Case Studies for *Global Health*

Building relationships. Sharing knowledge.

Alliance for Case Studies for Global Health

AUTM
Association of University Technology Managers®
Advancing Discoveries for a Better World

BILL & MELINDA GATES *foundation*

Global Health Progress

iavi

TDR

www.casestudiesforglobalhealth.org

Vaccine Vial Monitors: Small Labels With an Immense Impact

Lessons Learned:

- *Be thoughtful about making or demanding technical or manufacturing changes to a product to avoid making it impossible for the supplier to provide.*
- *Widespread support of an initiative like vaccine vial monitors can facilitate changes in global policy that allow more flexibility in the way that vaccines are used, resulting in further cost savings.*
- *A cost increase, even though minimal, can become a large obstacle to ensuring supply as procurers are often extremely price sensitive.*

Lab workers in the Bandung Bio Farma facility in Indonesia examine vials that have vaccine vial monitor technology incorporated into their labels.

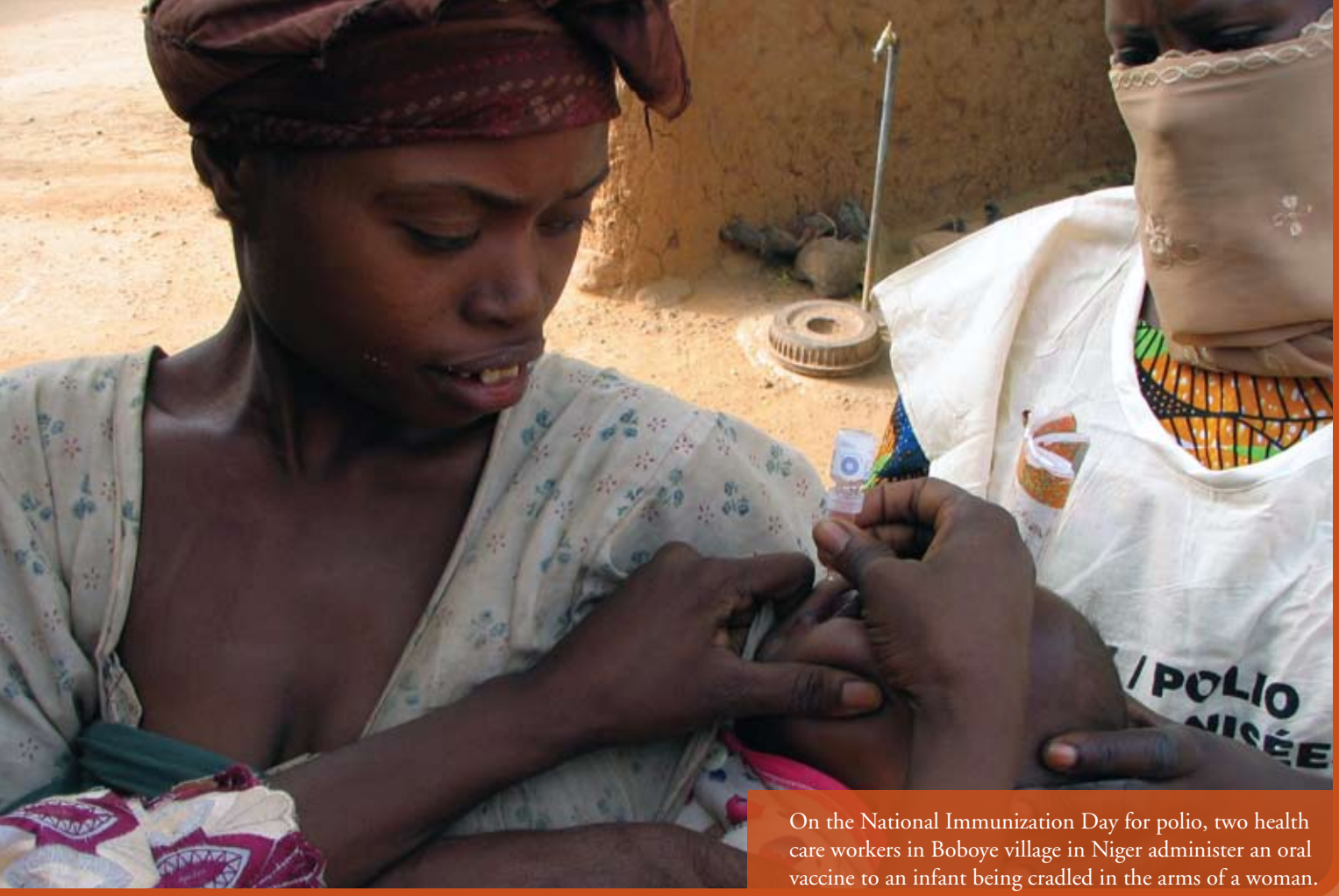
Photo by Umit Kartoglu

Vaccines can be rendered useless by just a few degrees difference in temperature or by temperature changes over a prolonged amount of time, thus, making transporting these delicate solutions difficult. "All vaccines are sensitive to heat and some to freezing," explains Umit Kartoglu, technical officer and scientist at the World Health Organization.

