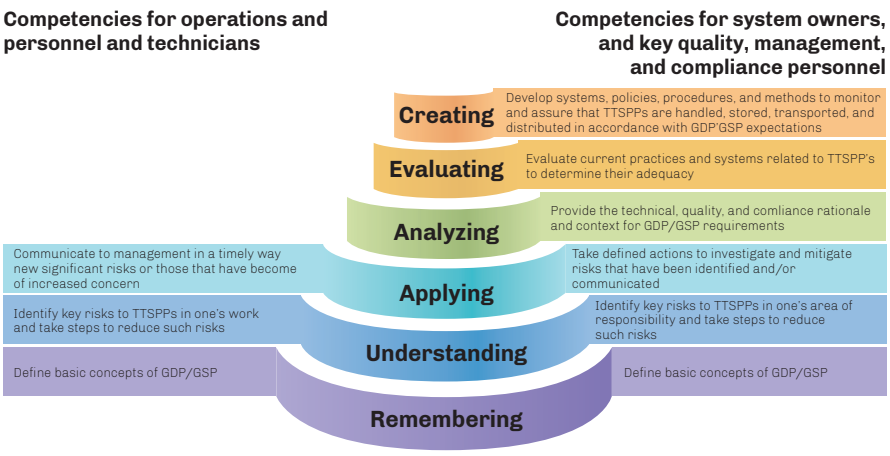
Learning tools for VVM based vaccine management

Expertise is the hallmark of an expert. It includes an in-depth set of knowledge, cognitive and motor skills, as well as the analytical ability to determine how to approach a given situation. Brothers Hubert and Stuart Dreyfus quoted Aristotle in saying that the expert straight away does ‘‘the appropriate thing, at the appropriate time, in the appropriate way”. In the context of handling time and temperature sensitive pharmaceutical products (TTSPPs) and in particular vaccines, expertise involves more than just knowing the rules and requirements. Rather, it necessitates people being able to apply those requirements and solve sometimes very complicated, conflict-filled problems in a way that is consistent with both the letter and the spirit of the requirements.

People involved in the distribution, storage, and transportation of supply chains perform a range of activities as described in their job descriptions. Those involved in operations typically execute procedures and tasks. Professionals in quality and management functions develop, optimize, and monitor system performance. To identify the best ways of providing opportunities to develop the appropriate knowledge and skills for different jobs requires learning professionals that are able to define the specific competencies required to successfully perform a job. Broadly speaking, those who develop and improve systems need to have a

higher-level set of cognitive skills than those who are required to consistently and flawlessly execute standardize procedures. The figure below shows examples of competencies for two different groups involved with TTSPPs and how they align with Bloom's revised taxonomy.

Competencies and learning taxonomy



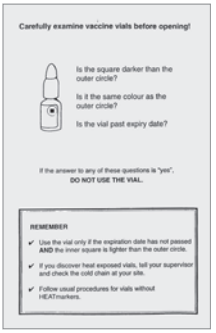
PATH training materials

From the very early days of VVM introduction, training efforts focused on both practitioners who would use the tool in the field and managers who would incorporate VVM in national policies. A huge training effort took place in all countries where VVM was planned to be introduced. The tool and the message were simple:

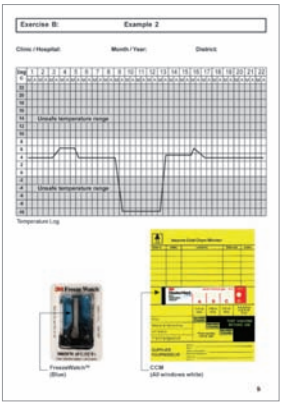
If the inner square of the VVM is lighter than the outer circle, use the vial,

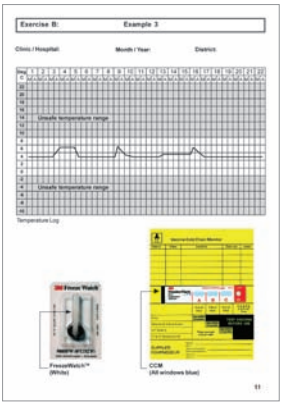
If the inner square of the VVM the same color or darker than the outer circle, do not use the vial.

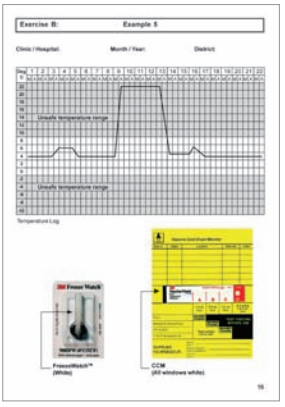
This simple tool/message was to bring about dramatic changes in vaccine management. We were telling health staff not to automatically throw away vaccines when they had been exposed to temperatures beyond 8°C and, instead, check the VVM to decide whether to use the vaccine or not. They had to see and experience this themselves.



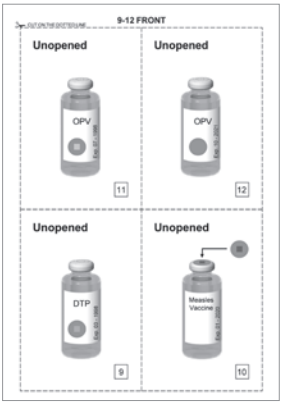
Many of the early VVM learning materials were developed by PATH. The most widely used package was an example of authentic learning material that was available in both English and French language. In this material, participants were introduced to realistic temperature scenarios illustrated with the help of a temperature recording chart, and images of a Freeze Watch™ and CCM card. Based on these temperature scenarios, participants were challenged to respond as to whether a series of given vaccines could be used or not. Vaccines were presented on cards with explanations on type, status (opened or unopened), expiry, and VVM status. The reverse side of the vaccine cards contained the answers.

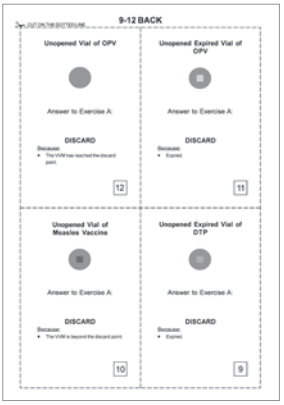


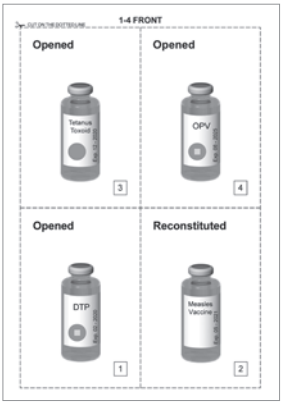




In 2002, WHO published the *"Getting Started with Vaccine Vial Monitors" (WHO/V&B/02.35)* guide. This document was written in a question and answer format, taking readers from what is a VVM and how it works, to its impact on programme operations. Although it was published as a guide, it was widely used as a resource material in VVM-related training programmes at country level.



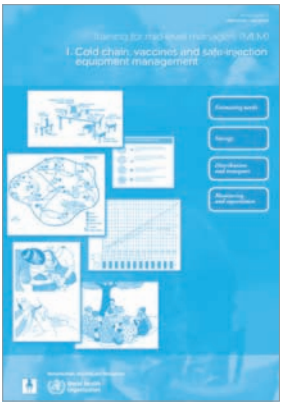


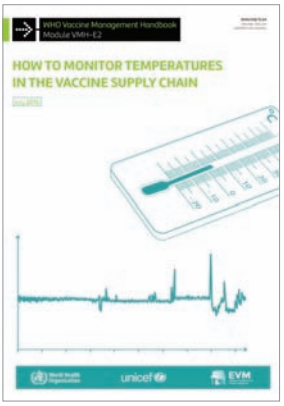


The other two resource materials widely used in training were the 'Immunization in Practice' and the 'Mid-Level Manager' series both published by WHO. However, the depth of information on VVM in both documents is quite basic and does not cover the full potential of VVM use.

None of the above-mentioned learning programmes were using authentic materials -actual VVMs - in the training sessions. However, participants were encouraged to keep expended vaccine vials to observe how the VVMs would change in practice.

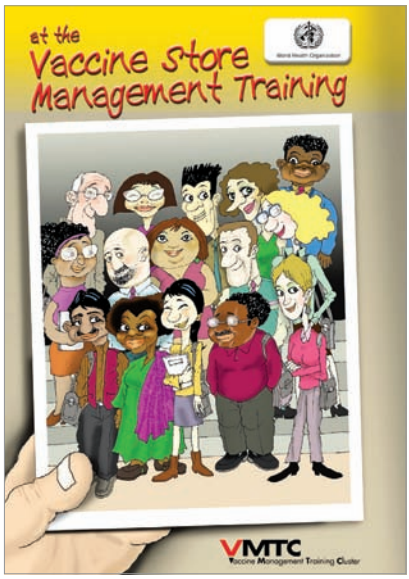
One recent publication as a resource material comes from WHO on how to monitor temperatures in the vaccine supply chain, published in 2015.

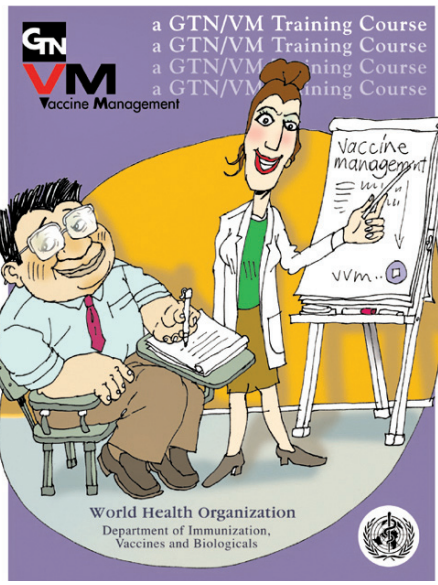




Experiential and authentic learning solutions

WHO Global Learning Opportunities (originally called the "Global Training Network") between 2004 and 2006 offered vaccine store management and vaccine management courses for selected staff from countries where effective vaccine store management (EVSM) assessments and vaccine management (VM) assessments were conducted.

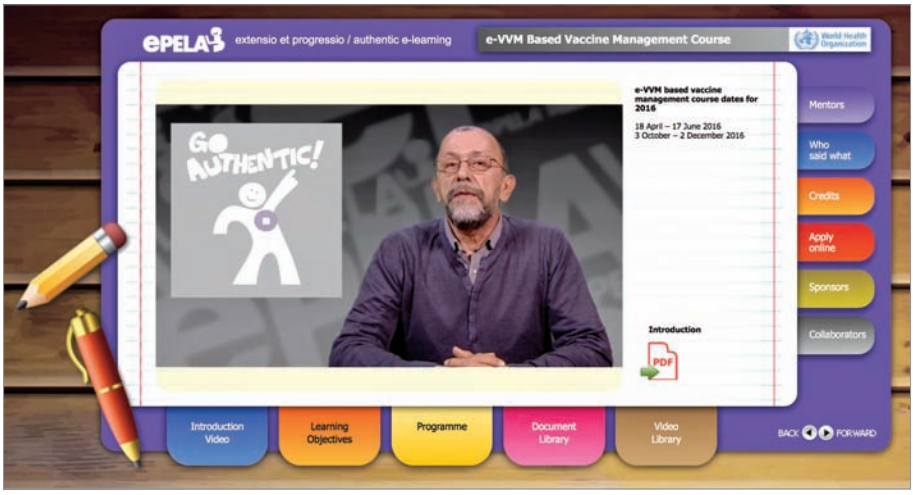




As a second step, course graduates were offered the opportunity to attend a "vaccine management on wheels" course that enabled 15 participants with three mentors to physically travel along the entire cold chain on a bus. In 2007 the course was extended to embrace stakeholders from the wider integrated supply chain and included participants from the pharmaceutical and biopharmaceutical sectors as well as national regulatory authorities. The ''wheels course" encourages participants to make direct observations at the storage, warehousing, distribution, and health care delivery facilities that they visit, as they physically travel with mentors by bus down the entire length of the vaccines cold chain. Throughout the wheels course, guided observation exercises take place at the visited facilities under the supervision of the mentors. Participants are provided with guidance notes and tools to support their critical observations. Participants interact with operational staff and management at these facilities. Presentations and group discussions take place on the bus, in restaurants, and in the open air before and after the visits to the facilities.

