
CHAPTER 7

VACCINE VIAL MONITORS:

Access to Devices



THE COLD CHAIN SYSTEM, DEVELOPED IN THE 1970S BY THE WHO EXPANDED PROGRAMME ON IMMUNIZATION (EPI), is an international protocol dictating procedures for maintaining the recommended conditions for storing and transporting vaccines from manufacture to use. These conditions include near-constant refrigeration that is often costly and cumbersome.¹ In climates where extreme heat occurs, the cold chain is considered “fragile.” If health workers suspect either heat damage or extended storage in a nonrefrigerated container, the cold chain protocol requires the disposal of entire batches of vaccines to ensure damaged vaccines are not administered to children.² Though these safeguarding rules have been effective in ensuring that immunization programs administer only vaccines not exposed to heat, the inability to confirm vaccine damage often leads to vaccine wastage. Vaccine wastage is costly for cash-strapped ministries of health in developing countries and can result in fewer vaccinated children. Furthermore, maintaining the recommended conditions for storing and transporting vaccines is often difficult for health workers in poor countries, especially in remote areas. As a result, multiple problems in following the cold chain protocol reduce access to vaccines that prevent debilitating diseases in children.

The vaccine vial monitor (VVM) is a miniaturized time-temperature technology that can help health workers reduce vaccine wastage and assure coverage in hard-to-reach areas. This technology adds value to an existing technology (vaccines) in order to address a specific barrier to access (vaccine availability in areas where the cold chain is fragile). A VVM is a low cost indicator (ranging from US\$0.0328–0.055) that is printed onto the label of a vaccine vial, attached to the vaccine vial cap, or affixed on the ampoule neck. The indicator changes color when the vial has been exposed to warm temperature over an extended period of time. The technology allows health workers to assess vaccine heat damage from production through delivery, greatly improving the reliability of the cold chain system. The VVM does not measure the actual potency of the vaccine inside the vial but instead indicates if unacceptable heat exposure has occurred and probably damaged the vaccine in that specific vial.

This case study examines the story of creating access for vaccine vial monitors. It begins with calls in 1979 to create a new kind of technology for monitoring temperature exposure of individual vaccine vials, then follows the phases of product development, introduction on the oral polio vaccine (beginning in 1996) and scaling up for other vaccines (beginning in 2001). The case shows how VVMs contributed to decreased vaccine wastage and improved health workers’ ability to vaccinate hard-to-reach populations based on changes in the cold chain protocol.

In detailing the technology's flow from product development to use by health workers in poor countries, the narrative highlights the challenges encountered and strategies used to address barriers to access. In this instance, access depended crucially on assuring the availability of high-quality VVMs designed for different kinds of vaccines and the adoption and use of VVMs by global vaccine producers. The success achieved in creating access for VVMs relied on the efforts of product champions within the immunization program of the World Health Organization and the non-governmental organization Program for Appropriate Technology in Health (PATH) in Seattle. Even here, however, the VVM success has occurred for UNICEF-supplied vaccines but not for two other important vaccine markets for developing countries (vaccines provided by PAHO and those sold by developing country domestic manufacturers). Challenges to full VVM access thus persist, as we explain below.

Discovery and Testing of Vaccine Vial Monitors (Phase 1)

Staff at WHO's Expanded Programme on Immunization (EPI) first began thinking about a heat exposure indicator for individual vaccine vials in 1979 after recognizing the success of using heat exposure indicators on cartons of vaccines during shipping.³ EPI staff proposed the idea of creating similar temperature monitors for use at lower levels of the cold chain—a new technology for each vaccine vial that would extend monitoring to delivery levels where temperature control was most fragile.⁴ WHO thus became an early advocate of VVMs by articulating the need for a new technology.

PATH responded quickly to WHO's call for creating a vaccine vial monitor product. The organization began seeking a potential technology and identified the diacetylene indicator technology that was under development at Allied Chemical Corporation. (Allied Chemical Corporation was established in 1920 as an amalgamation of five American chemical companies. In 1985 the company became AlliedSignal and today is part of Honeywell International, Inc., in Morristown, New Jersey.) Ray Baughman, a materials scientist within Allied, conceived the idea of using color changes associated with diacetylene polymerization for time-temperature indicators and made advanced indicator prototypes with his team.⁵ Their initial focus was on a PTS (p-toluene sulfonate) diacetylene. Baughman headed the Color Responsive Materials Group within Allied, and he and his colleagues began visiting pharmaceutical and other companies to discuss potential applications of time-temperature technology to blood, vaccines, and perishable foods.