"The vaccines leave the production site in temperature-controlled trucks, 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," explains Kartoglu. "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 of damage."

In the past, there was no way for health care providers in these tiny, rural villages to determine if the vials were unspoiled. Do they risk using costly but now worthless vaccines on patients and leave them vulnerable to the disease in the end? Or, do they toss expensive and perfectly good vaccine as a safeguard any time there is doubt of the vaccine's viability? Neither alternative is acceptable where disease might advance quickly and resources to prevent or treat the illness are far too few.

A tiny sticker is now available that can warn health care providers if the vaccine has been exposed to heat and, therefore, spoiled. The label is small enough to fit on the vial label, the top of the vial



On the National Immunization Day for polio, two health care workers in Boboye village in Niger administer an oral vaccine to an infant being cradled in the arms of a woman.

Photo by Umit Kartoglu

cap or on the neck of the ampoule. A simple color change on this sticker indicates the viability of the vial's content with respect to heat exposure.

"Although developed as a heat-exposure indicator, vaccine vial monitors, often referred to as VVMs, also contribute significantly to the reduction of vaccine freezing," says Kartoglu. "VVMs allow health workers to see the heat stability of vaccines and accept the fact that freezing is a greater danger than mild heat exposure."

VVMs are a simple but effective system adapted from a similar labeling scheme used to guard refrigerated food during transport. The adaptation was an uncomplicated idea but a difficult reality. To date, only a single provider, Temptime, has perfected the technology to work on vaccines.

The tribulations did not end once the technology was mastered, however. It took more than two decades to turn this idea into a common practice in developing countries where adding even a penny's worth of difference to the price of vaccines was a burden they hesitated to bear. The price of the vial monitors was small, but still it was a price increase and, thus, a burden to overcome.

If it were not for the prolonged and consistent push by organizations like the World Health Organization (WHO), PATH, the United States Agency for International Development (USAID), the Global Alliance for Vaccines and Immunization (GAVI), United Nations Children's Fund (UNICEF), and the Centers for Disease Control and Prevention among others, the tiny label would have become stuck to a pricing hurdle. By adding the simple procurement specification requiring the VVMs, low-resource countries, where vaccines are the most at risk, now benefit from its simple but urgent warning.

Today, most vaccine suppliers comply with the UNICEF labeling requirement even though some organizations, such as the Pan American Health Organization (PAHO) still do not require it. PATH estimates that VVMs will enable workers to effectively manage vaccine supplies and replace more than 230 million doses of inactive vaccine and deliver 1.4 billion more doses in remote settings. UNICEF and WHO have estimated that the use of VVMs could save the global health community $5 million per year if it's applied only to basic vaccines, and far upward of that figure if applied more broadly.

The Road to Certain Knowledge

Today's VVMs appear elementary in terms of design. A square of heat-sensitive material rests in the center of the circle-shaped label; it changes color after heat exposure. If the square becomes the same color as the outer circle, then the vaccine must be discarded because it is no longer effective. If the inner square is darker than the outer circle, the vaccine is long past the discard point. The color change is a continuous process and, thus, continues to indicate how quickly the vaccine should be used or even if it should be used at all. The combined effects of time and temperature cause the inner square of the vaccine vial monitor to darken gradually and irreversibly.

The simplicity of the label belies the difficulty in its development. The adaptation from existing cold chain (or temperature-controlled supply chain) labeling technologies used for refrigerated foods proved far more challenging than anticipated. Even Temptime, the sole producer of VVMs for vaccines today, abandoned earlier developmental attempts. PATH interceded and made a compelling humanitarian case for the product, and Temptime renewed its efforts until the product eventually was developed. To date, no other producer has been able to achieve the same success, although several are still trying.

PATH first tried to develop the technology on its own. The initial concept for a heat exposure indicator for vaccine vial use is attributable by all accounts to WHO officials in 1979. PATH responded by developing first generation prototypes for measles vaccine using a chemical licensed from Allied Corp. While this approach worked well with measles vaccine, it soon became apparent that it had limitations as the chemical was not responsive enough to work with the more heat-sensitive oral polio vaccine. The early work was funded by non-USAID sources, but USAID — through the HealthTech program — eventually became the most important financial supporter of VVM development and advancement. In the early 1990s, PATH/HealthTech worked with the Temptime Corp., then known as Lifelines Technology, to successfully modify its proprietary heat indicator technology for use with all vaccines of varying heat sensitivities. The resulting products became generically known as vaccine vial monitors. The Temptime brand is HEATmarker™, and it became commercially available in 1996.