The importance of offering professional development opportunities for staff is widely recognized across sectors. Increasingly, professional development programmes and courses are offered online. However, the intended outcomes of professional development, online or otherwise, are not always attained and the competencies, skills, knowledge and abilities that the professional development set out to enhance are all too frequently not successfully transferred into professional practice. Moreover, online professional development programmes are often seen as being better suited for transmitting theoretical content rather than supporting the development of practical skills. In order for professional development programmes to lead to sustainable professional growth and transfer of learning, both offline (typical leader-led courses) and online learning environments must prepare the learner to ''... draw on a range of resources and to adapt learning to complex and ill-structured workplace problems", rather than simply promote memorizing and regurgitating factual knowledge. With these principles in mind, I teamed up with Thomas Reeves, Professor Emeritus of Learning, Design, and Technology from The Georgia University, James Vesper from LearningPlus, USA and Hanna Teräs from Curtin University, Australia to work on e-learning solutions for both cold chain management and VVM.

These e-learning solutions were presented on a new platform, EPELA. The first course on e-pharmaceutical cold chain management was launched in 2013 followed by VVM-based vaccine management in 2014.



e-VVM based vaccine management course runs for nine weeks and have 13 specific objectives:

1. *Explain the relation between the VVM categories and reaction rates.*
2. *Given five different situations over a time, observe and read status of four VVM types.*
3. *Given five different situations, explain difference in VVM reactions rates.*
4. *Given a situation of an international arrival, decide whether to accept or reject the shipment.*
5. *Create a decision tree for examination of shipment on arrival to decide whether to accept it.*
6. *Given a storage situation, analyze factors contributing exposure of vaccines to temperature exposure and suggest corrective actions to reduce the risks.*
7. *Develop a standard operating procedure (SOP) for checking status of vaccines during their storage time.*
8. *Given a stock situation with different vaccines, various expiry periods and batches and VVM status, decide which products to be dispatched against a requisition order.*
9. *Create a decision tree for dispatch of vaccines involving all relevant factors.*
10. *Given a situation of refusal of an in-country shipment, communicate the reasoning behind your selection of a particular batch with certain temperature exposure.*
11. *Given two different scenarios of temperature exposure, expiry date, VVM status and opened/unopened multi dose vials, judge whether the vaccines are suitable for use.*
12. *Given a stock situation of vaccines with different VVM status in open/unopened multi-dose vials and expiry dates, decide which vaccines to be used first in fixed immunization session and short/long outreach activities.*
13. *Develop a plan of action to adopt VVM policies for national use based on the analysis of vaccine management practices in your own country.*

VVM e-learning course is unique in that it is not a typical ‘‘me and the computer screen” course; there is always a human face that supports participants


Ümit Kartoğlu


Julie Milstien

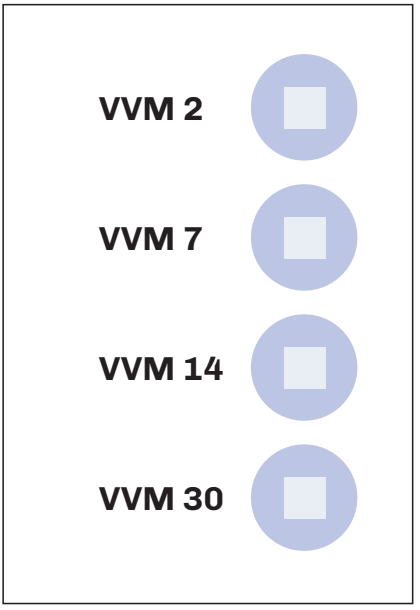

Ticky Raubenheimer


Denis Maire

whenever they need help and encouragement. Scaffolding is provided by four mentors.

The VVM e-learning course mimics the real world through authentic context and tasks. None of the problems are presented in a "prescribed" manner with each task forcing participants to find additional information to solve the problem. Assessment is mainly embedded in the authentic tasks, but we also see what the participants are learning by how they comment on other reports, how they reflect on their experience in diaries, how they express themselves through "Flipgrid" videos, and how they raise issues or contribute to ongoing discussions. We even see how they engage in fun learning activities such as a "scavenger hunt" where participants are given situations to photograph and post the results in a blog. The infusion of rigorous individual and group authentic assessments may be the most distinguishing feature that sets GLO/EPELA courses apart from other forms of e-learning. Most importantly, participants work with real VVMs, expose them to different situations, observe changes and write reports on their observations.

VVM cards participants place in freezer, refrigerator, in a table drawer, on the desk and in window sill

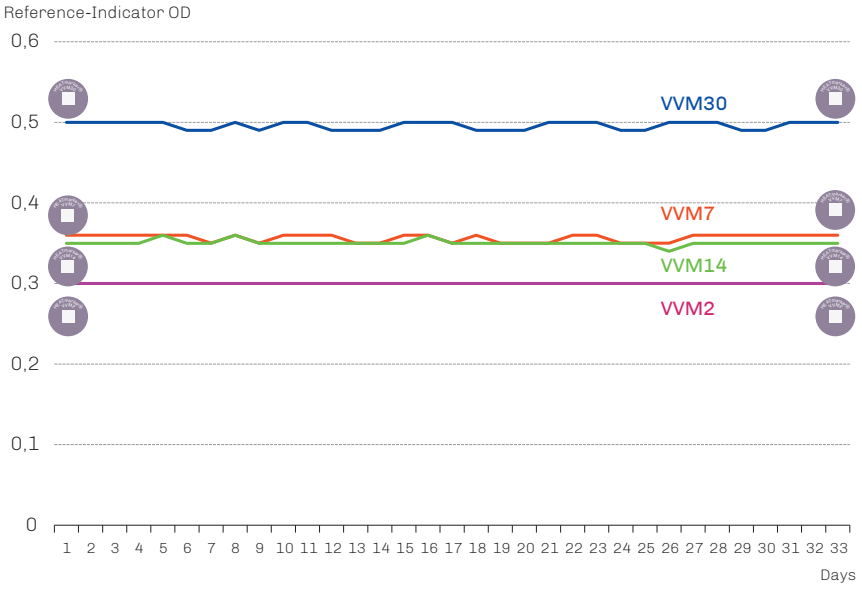


When participants observing the color change in VVM exposed to five different situations, the same experiment is then repeated, but instead of making photographs of the cards on a daily basis, I use a spectrodensitometer to measure the color change and prepare the following graphs as feedback that I send to participants once the task is over.

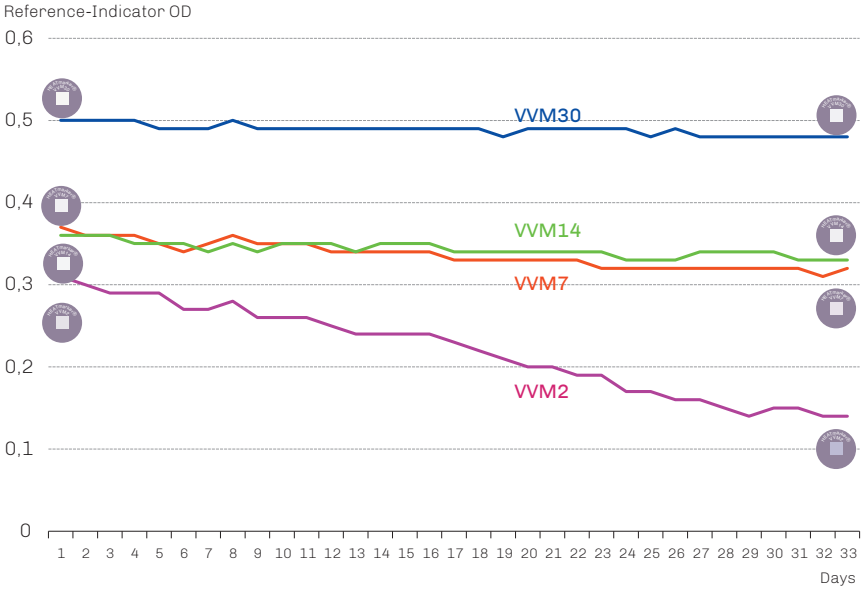
Optical density (OD) readings of the reference ring and the indicator surfaces

The following graphs illustrate the OD difference between the reference ring and the indicator surface of four different VVM categories plotted against time from the beginning of the experiment until the end, covering a 33 days period (Reference and indicator OD difference of zero corresponds to the discard-point of VVM). Measurements are done on a daily basis.

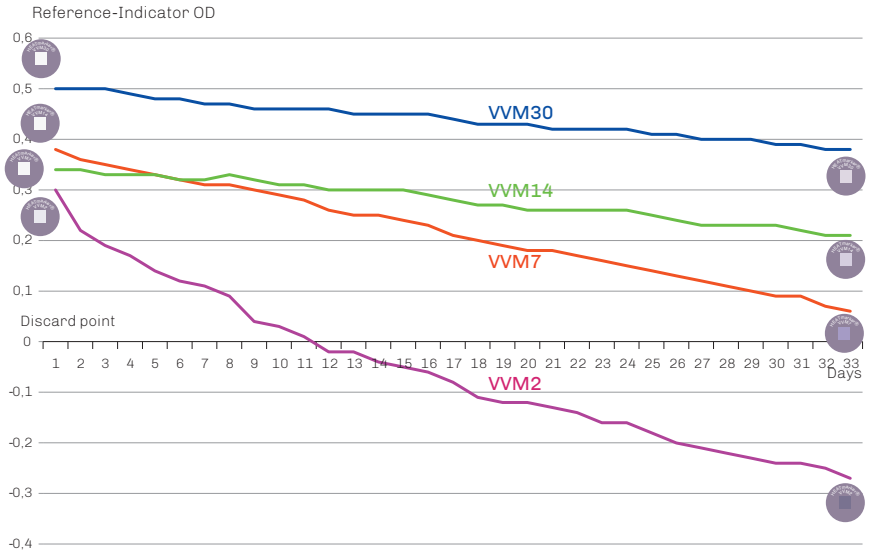
Reference-Indicator OD measurements for VVM2, VVM7, VVM14, VVM30 kept at FREEZER from 27 January to 28 February 2014 (average temperature -15°C)