The efforts of Baughman and his team to interest companies in the technology were initially unsuccessful. PATH, however, learned of their work and sent two representatives—PATH president Gordon Perkin and Patrick Tam—to Allied to discuss the technology's possible application to vaccine vials. As a result of these discussions, Allied granted PATH a license to use the PTS chemical. In 1979, the same year as WHO's call for a new technology, PATH began developing first generation prototypes of a VVM for the measles vaccine. To do this, PATH used funding from various sources, including Alberta AID, the Edna McConnell Clark Foundation, the International Development Research Centre of Canada, and Oxfam.⁶

Between 1982 and 1985, PATH, WHO, and ministries of health conducted field tests to validate PATH's VVM prototypes in 10 countries (Argentina, Brazil, Egypt, Kenya, Nepal, Pakistan, Peru, the Philippines, Yemen, and Zimbabwe). Introductory field trials followed between 1987 and 1990 in five countries (Indonesia, Kenya, Sierra Leone, Thailand, and Zambia).⁷ The validation and introductory field trials highlighted three problems with the prototypes based on PTS diacetylene technology: (1) the reaction rate was too slow for use with the least heat stable vaccines such as the oral polio vaccine (OPV); (2) the indicator created problems of dermal toxicity for some workers; and (3) the label with temperature indicator had some printing difficulties.⁸ The slow reaction rate was particularly significant because during this period WHO decided that the new technology should be introduced first on OPV. The growing momentum of the polio eradication campaign provided a good opportunity to demonstrate the product's value since OPV is the most heat-sensitive vaccine.⁹

PATH used a subproject in its USAID-funded Technologies for Health (HealthTech) program to begin looking for a more suitable technology than PTS for the extremely heat-sensitive OPV. In 1988, while introductory field trials for PTS prototypes for the measles vaccine were ongoing, PATH staff identified a new technology owned by New Jersey-based Temptime Corporation (previously LifeLines Technology, Inc.) also based on diacetylenes. The Temptime researchers working on this new technology were actually the same people who previously developed the PTS technology at Allied. Temptime was a new company, formed in 1987 by staff from Allied Chemical Corporation after management at Allied decided that the diacetylene technology was not commercially significant for the company. Staff within Allied's Color Responsive Materials Group then decided to spin off and form a new company. Staff members at Temptime shifted their work from the PTS technology to devices based on alternative diacetylenes.¹⁰ While the

PTS chemical in the first product changed color abruptly when a critical accumulated time-temperature exposure was exceeded, the color changes of the diacetylenes used in the new Temptime technology were more continuous. The new technology, therefore, could be applied to all vaccines. Furthermore, the new diacetylenes were easier to manufacture and print and also addressed the dermal toxicity issue.¹¹ This new technology became the basis for Temptime's broader business of time-temperature indicators for food and other applications.




With Temptime's identification of this second technology, PATH took on a new role in VVM development. Instead of seeking to develop its own prototypes, PATH began working with Temptime in 1989 to modify the company's core technology for use with all vaccines in developing country immunization programs. After months of failing to achieve technical success with the VVM, Temptime informed PATH that the company had decided to give up on the program. According to Ted Prusik, senior vice president of Temptime, PATH representatives visited the company, explained the global significance of the VVM, and persuaded Temptime to continue its work, even without additional funding.¹²

Shortly thereafter, Temptime succeeded in developing a VVM technology that worked well and called it HEATmarker. (In the rest of this chapter, any reference to the VVM is specifically to the HEATmarker product unless otherwise stated.) PATH began field trials of HEATmarker in 1990 in eight countries (Bangladesh, Bolivia, Cameroon, Indonesia, Kenya, Sierra Leone, Thailand, and the United States). The HEATmarker product consists of a circle with an inner square made of heat sensitive material that is light colored at the starting point and becomes darker with thermal exposure. The combined effects of temperature and time cause the inner square to gradually and irreversibly grow dark. (Table 7.1 shows the start and end points of the Temptime VVM.)