Design field trials were conducted from 1990 to 1992 in Bangladesh, Bolivia, Cameroon, Indonesia, Kenya, Sierra Leone, Thailand and the United States. An additional detailed study on the impact of VVMs on measles vaccine discard rates due to heat exposure was conducted in Zimbabwe with the aid of the Ministry of Health. At the same time, WHO and PATH representatives met with eight U.N. vaccine suppliers to explore the feasibility of integrating the labels with their products. Prototypes were then sent to vaccine suppliers for integration feedback. In 1993, Lifelines, now Temptime, developed the means to print VVMs directly onto vial labels, reducing manufacturer resistance to purchasing additional labeling equipment for a separate VVM label. PATH has assisted vaccine producers with VVM implementation throughout the program.

High on the list of acceptance problems early on was the fact that VVM is a paradigm-shifting technology available only from a single supplier, Temptime. The UNICEF Supply Division was not comfortable with the single-source issue, the subsequent deviation from procurement of commodity products and the added burden that the requirement placed on relationships with suppliers. PATH and WHO have continuously sought to develop other suppliers to address this issue. Technical assistance was provided to Albert Browne (U.K.), 3M (U.S.), Rexam/Bowater (U.K.), CCL Label (U.S.), and Sensitech (U.S.) but none have been successful in developing a price-competitive product that reaches performance requirements established by the U.N. agencies. PATH also assisted Temptime with obtaining low-cost loans to ensure production levels could meet global need.

Lab worker in the Bio Farma facility in Bandung, Indonesia, monitors the application of labels with incorporated vaccine vial monitor technology.

Photo by Umit Kartoglu

Two vaccination campaign workers give an injection to an indigenous inhabitant of a rural area in Peru.

Photo by Carib Nelson, provided by PATH

The principal patents owned by Temptime have expired, but since Temptime is able to meet global need easily enough and retains extensive knowledge and experience in manufacturing the VVMs. Technology transfer to other companies is not currently being pursued.

Strong support from several prominent agencies was necessary to continue to move the availability of VVMs forward. WHO was on board from the start. WHO staff members brought the need for this type of technology to PATH's attention, and PATH responded by identifying and testing appropriate solutions. PATH and WHO worked collaboratively on every aspect of VVM development and advancement.

UNICEF was kept apprised of the technology by WHO throughout the development process. Once the VVM technology was appropriately validated, WHO and UNICEF published a joint policy statement encouraging the inclusion of VVMs on vaccines. Eventually this policy translated into incorporation of VVMs into vaccine specifications for vaccines purchased by UNICEF.

WHO and the United Nations issued a joint statement in 1999 recommending VVM use on all vaccines, and the labels have since become a standard feature of all vaccines purchased through U.N. agencies. GAVI endorsement was a natural next step and was a straightforward process given the previous endorsement by WHO and UNICEF. In 2002, the GAVI board also stipulated that, from the beginning of 2004, all vaccines purchased through the vaccine fund must include VVMs. In the intervening years, PATH worked with Temptime, WHO and other collaborators to test, evaluate and advance the product.

A new advantage to using VVMs is beginning to surface. "VVM shapes the future of cold chain today, a future in which dependency on the cold chain is removed," says Kartoglu. "Today, VVM is seen as a catalyst for much-needed changes in strategies of vaccine distribution via the cold chain. VVM allows immunization programs 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."

The Struggle for Consistent VVM Use

Even with the advances in VVM technology and the spread of advantages the technology seems to present, consistent use of the product has been difficult to ensure.

While VVMs are increasingly supplied on vaccines purchased for the international market through UNICEF, they are not yet available on many of the vaccines produced in developing countries for domestic markets, the exceptions being India, Indonesia and Pakistan.

Vaccine procurement for developing and emerging countries is becoming increasingly decentralized, meaning that a variety of purchasers must include VVMs in their tender specifications to ensure consistent availability to immunization programs. In 2007, WHO and UNICEF released a policy statement encouraging member states, donors and nongovernmental organizations procuring vaccines to include VVMs in their specifications. Continued work to strengthen procurement at the country level, e.g., through interagency coordinating committees, will be necessary to ensure vaccine quality and availability of vaccines with VVMs.

Although PAHO supported a number of field trials with early VVM prototypes, it has never required VVMs on products purchased through the PAHO revolving fund, citing lack of cold chain difficulties in its region and unwillingness of consumers or purchasers to pay the slight price increases for products with VVMs. Vaccine suppliers complained that they had to supply vaccine with VVMs for UNICEF and without for PAHO, but eventually most complied with the UNICEF requirement.

One repeated difficulty has been the inability of the UNICEF supply system to consistently send the same brands of vaccines to countries or to notify WHO with regard to which countries would receive vaccines with VVMs. WHO was, therefore, unable to target early training efforts to countries that would definitely receive the VVMs. For many years, countries received supplies of vaccines both with and without VVMs and, therefore, could not rely on VVM use as a routine management tool. This situation is improving as more vaccine suppliers have integrated VVMs into their products.

Immense Impact

Despite these 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.

By Pam Baker

Immunization session in Uganda
Photo provided by PATH