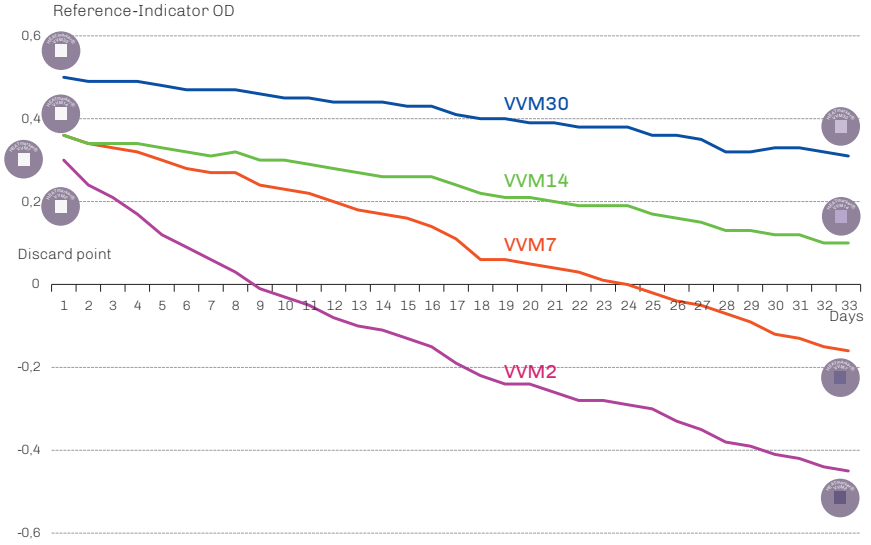
Reference-Indicator OD measurements for VVM2, VVM7, VVM14, VVM30 kept at REFRIGERATOR from 27 January to 28 February 2014 (average temperature +7°C)



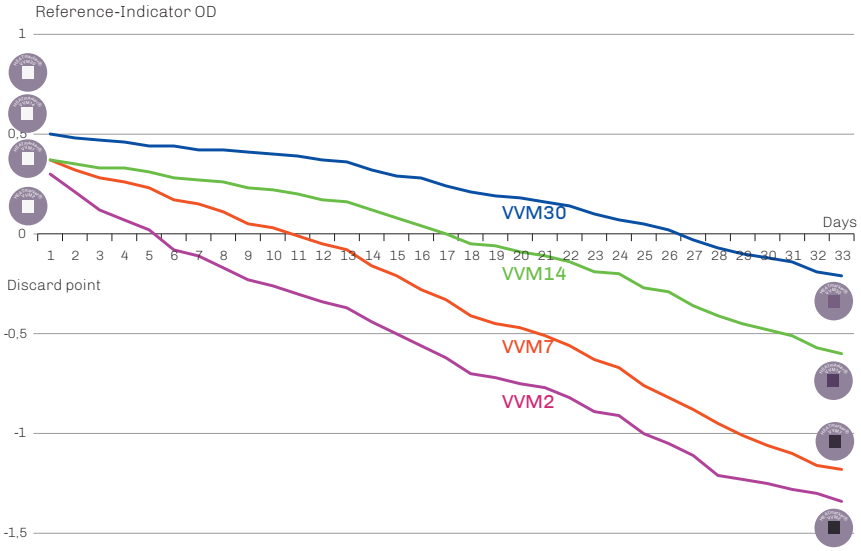
Reference-Indicator OD measurements for VVM2, VVM7, VVM14, VVM30 kept in a DRAWER from 27 January to 28 February 2014 (average temperature +17°C)



Reference-Indicator OD measurements for VVM2, VVM7, VVM14, VVM30 kept on the DESK from 27 January to 28 February 2014 (average temperature +20°C)

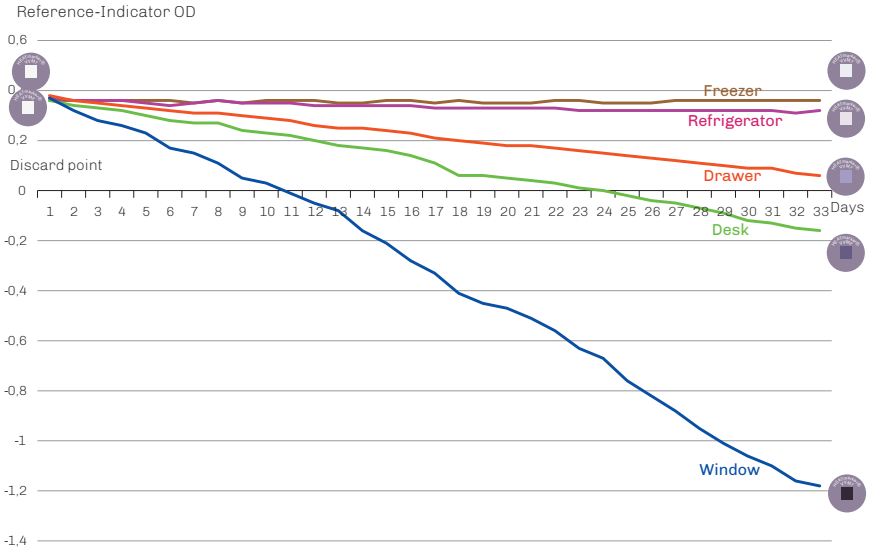


Reference-Indicator OD measurements for VVM2, VVM7, VVM14, VVM30 kept next to a WINDOW from 27 January to 28 February 2014 (average temperature +23°C)



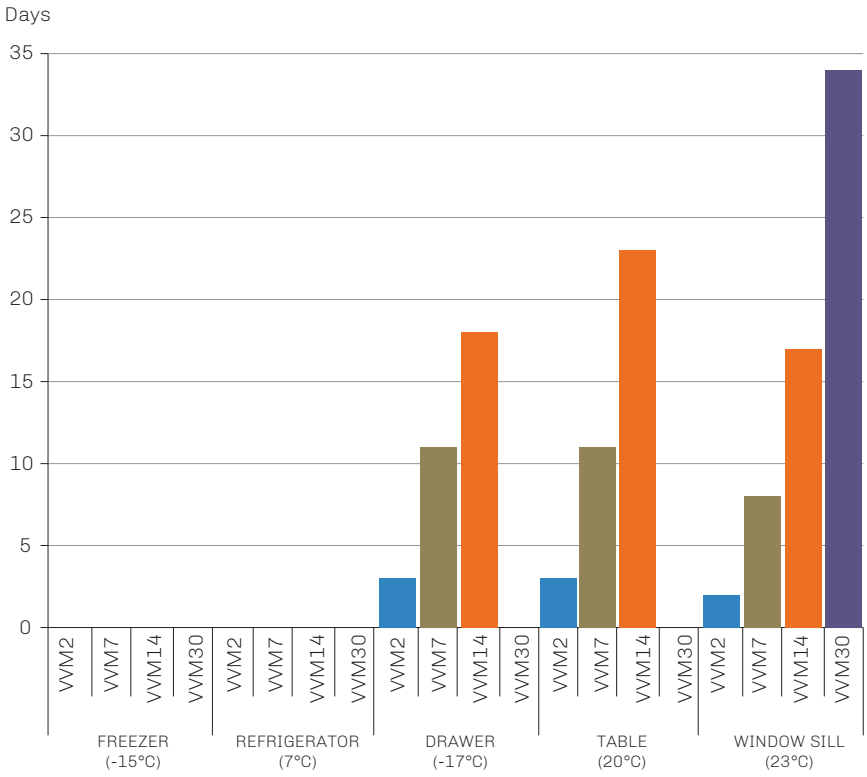
In order to show the impact of the conditions on the same type of VVM, different sets of graphs are produced. Below is an example of a VVM7 reaction to five different conditions.

Reference-Indicator OD measurements for VVM7 exposed to 5 different conditions from 27 January to 28 February 2014



Through these graphs, mentors also highlight the impact of UV light on the VVM reaction especially with VVMs that are placed on the desk and next to a window. Despite participants making only visual observations during this period, some come up with creative ways of presenting the data. Here is an example of a visualization of the VVM reaction observation by highlighting the number of days it took to reach the discard-point under different conditions.

Discard-point in days for four different type VVMs exposed to different conditions

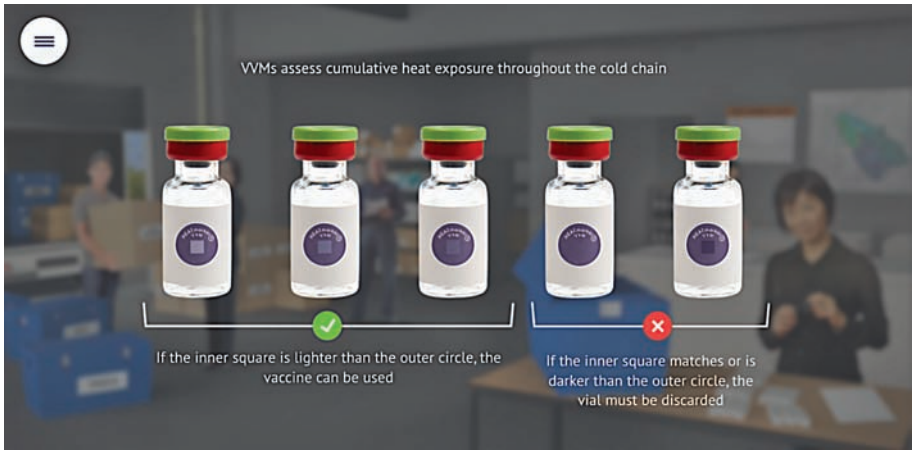


Immunization eLearning initiative

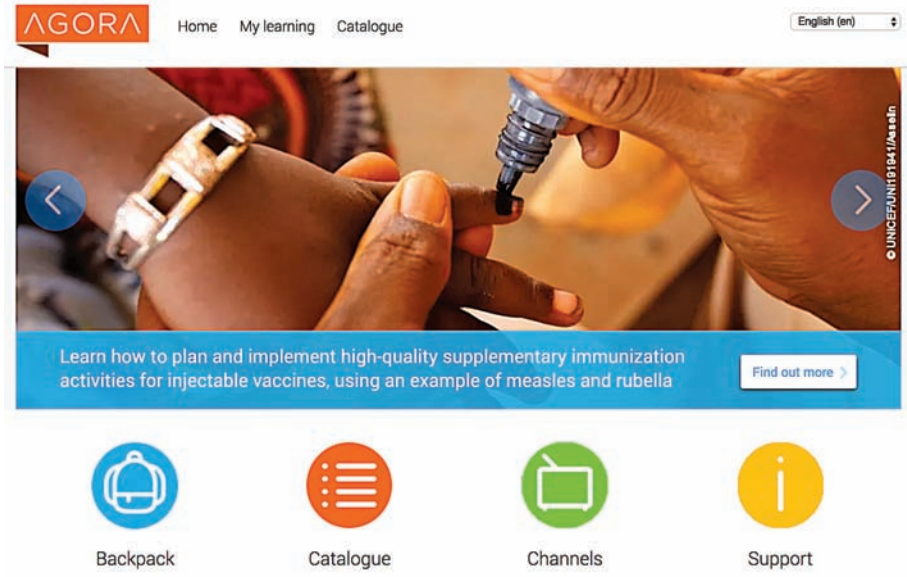
Developed jointly by UNICEF and WHO, the Immunization e-learning Initiative provides all immunization staff with access to training in areas deemed vital to the advancement of the Global Vaccine Action Plan and its vision that everyone should live a life free from vaccine preventable diseases. The VVM short eLearning course (micro-teaching activity) reviews the effect of heat exposure on vaccines, and demonstrate how to interpret and use VVMs in different situations including MDVP. The course is comprised of one self-paced module and takes approximately 20 minutes to complete. To register for the course, you may check https://uni.cf/2H1HVhQ.