The end point is reached when the inner square is the same color as the outer circle. The inner square continues to darken with heat exposure until it is much darker than the outer circle. Whenever the inner square matches or is darker than the outer circle, the individual vaccine vial should be discarded. The technology only monitors heat exposure and does not indicate whether a vaccine has been exposed to freezing.¹³

It took 12 years of product development (1979–1991) before a suitable vaccine vial monitor was ready for introduction. PATH used funding from USAID and other sources to explore potential core technologies and work with Temptime to achieve success in product development. Having conceived of the initial idea for the technology, WHO staff collaborated throughout product development by

Table 7.1 | VVM start and end points

Start point		Square lighter than circle (Use vaccine vial if expiry date not reached)
End point		Square matches the circle (Discard vaccine vial)
End point exceeded		Square darker than the circle (Discard vaccine vial)

Note. From *PQS Performance Specification for Vaccine Vial Monitors* by World Health Organization, 2006, Geneva: Author. Adapted with permission.

providing product specifications to potential VVM manufacturers, including Temptime. With product development nearing completion, WHO, PATH, and Temptime confronted the next challenge—introducing the new product so that it would be used and achieve its objectives.

Introducing VVMs on the Oral Polio Vaccine (Phase 2)

During the final stages of product testing in laboratory and field studies, PATH and WHO staff members began formulating plans to introduce VVMs on the oral polio vaccine (OPV). They focused initially on gaining product adoption by the UNICEF Supply Division and WHO-prequalified OPV producers. Responsible for UNICEF’s global procurement operation, the Supply Division purchases all vaccines for the global campaign to eradicate polio (as well as purchasing vaccines for other global campaigns, UNICEF-supported programs, and the GAVI Alliance). In 1990, WHO and PATH staff met with OPV producers to present the VVM and persuade the producers to add the new technology to their product labels.¹⁴ (The eight vaccine producers in the 1990 meeting were Connaught Laboratories, Conpharma Vaccines, Evans Biologicals, Interexport, Pasteur Merieux, Sclavo, SmithKline Beecham, and Swiss Serum.) Vaccine producers then received HEATmarker prototypes for evaluation. The following year, WHO, 10 vaccine producers, and the Pan American Health Organization (PAHO) participated in a further appraisal of “live” HEATmarker VVMs. (The ten producers included the same eight as before, minus Conpharma Vaccines, plus Human Institute, Institute of Immunology, and MAIMEX.)

A number of other actions helped promote VVMs around this time. In 1990, UNICEF organized a Technology Introduction Panel in New York to discuss VVM technology for OPV. A year later, during a second meeting at UNICEF, WHO staff asked UNICEF representatives to include VVMs for OPV in the

global tender (an invitation to submit a competitive bid) for the 1992–1994 vaccine supply. UNICEF responded by including a clause in the tender announcement requesting producers to add VVMs to their OPV labels. UNICEF went a step further in the next tender announcement in 1993 for the vaccines to be supplied in 1994–1995 and requested that bids for measles vaccine and OPV include VVMs on the labels. Despite UNICEF’s efforts, however, only a few vaccine producers responded with bids that included VVM labeling.¹⁵

Vaccine producers resisted VVMs for two reasons. First, they were concerned that no one had independently validated the HEATmarker VVM. To address this concern, WHO hired the Maryland-based firm of Strasburger and Siegel, Inc., Food Testing Laboratories to conduct an independent evaluation of the Temp-time product. This laboratory evaluation was completed in 1992.

Second, OPV producers did not want to purchase new labeling equipment to print the VVMs. To solve this issue, PATH provided a loan to Temp-time in 1993 for the purchase of special labeling equipment. The new equipment allowed Temp-time to print VVMs directly on vaccine producers’ vial labels. This technical innovation allowed producers to use a single label printed with both the VVM and the vaccine’s traditional label information, rather than incur additional costs from two separate labeling processes. Debra Kristensen, senior technical officer of PATH, pointed out that Temp-time’s willingness to go “the extra mile” in resolving producers’ labeling concerns was key to securing acceptance by OPV producers.¹⁶

In 1994, WHO, UNICEF, and the OPV producers met and decided that following pilot introduction in Tanzania and Vietnam starting in April 1995, all OPV would include VVMs as of January 1996. WHO released official specifications for VVMs for OPV in 1995 that stipulated the purpose, design, and use of VVMs. One year later, all five OPV suppliers to UNICEF (SmithKline Beecham, Biocine, Pasteur Merieux Connaught, Chiron Behring, and PT Bio Farma) provided OPV with VVM labels.

Once VVMs appeared on OPV in immunization programs, research focused on health worker acceptance and experience with the technology and on assuring the technology’s impacts in the field. WHO conducted four impact studies in conjunction with ministries of health during national immunization days in Kenya, Nepal, Tanzania, and Turkey (completed in 1997). An additional impact study was conducted in the Kingdom of Bhutan (1998). In Turkey, the study compared wastage due to heat exposure in a first-round National Immunization Day without VVMs (the baseline), with that in a second round after VVM implementation. Wastage due to heat exposure declined a remarkable

77%.¹⁷ In addition, EPI managers in the study reported that most staff found VVMs easy to recognize and interpret, though systematic data on perceptions and practices were not collected.¹⁸ In the Bhutan study, a Knowledge, Attitudes, Practices Survey found that health workers understood the purpose of VVMs and correctly interpreted the new technology.¹⁹ Finally, a study of vaccine wastage during a polio campaign in India found that VVMs played an important role in health workers' decisions to discard vials exposed to heat.²⁰

Overall, the process of making VVMs available on OPV required six years, from the moment WHO and PATH began their introduction strategy (1990) to compliance by all OPV suppliers to UNICEF (1996). As PATH's Debra Kristensen stated, "At the time, we felt that it had taken a long time to introduce VVMs on OPV. But we had no idea how much longer it would take when we enlarged the program to all EPI vaccines."²¹

Scaling Up Vaccine Vial Monitors on EPI Vaccines (Phase 3)

In 1998, WHO officials and researchers presented the VVM impact studies for OPV at the WHO Technical Network for Logistics in Health (TechNet) meeting held in Copenhagen. TechNet is a WHO initiative that links experts and organizations working in logistics for health, mostly in the area of national immunization programs and primary health service delivery in developing countries. The Bhutan impact study generated particular interest because in addition to the Knowledge, Attitudes, Practices Survey, it assessed whether VVMs on OPV vials could be used to monitor heat exposure to other vaccines transported with OPV. The authors recommended against this practice given the strong probability that other vaccines could be exposed to temperature conditions different from OPV even when transported together.²² In response to this conclusion from the Bhutan study and evidence of reduced vaccine wastage from several studies, TechNet formally recommended that all vaccines use VVMs on individual vials as soon as possible.

Implementing VVMs on all EPI vaccines required Temptime to modify its temperature indicators for different categories of vaccines. This scaling up to other vaccines also required processes of policy development by WHO and the UNICEF Supply Division, as well as product adoption by a larger group of vaccine producers. PATH continued to lead the advocacy efforts for VVMs during this scaling-up period, providing assistance to WHO and Temptime. PATH financed these activities with funds from its HealthTech project (funded by USAID) and other sources such as the U.S. Centers for Disease Control and Prevention (which jointly funded scaling up VVMs on the measles vaccine along with HealthTech).

Product Modification

WHO staff specified the need for four categories of VVMs because of the different temperature and time sensitivities of EPI vaccines:

1. VVM2 for the least stable vaccines (2 days to end point at +37°C)
2. VVM7 for moderate stability vaccines (7 days to end point at +37°C)
3. VVM14 for medium stability vaccines (14 days to end point at +37°C)
4. VVM30 for high stability vaccines (30 days to end point at +37°C).

In 1998, WHO sent a letter to all WHO prequalified vaccine producers requesting their reaction to the proposed new VVM specifications. At the same time, Temptime modified its VVM product to meet the requirements of these four categories of stability. Independent third parties, mostly under WHO contract, then conducted conformity tests of the new HEATmarker types.²³ These product modifications represented an essential step in expanding adoption of VVMs to other vaccine producers.

Global Adoption and Policy Development

Global adoption of VVMs in the scaling-up phase depended on specific actions by WHO and the UNICEF Supply Division. WHO assumed responsibility for deciding on VVM specifications and assigning each WHO prequalified vaccine to one of the four VVM categories (VVM2, VVM7, VVM14, or VVM30). The UNICEF Supply Division included VVMs in its tender specifications and discussed VVMs with vaccine producers.