The UNICEF Agora platform also hosts other eLearning courses, all self-paced. VVMs appear in some of these courses as part of the curriculum, e.g. how to manage immunization stock, temperature monitoring.

VVM information in "how to manage immunization stock" eLearning course



All courses offered by the Agora platform can be found at https://agora.unicef.org/.

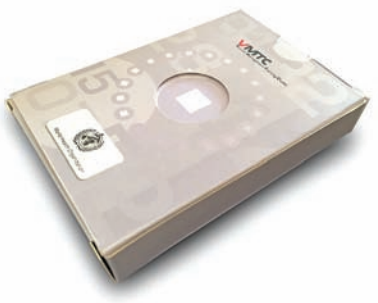


VVM games for learning

In the learning process, the face-to-face courses use various games based on VVM.

VVM card game

The VVM card game that we play in "Vaccine Management" courses is a modified version of *bastra*, popular in Turkey, Egypt, Lebanon and Middle East countries.



The VVM card game is designed to improve skills in comparing VVMs, in order to decide which vial to use first. It comes boxed as a 52-card deck randomly numbered from 01 to 52. Card #53 is a reference card, listing all the cards in order, starting with the number belonging to the card with the lightest VVM square, and ending with the card with the darkest VVM square. The game requires a minimum of three people - two players and a referee - and has six rounds.

Here are the rules:

1. The dealer shuffles all the cards (except the #53 reference card – this card remains with the referee).
2. The dealer deals four cards at a time, face down, to each player. For the very first hand, after dealing cards to the players, the dealer places three cards face down and one card face up to the middle.
3. The player to the right of the dealer begins by placing one card face up in the centre of the table (alongside the three face down cards and one face up card).
4. Going around the table in a counter clock-wise direction, each remaining player places one card of their choice, face up, in the centre.
5. After each player has put down one card, the player who played the lightest VVM square wins the hand and collects all the cards from the middle (the idea is to beat others with the lightest VVM card).
6. If players cannot decide on the winner (i.e. if they cannot tell which card has the lightest VVM square), the referee will choose the winner by using the reference card. The referee does not show this card to the players.
7. The dealer then deals four more cards to all players, all face down.

8. Since the cards from the middle are already picked up, naturally there are no cards in the middle. The first player must now drop one card face up to the middle.
9. The round continues until the entire deck has been used up.
10. At the end of the round, players count the number of cards that they have collected, getting one point for each card they have.
11. This is then repeated six times.

Vaccine management board game

A vaccine management board game has been developed as a modified combination of *Monopoly* and *trivia quizzes*, incorporating a review of knowledge, challenged by the luck factor. Though it may seem like a competition, the original idea behind the game was to answer as many questions as possible to help participants to review the whole course content. This is why we have introduced pretty mean rules when the answer given is incorrect (e.g. *go back to start* type punishments). Even the luck factor becomes extremely critical when a player reaches the swamp area in the game!

The game is played by at least two participants, preferably four. In a course of 15 participants, you may have groups like 4+4+4+3 playing the game. Though this game is mentioned under summary, it is too long an activity to summarize a session. We play this game as the summary at the end of the course which gives participants a chance to review everything they have gone through in the learning sessions. We also give a set as a gift to each participant. The game comes in three languages, English, French and Russian.

The game box contains the following:

- One game board
- 50 cards with questions numbered from 01 to 50
- 50 cards with answers numbered from 01 to 50
- Two dice
- Six pawns in different colors
- Information sheet (how the play the game)

Here are the rules:

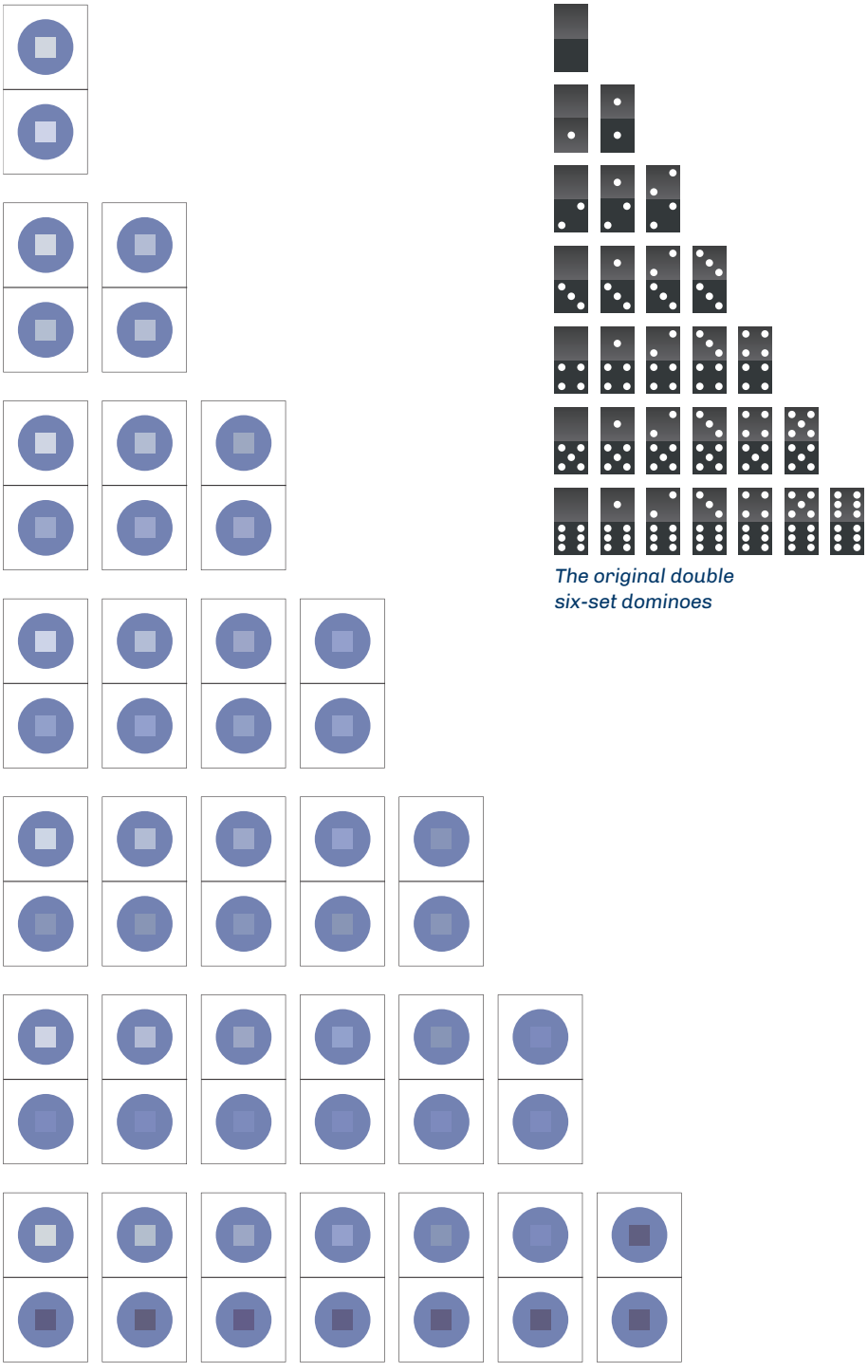
- Players should shuffle the questions cards and keep them faced down.
- Players throw one dice to decide who goes first, second, third and fourth.
- To start playing, the first player throws a dice and moves his/her pawn to the corresponding number of squares on the board, and draws the top question card, and answers the question.
- The next move is indicated in the rules paper. For example, if the first player comes to square 5 and answers the question correctly, he throws again. In the case of wrong answer, he/she waits for one round. Then the next player throws the dice.
- If players cannot decide whether the answer is correct, they consult the corresponding answer card (remember that for easy finding, answer cards should always be kept in numerical order).

When players come close to the end, to finish and win the game they have to land directly on the FINISH point. For example, the player on point 50 should throw six to finish. If he/she throws less than six and lands on two or four in the water, he/she returns back to the start. But if he/she lands on 1, 3 or 5 rocks, he/she waits for his/her next turn. If he/she is on rock #3, to finish he/she must throw three to land on FINISH. Throwing one which lands the players in swamp, makes the player to start again. Throwing two lands the player on rock #5, which is OK. If the player is on rock #3 and throws four, five, or six, that's OK, he/she just cannot finish the game, and has to wait for more rounds.

VVM dominoes

Dominoes is a game played with rectangular *domino* tiles. Each domino is a rectangular tile with a line dividing its face into two square *ends*. Each end is marked with a number of spots (also called *pips*, *nips*, or *dobs*) or is blank. The backs of the dominoes in a set are indistinguishable, either blank or having some common design.

The most basic domino variant is for two players and requires a double-six set. The 28 tiles are shuffled face down and form the *stock* or *boneyard*. Each player draws seven tiles; the remainder are not used. Once the players begin drawing



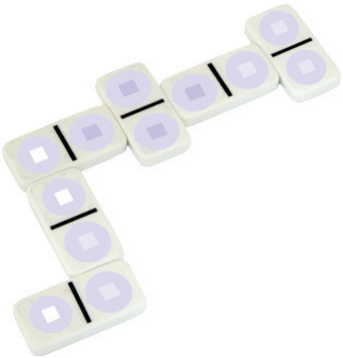
The original double six-set dominoes

tiles, they are typically placed on-edge in front of the players, so each player can see their own tiles, but none can see the value of other players' tiles. Every player can thus see how many tiles remain in the opponent's hands at all times during gameplay.

One player begins by downing (playing the first tile) one of their tiles. This tile starts the line of play, in which values of adjacent pairs of tile ends must match. The players alternately extend the line of play with one tile at one of its two ends; if a player is unable to place a valid tile, they must keep on pulling tiles from the stock until they can. The game ends when one player wins by playing their last tile, or when the game is blocked because neither player can play. If that occurs, whoever caused the block gets all of the remaining player points not counting their own.

We have replaced the double-six set dominoes with seven different VVM shades. In the original double-six set dominoes there is one blank and six numbers, since we have replaced the blank one with a VVM, we have seven VVM shades in the game. The game helps participants both having fun and sharpen their judgement on the VVM colors.

The game follows the same rules as a standard game of dominos. The game can be played both during the body of a session or as a summary game at the end. Since dominoes can only be played by two people, you need to have enough sets for the groups. In the case of an odd number of participants, one of facilitators may join as a player.



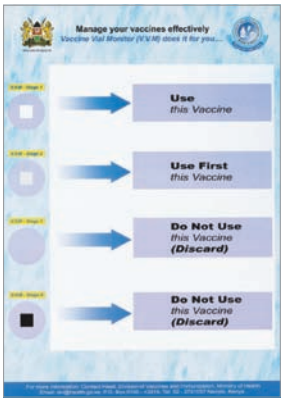
You can make your own domino sets by printing VVMs in sticky label sheets, and placing them on either plastic or wooden domino tiles. If you do not have a domino set, you may prepare your own domino tiles from wood.