The UNICEF Supply Division expressed two major concerns about availability in scaling up VVMs to all EPI vaccines. First, Temptime was the sole supplier of VVMs with no competitors. UNICEF's policy is to avoid working with sole suppliers (unless no other option exists) because if the monopoly company encounters problems with its supply, then UNICEF has no other sources of product.²⁴ Both PATH and WHO had encouraged other companies to develop competitive VVM products, including Albert Brown, Ltd. (U.K.), 3M (U.S.), Rexam/Bowater (U.K.), CCL Label (U.S.), and Sensitech (U.S.). WHO and UNICEF invited all potential suppliers to meetings about VVMs, and PATH provided start-up funding through its USAID HealthTech project to potential VVM suppliers.²⁵ None of the companies, however, succeeded in developing a product that met the performance requirements of WHO and UNICEF and that could compete with the price of Temptime's HEATmarker VVM.²⁶ Their inability to develop competitive products may be related to these firms' choice of different core technologies as well as Temptime's comparatively low overhead.²⁷

UNICEF's second concern about availability related to the global vaccine market, which at that time had a limited number of producers. The main goal of UNICEF's Supply Division is to procure sufficient vaccines for developing country immunization programs. In this context of limited vaccine supply, UNICEF needed to purchase all vaccines produced, regardless of whether they included VVMs.

These two leading international agencies wielded enormous market power by setting global norms (WHO) and procuring global vaccines (UNICEF). Despite their concerns about the availability of VVMs and the availability of vaccines, WHO and UNICEF issued a joint policy statement in 1999 advocating the use of VVMs on all vaccines. The statement read, "All agencies purchasing vaccines should request manufacturers to supply all vaccines with VVMs that meet WHO specifications."²⁸ In UNICEF's invitation to bid for the 2001–2003 global tender for vaccines, UNICEF included VVMs among the minimum requirements for vaccines to be procured by UNICEF. That same year, the Global Alliance for Vaccines and Immunization (GAVI) included VVMs among the minimum requirements for vaccines in its first Request for Proposals for underused vaccines, related products, and contributions. The inclusion of VVMs in these official policy statements and tender announcements gave great impetus to the global adoption of this technology.

Vaccine Producer Adoption

Yet vaccine producers still lagged in adopting VVMs. Following the WHO and UNICEF announcements in 1999, only three vaccine suppliers to UNICEF fully met the terms to include VVMs on vaccine labels (Japan BCG, Pasteur Dakar, and Chiron). In response, UNICEF asked vaccine producers to explain why they had not incorporated VVMs into their labels. WHO reviewed the replies, provided UNICEF with an assessment of each technical concern, and revised the VVM specifications and test procedures.²⁹ Despite these efforts, only two more prequalified producers (Bio Farma and LG Chemical Inv., Ltd.) fully complied with the VVM requirement for EPI vaccines (apart from OPV). Eighteen WHO-prequalified vaccine producers (supplying yellow fever, measles, measles-rubella, measles-mumps-rubella, hepatitis B, tetanus toxoid with Uniject, and Bacillus Calmette-Guérin vaccines) did not comply, with some asking for additional time to make adjustments.³⁰

WHO staff next sent a letter to all prequalified vaccine producers requesting feedback on the revised VVM specifications and test procedures. They compiled a list of all the issues and prepared a question-and-answer document to address

the concerns one by one.³¹ The 20 issues covered five categories: validation, logistics, regulatory, program, and commercial (see Table 7.2). In March 2002, WHO hosted a technical review of VVM implementation in Geneva to discuss the issues and included representatives from PATH, the UNICEF Supply Division, vaccine producers, Temptime, and other potential VVM suppliers.

Vaccine producers expressed disquiet about three issues in particular. First, like UNICEF, vaccine producers were uneasy having Temptime as the sole supplier of VVMs. To address this problem, UNICEF agreed to specify in contracts with vaccine producers that if Temptime could not provide the needed VVMs, the vaccine producers would not be liable for the absence of the technology on their vaccine labels.³²

Second, vaccine producers questioned the need to introduce a different labeling system for VVMs into their existing vaccine production. As discussed above, Temptime and PATH had worked together to improve the labeling system so that one label, instead of two, could be used on the oral polio vaccine product. VVMs for OPV and other liquid vaccines can be placed on custom labels. But for freeze-dried vaccines such as measles and yellow fever, labeling with VVMs is more complex because the product must be removed during the reconstitution process. VVMs for freeze-dried vaccines in *vials* are placed on the top of the vial. VVMs for freeze-dried vaccines in *ampoules* are placed on the ampoule's neck. At the time of the March meeting, two companies who were early VVM adopters had already developed new methods for the labeling process for freeze-dried vaccines: Japan BCG for ampoule neck labeling and Chiron for top labeling on vials.³³ At the WHO meeting, Temptime agreed to work with each producer to identify the best solutions for their particular label applications and to seek solutions that would have minimal investment and production costs for the producers.³⁴