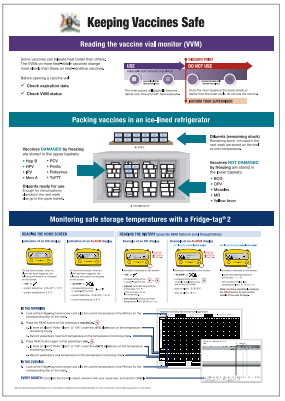
You may also give one domino set as a gift to each participant at the end of the game.

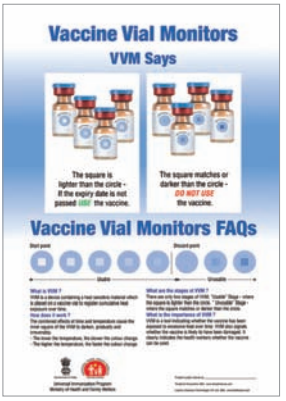
VVM posters

Many countries have adopted VVM posters as a visual reminder to health workers. They come in various sizes and shapes either as a poster or a sticker. All these visual reminders display four different colors of VVM to indicate the start-point, a heat affected VVM but still at a usable stage, the VVM end/discard-point and a VVM beyond the discard-point.

VVM posters from Kenya, Uganda, and India EPI programmes



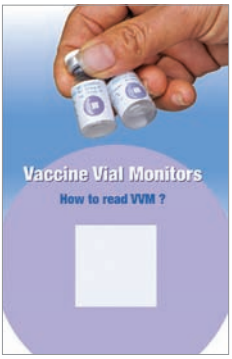


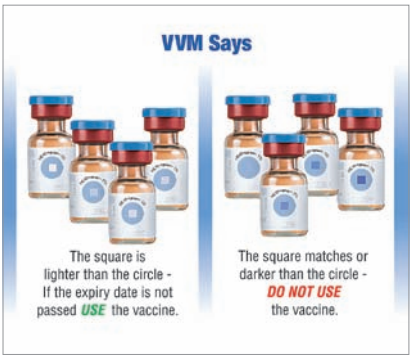


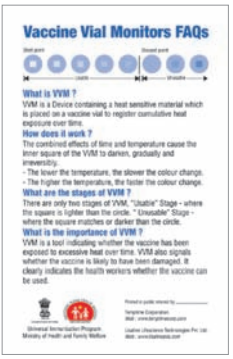
VVM stickers from Haiti and Albania EPI programmes

The following two examples are from the India EPI programme: pocket brochures, a beautifully designed reminder to health workers.

Pocket brochure job-aids, India

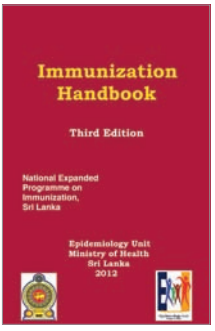


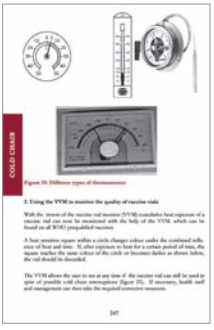


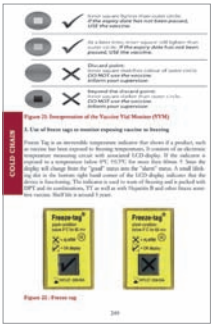


Countries also include VVM related information in their EPI programme guidelines.

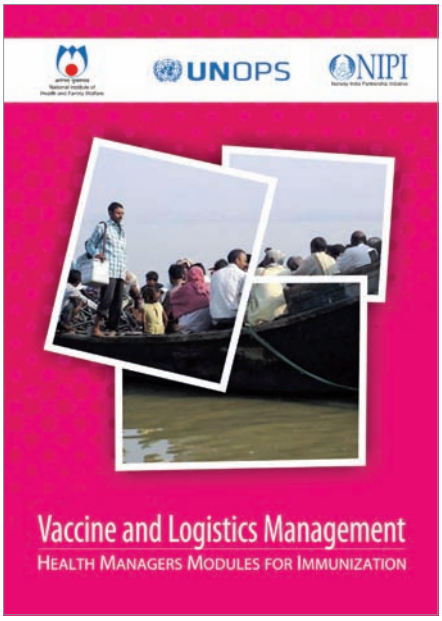
Example of VVM information in EPI programme guidelines, Sri Lanka







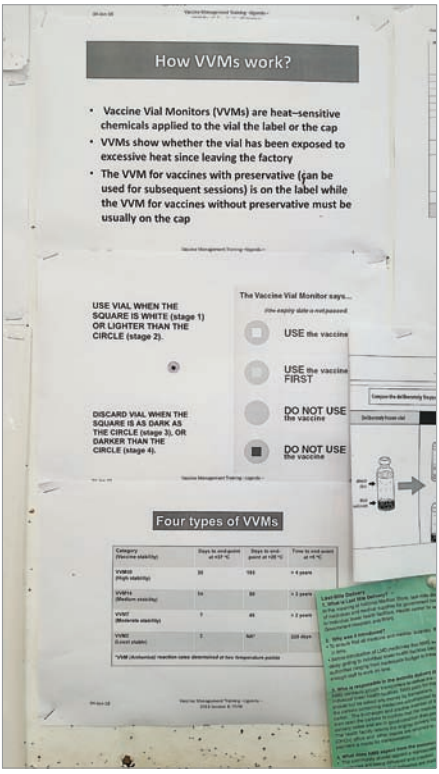
Example of VVM information in EPI programme guidelines, India

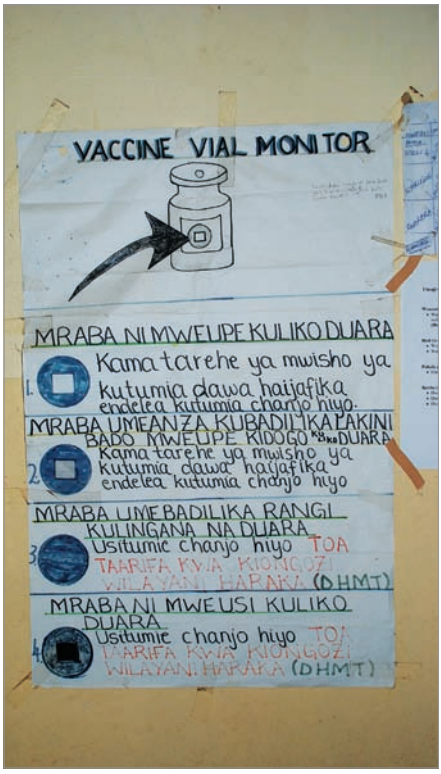


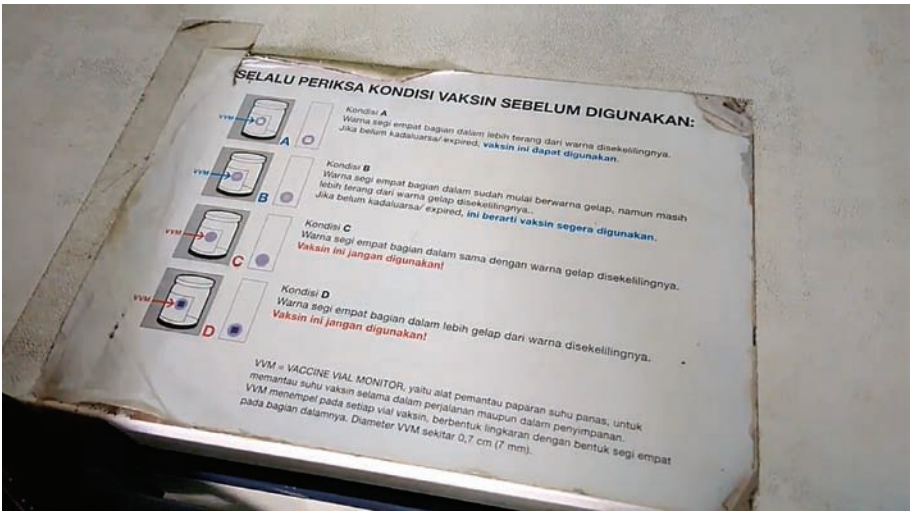
Example of VVM information in Colombia EPI programme guidelines on bivalent poliomyelitis vaccine

It is very rewarding to see some of the individual initiatives of health workers from low resource settings. The creativity of the staff from Uganda and Zanzibar in this respect can be seen from their displays of VVM information posted on the wall.

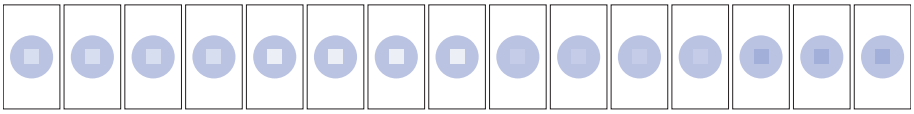
Staff creativity in production of VVM posters/visual aids from Uganda, Zanzibar and Indonesia







Since VVMs provide a visual guide, the programme job-aids can be made quite colorful with VVM information vividly displayed on posters, stickers, games, and so on. Staff can also produce their own visual-aids using their personal creativity. In training programmes, VVM shades can also be used as means of dividing groups with the dividers serving at the same time as a learning tool for recognizing the color shades of VVMs.



Since new staff continuously join the EPI forces and there can be considerable staff turnovers in some countries, it is important that new and refresher learning opportunities on VVM based vaccine management are always available. This schooling and practical training is also instrumental in encouraging staff to use the VVM to its utmost potential.

Fascination and inspiration

The success of VVMs has been a true inspiration to many individuals and organizations on many fronts.

Yesterday

In November 2005, the cover of Time magazine featured a story, "How to save a life", a special report on the world's most dangerous diseases – and the heroes fighting them. The special report by Nancy Gibbs was presented with photographs by James Nachtwey. *"Six million children – and even more adults – die unnecessarily every day"* remarked Nancy, *"Good people all over the world are doing their best to save them. You can too."*

In a special section entitled "The power of example" eighteen people are presented as dedicated champions in the battle against killer diseases in the developing world. VVMs appear in a section of "High tech for low-tech world" by Alice Park. *"Battling diseases is easy if you are on a power grid with access to effective treatments"* says Alice, *"But what if clean water and electricity are unavailable luxuries? These products are designed for use in just those low-resource settings."*

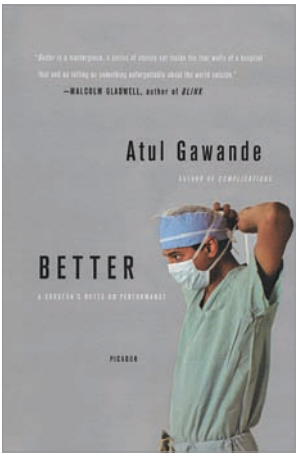
In 2008, Dr. Atul Gawande, a staff writer for The New Yorker and a surgeon at Brigham and Women's Hospital in Boston, published his second book *"Better: A surgeon's notes on performance"*.[52] In this book, Dr. Gawande explores how doctors strive to close the gap between best intentions and best performance in the face of obstacles that sometimes seem insurmountable. Gawande's enthralling stories take us to battlefield surgical tents in Iraq, to labor and delivery rooms in Boston, to a mop-up polio vaccine campaign in India, and to malpractice courtrooms around the U.S. In the Mop-Up story, he follows immunization supervisor Pankaj in the field. In this story Dr. Gawande underlines the critical importance of VVMs.

"Going around to a few more huts, we bumped into a vaccination team – a social welfare worker wearing sandals, a blue sari, and a flower in her hair, and a younger, college-student volunteer with a flower in her hair too, and a square blue cold box of vaccine slung over her shoulder. They were standing in front of a hut they'd marked with an "X" instead of a "P" – the woman of the house had said that three children lived there, but one was absent and could not be vaccinated. Pankaj asked the vaccinators to open their cold box. He checked the freezer packs inside – still frozen, despite the heat. He inspected the individual vaccine vials – still fresh. There was a gray-and white target sign on each vial. Did they what it meant? That the vaccine was still good, they said. What does it look like when the vaccine expires? The white inside the

52 Gawande A. (2008). *Better: A surgeon's notes on performance.* Picador

target turns gray or black, they said. Right answer. Pankaj, moved on."

Laura J. Frost and Michael R. Reich published the book *"Access: How do good health technologies get to poor people in poor countries?"* in March 2009.[53] In this book, Frost and Reich analyze questions such as 'why do problems in access persist in many developing countries and what can be done to improve access to good health technologies, especially for poor people in poor countries?' They do this by developing a comprehensive analytical framework for access and examining six case studies to explain why some health technologies have achieved more access than others. The technologies include praziquantel (for the treatment of schistosomiasis), hepatitis B vaccine, malaria rapid diagnostic tests, vaccine vial monitors, the Norplant implant contraceptive, and female condoms. Based on research studies commissioned by the Bill and Melinda Gates Foundation to better understand the development, adoption, and uptake of health technologies in poor countries, the book concludes with specific lessons on strategies to improve access. These lessons will be of keen interest to students of health and development, public health professionals, and health technology developers - all who seek to improve access to health technologies in poor countries.

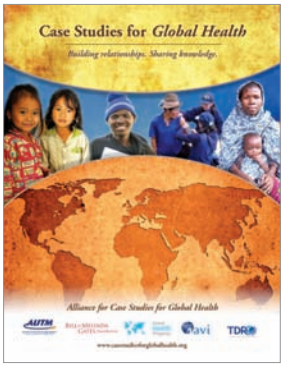


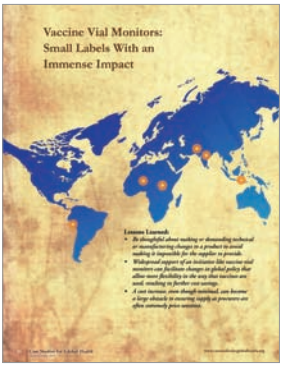
The authors conclude that the story of VVMs demonstrates that creating access to this innovative technology required much more than simply putting a label on a vaccine vial. *"Producing access to VVMs on vaccines procured through UNICEF has been successful and has created far-reaching impacts - reducing vaccine wastage, allowing health workers to take vaccines to remote areas, pinpointing weak links in the cold chain, implementing a multidose vial policy, and ultimately expanding the reach of immunization programs - to improve health and save lives in developing countries. Achieving these impacts has required diverse agencies to work together, overcome logistical issues, address limited uptake by vaccine producers, and embrace new ways of thinking about the cold chain and*

53 Laura J. Frost and Michael R. Reich (2009). *Access: How do good health technologies get to poor people in poor countries?* Harvard University Press.

vaccine management. This could only be achieved through the efforts of dedicated product champions like PATH and WHO collaborating with public and private actors to achieve access and technology uptake. Achieving the full potential cost gains and health gains offered by the VVM, however, will require continued advocacy by product champions to expand access to the device for all EPI vaccines used in developing-country immunization programs."

In October 2009, Alliance for Case Studies for Global Health published a series of case studies including VVMs authored by Pam Baker. The author concludes that despite all the difficulties and challenges, the overall impact of VVMs has been considered a global success. *"Future vaccine storage and transport will likely rely even more heavily on VVMs as the existing cold chains become constrained by the introduction of many new vaccines. VVMs could enable the removal of some heat-stable vaccines to higher temperature storage areas to make room for more heat-sensitive vaccines in refrigerators. The labels also have a proven history of enabling outreach to difficult areas and can continue in this role with new vaccines, such as conjugate meningococcal A vaccine. The Optimize project is a joint WHO/PATH project focused on developing the strategies for the future of immunization logistics. Project Optimize is working to further improve the availability and utilization of the VVM as a vaccine management tool within countries."*





In August 2017, Stanford Graduate School of Business started to offer a case study on VVM by Steve Davis (PATH) and Debra Schifrin (Stanford) for students to understand the challenges and complexities of bringing an innovation to scale, especially in the global health sector. Steve Davis and Debra Schifrin explains where the title of the case study *"Vaccine Vial Monitors: 'The little big thing:' Taking social innovation to scale"* comes from:

"Starting in 1979, PATH and WHO led an almost 30-year journey to develop, test, approve, introduce, and scale up VVMs. By early 2017, VVMs had been used on over 6.5

billion vaccine vials globally, and VVM use around the world continued to expand. Umit Kartoglu, a WHO scientist who played a pivotal role in the expansion of VVMs, called this small, inexpensive but extraordinarily impactful innovation "The Little Big Thing.""

Davis and Schifrin further explain that even with a simple innovation idea, the development and large-scale adoption of a global health product can take years, and often requires extensive collaboration between public, social, and private sector players. The case teaches about the risks faced by each sector and the challenges inherent in scaling a social innovation sustainably.

Steve Davis

Debra Schifrin

Davis and Shifrin conclude the case as follow:

"In the long journey of VVMs from concept to innovation to widespread adoption, the multisector partnership was critical between public sector, social sector, and private sector. These players experienced the challenges of getting a social innovation to scale and overcame them. It took patience, determination, good collaboration, and communication. It also took a willingness to look at the perspectives of the other players, the ability to adapt, and sometimes a willingness to take risks. Zaffran added that things did not move quickly with scaling social innovations:

"Of course, you need a good product, a good idea, but you need to be very patient and you need to not be too naïve. Stop thinking that your product is something that has never been thought of or tried. Do your research and speak to the people who have been in the field for a long time to actually test your ideas and see how it can really meet their needs, and after that be patient."

Renaat Van den Hooff described what he and the team at Temptime experienced about innovation:

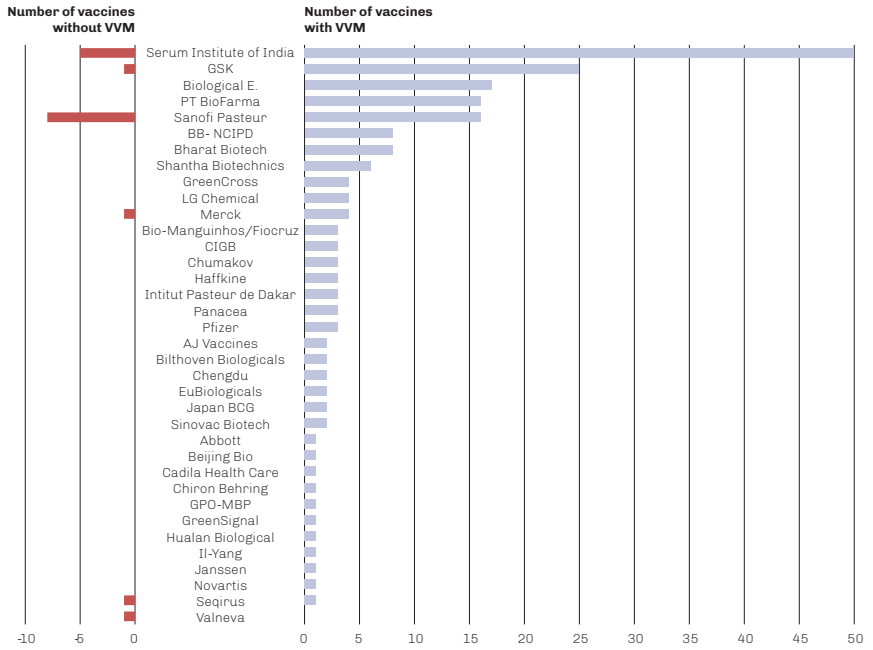
"There are a lot of idealistic ideas that stem from technology capabilities, but that is not sufficient. The ideas have to matter to customers and make a difference. Pursuing innovation without customer validation can be a major pitfall. We come up with a lot of great ideas at Temptime, but if we don't get any positive feedback from our stakeholders, or if they don't want to take it into some type of trial, we document the project and put it on the shelf.

"By 2017, the impact of VVMs had been proven with billions of VVMs sold and hundreds of thousands of children's lives saved across the world. With the new VVM products being developed, the hope was that these would have a similar impact and be the next 'Little Big Thing.'"

Today

By the time of writing this chapter (February 2019), there were a total of 212 vaccine products from 36 vaccine manufacturers prequalified by WHO. Out of these products, 196 of them come with VVMs.

VVMs on WHO prequalified vaccines by vaccine manufacturer, 28 February 2019



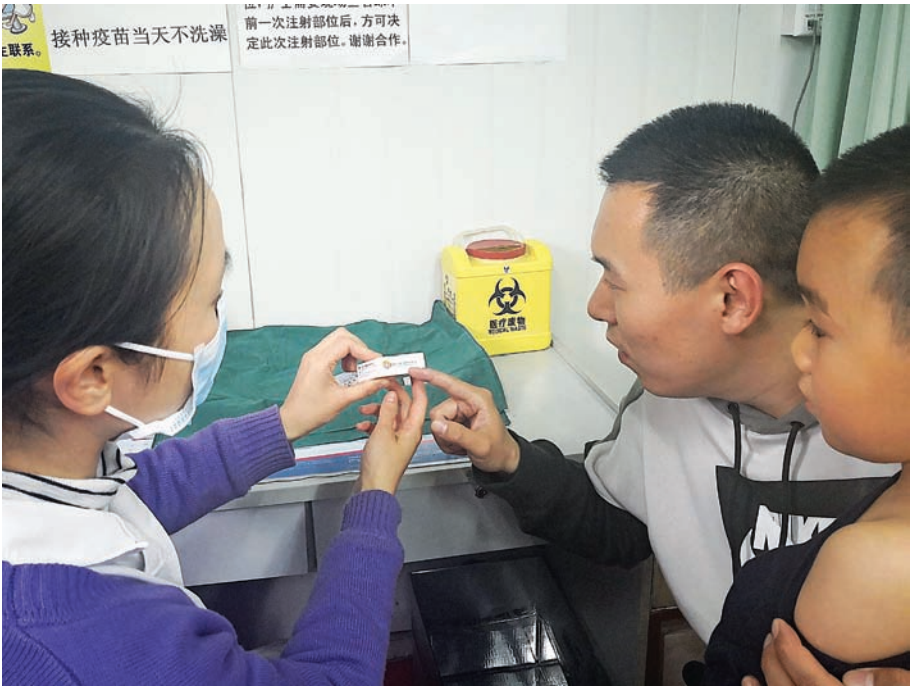
All vaccines without VVMs from the Serum Institute of India belong to single-dose vials of DT, DTP and TT vaccines in ampoules. Four of 16 vaccines with no VVMs are the seasonal influenza vaccines. The GSK product without VVM is produced only for PAHO.