VVMs subsequently became available in both full label and dot formats. The full label format is for liquid vaccines and is specific to each vaccine producer. Temptime prints the VVMs onto the vaccine producer's labels and sends the labels (with VVM) to the vaccine producer. The full label format therefore does not require an additional investment in VVM application by the vaccine producer.³⁵ The dot format, designed for all freeze-dried vaccines, requires additional equipment by the producer to apply the dot to the existing vaccine label.³⁶ Temptime agreed to work with each company to tailor the VVM product to each firm's particular labeling system.³⁷

The vaccine producers' third main concern focused on issues of legal and financial responsibility. Who would be responsible when a vial or shipment is

Table 7.2 | Questions and concerns raised by vaccine producers

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.

Logistics issues

7. Concerns exist about introducing a different labeling system for a portion of production.
8. How can suppliers maintain the logistics of import and inventory control?
9. There are different multilingual, multiproduction, and multipacked quantities.
10. Additional capital expenditures are incurred to implement VVMs.
11. Does the current GMP requirement prohibit preprinted labels or require an on-line printer with a blank roll?

Regulatory issues

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

Program issues

15. What is the benefit of having a VVM on a vaccine that is very heat stable, such as hepatitis B?
16. 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

17. Temptime Corporation is the sole supplier of VVMs. There is no competitor.
18. Why doesn't the Temptime warranty mirror the minimum shelf life required of the vaccine suppliers (18 months from the date of shipment from the vaccine supplier)?
19. Why does Temptime have a +/- 10% tolerance on the quantity of VVMs delivered?
20. Why does a minimum VVM order quantity have to be set?

Note. From *Technical Review of Vaccine Vial Monitor Implementation* by World Health Organization, 2002, Geneva: Author. Adapted with permission.

rejected following a VVM indication of excessive heat exposure? WHO staff explained that the vaccine producer is responsible for the product and for its transportation to the country using a number of monitoring devices, of which the VVM is only one. Once accepted by the buyer, the responsibility shifts to the buyer. Since VVMs are subject to strict controls before use, it is unlikely that a faulty VVM lot would reach the field. Should this happen, two scenarios are possible: (1) the faulty VVM would reach the end point early, leading to vaccine disposal and perhaps wastage but no increased liability; or (2) the VVM would fail to reach the end point in time, with the potential risk of health workers using a vaccine exposed to heat.³⁸ This latter scenario is the only one in which a potential liability exists. However, WHO staff pointed out that in “six years of experience and over 10 billion doses corresponding to more than 500 million VVMs used, it has never been documented that a faulty VVM lot has led to the use of vaccines of unacceptable potency.”³⁹ The March meeting concluded that liability issues exist with or without the use of VVMs and that VVMs would not create additional liability; instead, VVMs should reduce producer liability because the technology helps health workers avoid administering heat-damaged vaccine to children.⁴⁰

Though not articulated at the March 2002 meeting, vaccine producers may have resisted VVMs because the firms had no incentive to use the technology. At the time of scaling up VVMs, many vaccines were in short supply. UNICEF sought to purchase the entire available supply, and firms knew that they could sell their vaccines even if they did not use VVMs. Later, more companies began supplying most EPI vaccines (though not all), giving UNICEF more choices and decreasing vaccine producers’ power in the market. These changing market dynamics may have contributed to greater compliance with VVM use by vaccine producers.

Gaining acceptance for the VVM technology by vaccine producers proved to be a major barrier in scaling up the technology to all EPI vaccines. Many vaccine producers who raised concerns about VVMs at the March 2002 meeting were already using the product on OPV. PATH and WHO employed a series of strategies to persuade EPI vaccine producers to adopt VVMs. The strategies included proving the technology’s effectiveness through impact studies, requiring its use in vaccine specifications and tenders, making adjustments to the technology and labeling procedures, and conducting a series of international meetings with vaccine producers to provide ample opportunity for open discussion of issues. WHO and PATH also made explicit efforts to analyze and address producers’ concerns,

in preparation for the March meeting. All these factors contributed to the turnaround by vaccine producers in agreeing to use VVMs on other vaccines.