WHO prequalified vaccines with no VVMs by vaccine manufacturer and type, 28 February 2019	
GSK	Rotavirus (applicator – only for PAHO)
Merck	Rotavirus 1 dose
Sanofi Pasteur	Diphtheria-Tetanus (reduced antigen content) 10 dose
	Tetanus Toxoid 10 doses
	Tetanus Toxoid 20 doses
	Haemophilus influenzae type b 1 dose
	Rabies 1 dose
	Seasonal influenza 1 dose
	Seasonal influenza 10 dose
	Seasonal influenza 10 dose
Serum Institute of India	Diphtheria-Tetanus 1 dose in ampoule
	Diphtheria-Tetanus (reduced antigen content) 1 dose in ampoule
	Diphtheria-Tetanus-Pertussis (whole cell) 1 dose in ampoule
	Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B 1 dose in ampoule
	Tetanus Toxoid 1 dose in ampoule
Seqirus	Influenza seasonal 10 dose
Valneva	Cholera inactivated oral

Today, VVMs also appear on vaccines that are not part of the WHO prequalification programme. China is the best example of this. Following the Shandong disaster, province after province started to demand VVM on vaccines. Today almost half of the provinces have regulations to this effect. The other half is moving towards this position.

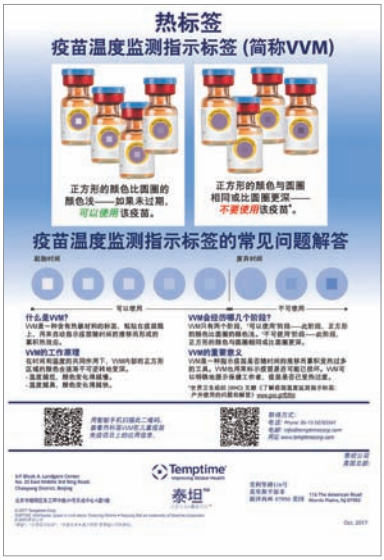
VVM implementation in China by province, May 2019

"Beyond the prequalified suppliers, beyond the WHO-UNICEF-Gavi world, we have 35 vaccine manufacturers who have handled and used the VVM in China" says Chris Caufield. *"The Chinese market is interesting, because it started with the Chengdu Institute of Biological Products (IBP), and a request from MOH to India to have JE vaccine delivered to India with VVM. So, they became the first manufacturer inside China to actually handle, evaluate, apply and use the VVM. From there Shanghai was the first province in China to request pneumococcal vaccine with VVM. Chengdu IBP has pneumococcal vaccine, and they replied to the tender saying that it could comply. They became the first user inside China to deliver VVM to the Chinese market. In October 2014, the head of Beijing CDC was on television, and demonstrated the VVM. He said all seasonal flu vaccine for Beijing that year would be coming with VVM attached (http://bit.ly/2ydY26w). He spent three minutes on television describing to a national audience how the VVM works, what people should look for, and how it is used. He actually asked viewing parents to ask the healthcare professionals to show them the VVM. I think this has a lot to do with the culture, 'the Government is taking care of you, and you should ask, and you should verify that you're being taken care of" – so they did that.*



Father verifying that the VVM is "good" prior to vaccination of his son, China

"And the use of VVM quickly spread to other vaccines beyond seasonal flu, with adoption starting to spread along the eastern coast of China province by province. It was a bottom-up not top-down progression. The idea that you can use the VVM to increase parental confidence in vaccine is something that's very real in China. I've gone into clinics in China, two years ago, and seen parents literally asking the vaccinator to show them the VVM. They had posters on the wall, showing what the VVM is all about, something that is really unique to their country. This is not a WHO mandate and it is not a Gavi mandate; it is a province by province requirement they are asking vaccine manufacturers to do, and it is something that has been well received by the people. Over the course of the last few years, following several vaccine scandals in China, the VVM has served them well, and reminds the citizens that they have been taken care of."



Until China decided to encourage parents to seek out VVM for as a mark of good handling verification, only health workers were referring to VVMs in order to take informed decisions. Taking VVMs to parents for them to check and confirm that the vaccine to be given to them/their children has been handled correctly is an important initiative. The "quality" message that can be confirmed directly by parents increases the trust both in the programme and in the vaccines. As for parents, the quality message is simple and clear: "If the square is lighter than the outer circle, vaccine is handled with care and good to be given." Kyrgyzstan (a Gavi-eligible country) will be the first country to be implementing a similar measure to increase public trust in vaccination programme and increase vaccination coverage among migrants and urban poor as part of their Health System Strengthening (HSS2) programme starting in the first half of the 2020. Although Kyrgyzstan's HSS2 application has just been approved by Gavi on 16 April 2019, and the implementation of new activities will start in the coming months, showing VVM to parents and vaccinated persons and assessing their reactions in small scale tests has been already taking place in Bishkek.

On 8 May 2019, Rima Imarova (UNICEF) posted on Facebook the following story:

"Today we made #vaccination 😎. I believe that #vaccineswork and that they will protect my children! I believe in proven medicine and in the quality of vaccines. The son checked just in case the indicator of the vial (square in the circle, it must be bright). Great, the cold chain is preserved! Well done medics! After the procedures, all the friendly came home. Did you protect your children from preventable diseases? 😊😊 "

It was Baiel taking his little sisters for vaccination to Polyclinic #5 in Bishkek. The nurse Damira Israilova, as part of this testing, explained and showed the VVMs of the vials she was about to use. Baiel being so excited about this novel "quality" indicator, happily wanted to pose with a VVM to encourage his siblings and to be seen as a role model, he decided to receive his shot first.

On 30 July 2019, Narayana Holla (India) in a posting in TechNet21 forum discussion suggested that the *"Beneficiaries have right to information; service providers can show the vaccine with useable VVM to the caretakers to gain their confidence for better community participation"* (http://bit.ly/30ZabZw). Narayana suggested this without knowing about the China and Kyrgyzstan cases, I was happy to hear that the initiative was spreading to other countries.

Tomorrow

VVM continues to evolve and respond to existing and emerging needs.

Controlled temperature chain, CTC, with specifically licensed vaccines allows vaccines to be taken out of cold chain at the last mile to increase access and therefore improve vaccination coverage. CTC cannot be successfully implemented without VVM and requires another temperature monitoring device, a threshold indicator for high temperatures. The new VVM+, to be introduced in the coming months, brings together the VVM and the threshold indicator into one, responding to a new challenge from the immunization programme. And a new innovation coming from Temptime will fill the digital temperature gap at the unit level by integrating VVM with a 2D barcode. In a world where the next generation supply chain will be digital, Temptime is reinventing this elegant chemical indicator to become the digital solution of the future.

Epilogue

In early spring 2004, I was in Port Elizabeth, South Africa, working with Ticky Raubenheimer and Dianne Phillips from the Collaborative Centre for Cold Chain Management (CCCCM) for the delivery of a vaccine store management learning event at the Humewood Hotel. With the help of Dianne, I discovered this beautiful flower, Brunfelsia pauciflora.

Brunfelsia blooms purple with a white throat, then turns lavender and then white. The shrub displays all three flower colors at once as more petals bloom. It is these three shades of colors carried simultaneously that led to its common name 'Yesterday, today and tomorrow'. The bushy evergreen shrub is quite dense and grows to about 2 to 3 m tall. Brunfelsia is also known as Morning-noon-and-night, Kiss Me Quick, and Brazil raintree. In my case, I call it the "VVM flower" because although VVM reacts from light to dark and Brunfelsia from dark to light, these amazing colors, continuously changing from violet to pale white always remind me of the VVM. Its inimitable romantic sweet scent and the wondrous beauty of the variegated colors brought me every evening to this remarkable plant.

Here I would sit down by the flowering bush and think of three people, Kevin, Serge, and Cherifa. These were three completely unrelated people who had no knowledge of each other but who unwittingly shared a common bond.

Kevin Keane lives in Rockaway, New Jersey, USA with his wife and two beautiful daughters. He works at Temptime Corporation as a press operator. He and his family live for outdoor activities, be it in summer or in winter. Kevin delights in camping and fishing as well as running with his favorite dog in the woods around his home. Every day he commutes 12 km to reach his work, a job which he loves. Kevin understands the positive end-result of what he is part of and knows that being attentive and precise is critical in having a quality product to help mothers and children anywhere in the world.



Serge Ganivet, originally from France, lives in Dakar, Senegal. He works for UNICEF as an immunization supply chain specialist. He is responsible for 23 countries in total in Western and Central Africa, and is continuously on the road throughout the year. Naturally, he misses his son and daughter back in France. Whenever he manages to find some free time, no matter where he might be, he immerses himself in nature, him and the wild life... He also loves to play squash, he runs to keep fit and, when he gets the chance, he goes on safaris with the Teranga Moto Riders Club. Each year Serge travels thousands of kilometers both in the air and on the ground for work and his huge experience has taught him that the key to success lies in working closely with the people on the ground.


Cherifa lives in Indaman village, in Niger. She is a mother of three, she cooks, cleans, fetches water, takes care of children. She does not commute for work, because wherever she turns, wherever she goes, is for work. It is only when the sun goes down that Cherifa, with her little Idrissa in her arms and gazing at her older girls sleeping on the floor, has time to think about her day. She caresses Idrissa and presses him to her breast. She does not know what she loves in this life, but she knows for sure that when the time comes, no matter how far or long she needs to walk, she will take Idrissa for vaccination. She did this for the girls, and will do it for the boy.



Ibrahim Ali, a health worker in Niger, welcomes Cherifa to his outreach session and commends her for bringing Idrissa for vaccination. He has been well-trained by Serge Ganivet and immediately checks the VVM label on the vaccine vial. It is a VVM that Kevin Keane has helped to produce. The VVM looks fine and Ibrahim quickly vaccinates Cherifa's son Idrissa, in one moment touching the souls of these three beautiful human beings.

In a remote village in the Tchin-Tabaradene region of Niger, VVM, the little big thing, is the incredible innovation in the hands of Ibrahim Ali that unconsciously links all of these people's lives.



Idrissa cries a little.
Cherifa smiles inside.


DO NOT FREEZE
B.NO.: 124X7017B
MFG.: AUG. 2017
EXP.: JUL. 2019
HEATmarker ® VVM14
SHAKE WELL

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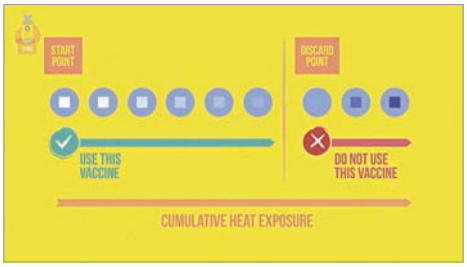
Recommended videos

HPV vaccine
by Immunization Academy
https://bit.ly/2VRdBPn
running time: 09:06 min

Produced in support of HPV introduction, discussing the target group, administration, storage and transport of the vaccine, including details on the VVM use.

How to read a VVM
by Immunization Academy
https://bit.ly/2JbovIS
running time: 04:45 min

A short video explaining how to read a VVM including types of VVMs (indicates only four types), and using VVM as a visual cue.



Monitoring temperatures at health facilities
by Immunization Academy
https://bit.ly/2Y6snz2
running time: 05:23 min

A short video explaining temperature monitoring at health care facilities including the role of VVM.

What temperatures should vaccines be?
by Immunization Academy
https://bit.ly/2DOYNXb
running time: 04:54 min

To keep vaccines safe, they must be kept at a right temperature. But temperature sensitivity can vary among different vaccines. A short video about the temperature sensitivity of the vaccines with references to VVM.

Using the MDVP
by Immunization Academy
https://bit.ly/2GWkGEB
running time: 05:36 min

Step-by-step explanation of WHO's MDVP implementation including the role of VVMs in using MDVP as visual cue.

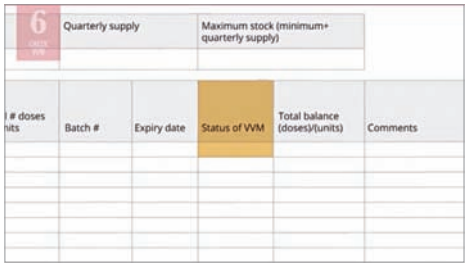
Arranging vaccines inside any refrigerator

by Immunization Academy
https://bit.ly/2PIRxRa
running time: 03:16 min

This short video gives tips for arranging vaccines in any refrigerator from the perspective of space utilization, types of vaccines, expiry dates, VVM status, and MDVP applications.

Monitoring vaccine and safe-injection stock

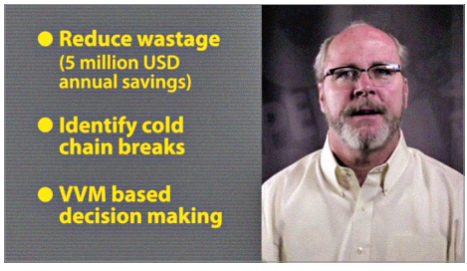
by Immunization Academy
https://bit.ly/2LorJLX
running time: 05:31 min



This short video focuses on the importance of stock records in order to prevent stockouts and overstocks, and viewers are taken through a stock ledger on what to record and how to record, including the role of VVM in stock movements.

A year in the life of a vaccine

by Kevin O'Donnell
https://bit.ly/2vDItUE
running time 07:50 min (2012)



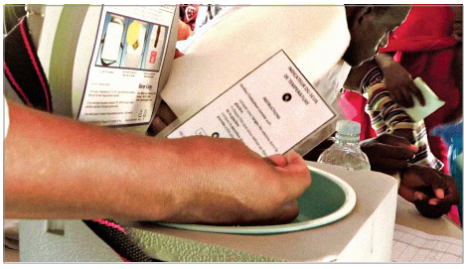
Kevin O'Donnell reviews the role of VVM and how it can be the answer to increase access and ensure quality of vaccine was not compromised due to unacceptable heat exposure.

Cold chain challenges everywhere
by Simona Zipursky
https://bit.ly/2J0OSlA
running time 03:48 min (2012)

Simona Zipursky reviews the cold chain challenges to demonstrate that problems are both in developing and industrialized countries and questions whether VVM should also be the answer for both.

Controlled temperature chain (CTC): Delivering vaccines more easily (episode 1 of 3)
by World Health Organization
https://bit.ly/2WxAnsg
running time: 05:28 min (2015)

The Controlled Temperature Chain, CTC, is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.

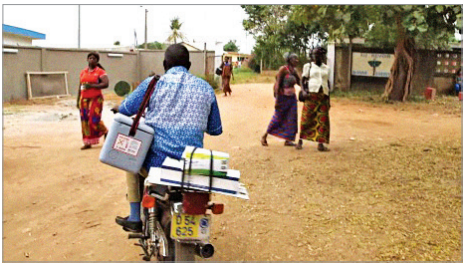


Controlled temperature chain (CTC): Implementing in the field (episode 2 of 3)
by World Health Organization
https://bit.ly/2VdFUI6
running time: 05:30 min (2015)

The Controlled Temperature Chain, CTC, is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.

Controlled temperature chain (CTC): Future development (episode 3 of 3)

by World Health Organization
https://bit.ly/2Y6VBOg
running time: 04:37 min (2015)



The Controlled Temperature Chain, CTC, is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen.

Exploitation of stability data to reach the unreached

by Ümit Kartoğlu
https://bit.ly/2ZYRuWk
running time: 10:53 min (2011)

Ümit Kartoğlu presents the critical aspect of exploitation of stability data to reach the unreached through overview of studies taking vaccines beyond the 8 deg C all published in peer-review journals as well as a new concept of cool water packs by the WHO and Vaccine Vial Monitors. As he indicates that vaccines have become more stable and there is a clear prospect of increased or even complete heat stability, and concludes that in these circumstances the dogmatic approach to the cold chain causes resources to be wasted and places unnecessary restrictions on field operations.

Five senses: Vaccine Vial Monitors

by World Health Organization
https://bit.ly/2V0WNAN
running time: 20:46 min (2007)

A movie, produced for the 10th year anniversary of the introduction of vaccine vial monitors (VVM). The movie focuses on how this simple tool expands the horizon of the immunization programme and empowers health workers serving people at the very periphery of the health system. The theme and the goal are specific but there are scenes, human conditions, and different livings for everybody to see and think about them. Shot in Niger, Vietnam and Indonesia in 2007.

How does a VVM work?

by Denis Maire
https://bit.ly/2J38PIr
running time: 08:39 min (2012)

Denis Maire summarizes the technical characteristics of VVMs and explains how they work.

Interpretation of VVM in relation to other temperature monitoring devices

by Ümit Kartoğlu
https://bit.ly/2H3H4xb
running time 12:49 min (2012)

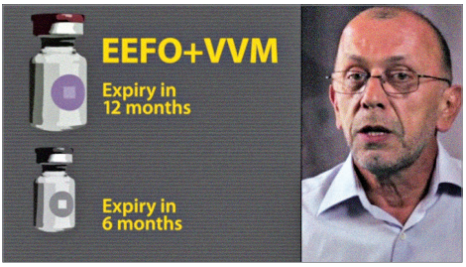
Ümit Kartoğlu reviews temperature monitoring devices used in a typical vaccine cold chain and analyzes how the readings relate to each other when there is more than one device at a particular point. This analysis is done from the VVM perspective.

Last Mile
by Ümit Kartoğlu
https://bit.ly/2WkCf7M
running time: 11:15 min (2011)

Ümit Kartoğlu reviews the critical last mile between the service point and the end user. He further discusses the best solutions for storage and transport of products and best practices for temperature monitoring.

Thermodynamics
by Kevin O'Donnell
https://bit.ly/2Llu0aw
running time: 08:53 min (2011)

Kevin O'Donnell discusses thermodynamics, the basis of heat transfer and how we can use heat energy to our benefit in packaging.



Using VVM as a stock management tool
by Ümit Kartoğlu
https://bit.ly/2vJNWZT
running time 08:22 min (2012)

Ümit Kartoğlu reviews the requirements for product arrival, storage and dispatch and analyzes the role of VVM in effective stock management for each step. Special emphasis is given to the relation of VVM and expiry date in illustrating how VVM over-rules earliest expiry first out principle.

Vaccines beyond the cold chain

by Simona Zipursky
https://bit.ly/2Jhwhkg
running time 12:48 min (2012)

Simona Zipursky reviews the studies on taking vaccines beyond the cold chain all published in peer-review journals and comments on how VVMs could be instrumental in these operations.

VVMs getting smarter

by Ümit Kartoğlu
https://bit.ly/2J0Qtrz
running time 03:32 min (2012)

Ümit Kartoğlu reviews the recent changes in integrity and location of VVMs and the new message VVM is giving whether a vial containing multi-dose vaccine can be kept for a subsequent session following opening the vial.

VVM use at the most periphery

by Serge Ganivet
https://bit.ly/2vEBt9W
running time 03:45 min (2013)

Serge Ganivet reviews the VVM use at the most periphery through different examples and brings new perspectives on how to make best decisions based on the expiry and VVM readings.

Vaccines work!
by Temptime/Zebra
https://bit.ly/2H1Tsh3
running time 01:24 min (2019)

VVM is the heart of a vaccine. With its color change, VVM signals to the health worker that vaccine is alive. Like a heart, it beats all the time. (Video produced on the occasion of the World Immunization Week 2019)

One life at a time
by PATH
https://bit.ly/2PJjB6Y
running time 03:13 min (2008)

This video vignette describes how the vaccine vial monitor reassures health workers that vaccine is safe and effective—or alerts them that vaccine has been damaged by heat on the long journey from a European manufacturing plant to a remote village in Kenya. Nurse Gladys Wambu remembers the days before the sticker was available and speaks to its impact.

Getting from innovation to implementation

by Global Health
https://bit.ly/2ZXKUPW
running time 1:18:19 hrs (2017)

Breakthrough and lifesaving innovations in global health like new vaccines or treatments for widespread diseases are exciting. But after the innovation is unleashed, often the hardest part remains: how to get these life-saving products and insights into adoption in places with the greatest need. Although VVMs are not mentioned in the discussions, it is worth listening to global health leaders how they are attacking these problems creatively.

Evan McGregor cold chain mission (CTC)

by GATES notes
https://bit.ly/1PR6oU9
running time 02:40 hrs (2013)

Vaccines spoil if they're not kept cold, which makes it harder to deliver them to very remote places. Watch Ewan McGregor, a UNICEF ambassador, learn about the ingenious solutions to this challenge.

Credits

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About the author

Ümit Kartoğlu is a medical doctor and has a doctorate degree in public health. He is co-founder and CEO of Extensio et Progressio SARL. Ümit began his career in Turkey, where he served at all levels of the national health system for over 10 years. He joined UNICEF in 1994 and proceeded to serve at the Headquarters of the World Health Organization WHO from 2001 to 2018.

Ümit brought to life the WHO-UNICEF Effective Vaccine Store Management initiative; the Global Training Network for Vaccine Management; the Performance, Quality and Safety (PQS) initiative, and the Global Learning Opportunities (GLO) network.

Ümit has developed a variety of courses, tools, and games for learning. He is the recipient of ten international awards in the field of research and communication, including the 2010 IQPC Cool Chain Excellence Award and the 2011 and 2013 Ludwig Rajchman Public Health Award. Ümit was named as one of the "Temperature Controlled Logistics Leaders for 2012" by the IQPC Temperature Control Logistics & Quality Network, an international industry peer group recog-

nizing 15 of the most influential and inspiring thought leaders in the global pharmaceutical supply chain.

He received the 2015 Golden Award in the e-Learning category of the Hermes Creative Awards for e-Pharmaceutical Cold Chain Management course and was honored to accept the 2016 Platinum Award in the e-Book category of the Marcom Awards for his book "Pharmaceutical and Vaccine Quality Illustrated". Another of his books - "Quality Risk Management Mental Modelling: Examples of exposure in everyday life" - received the 2018 Golden Award in the e-Book category of the Hermes Creative Awards. His most recent work, "Go Authentic: Activities that support learning", was published in 2018, and received the 2019 Platinum Award in the e-Book category of the Hermes Creative Awards.


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