The ultimate success in scaling up VVMs to EPI vaccines supplied through UNICEF thus resulted from a series of factors: the energies of PATH and WHO as product champions, the funding by USAID and other donors to PATH, policy development by WHO and the UNICEF Supply Division, the willingness by Temptime to continue making technological innovations to the product, and the changing vaccine market. These efforts by the product champions and the manufacturer paid off. In 2004, almost one third of the doses of non-OPV vaccines purchased and supplied by UNICEF suppliers had a VVM label. UNICEF estimated in 2004 that by the end of 2005, there would be 100% implementation of VVMs on seven of the twelve UNICEF-supplied vaccines.⁴¹ UNICEF also expected three other vaccines to be at or above 80% implementation, leaving only two with lower implementation rates. As of August 2005, these estimates were surpassed; only one UNICEF supplier, Sanofi Pasteur, was not using the VVM on non-OPV vaccines. (Sanofi Pasteur does use the VVM on its OPV product.)

Impact of Vaccine Vial Monitor Scale-Up

Success in scaling up VVMs on EPI vaccines provided through the UNICEF Supply Division has affected developing countries' immunization programs in two major ways. The first is that VVMs have decreased vaccine wastage and costs. As previously discussed, VVMs allow health workers to discard only those vaccines with a VVM reading showing excessive heat exposure. VVMs have also reduced vaccine wastage by helping health workers better manage the cold chain. As an indicator of cumulative heat exposure, the device allows health workers to assess which vaccines in their stocks have experienced some heat exposure but are still effective and should be used first.⁴² Ümit Kartoglu, project manager for VVMs at WHO, points out that learning to “incorporate the VVM into the whole management cycle is an art” and is harder than simply reading a VVM.⁴³ This aspect of VVM use, therefore, is the main focus of WHO's training of health workers.

Another way VVMs have decreased vaccine wastage is that they have assisted implementation of WHO's multidose vial policy of 1995 (revised in 2000). This policy allows health workers to use opened vials of some vaccines for more than one day (instead of discarding them).⁴⁴ The presence of VVMs on EPI vaccines allows health workers to decide if open vials should be used the next day if the VVM has not reached its end point.⁴⁵ The previous policy required health workers to discard all open vials at the end of the day's immunization session. This new

multidose vial policy has implications for vaccine wastage and costs. WHO estimates that the policy could reduce wastage rates by up to 30%, with annual vaccine cost savings of \$40 million worldwide.⁴⁶ A study carried out by PATH and the Kingdom of Bhutan, which assessed the impact of the multidose vial policy and VVMs on liquid vaccines, found wastage decreases of 48.8% for OPV, 27.1% for diphtheria-tetanus-pertussis, 55.5% for tetanus toxoid, and 23.8% for hepatitis B vaccine (PATH, 1999).

Health worker adoption of the VVM sometimes encountered obstacles when VVMs were introduced in tandem with the new multidose vial policy. In Turkey, for example, it was difficult to convince some health workers, who had received training on the old policy, not to discard OPV at the end of the day (so that remaining vaccine could be used the next day) if the VVM had not reached its end point.⁴⁷ These health workers felt that a VVM that had not darkened by the end of the day was “defective” because “it does not darken as fast as it should.”⁴⁸ The authors of the study in Turkey recommended that WHO clarify the reasons for the multidose vial policy and provide clear answers to questions raised by management and health staff to improve implementation by these workers in the field.

Analysts are currently studying whether VVMs can further reduce vaccine wastage by protecting against freezing of vaccines. Hepatitis B and tetanus toxoid vaccines (aluminum adjuvant-based vaccines) are heat stable but freeze sensitive, especially in the cold chain.⁴⁹ A baseline study in Indonesia found that 75% of hepatitis B vaccines were exposed to freezing temperatures.⁵⁰ Freezing problems decreased when the vaccine was transported and stored at ambient temperatures. In 2005 WHO staff drafted a policy paper proposing procedures to transport all vaccines without ice in order to prevent freezing of vaccines like hepatitis B and tetanus toxoid. The policy’s success will depend in part on how effectively VVMs can be used to ensure against heat damage for vaccines transported without ice.⁵¹

The second major impact of VVMs is that they have allowed a more flexible cold chain strategy so that health workers can take vaccines out of the cold chain for longer periods to travel to remote settings. In 2000, WHO developed a strategy for using VVMs in this way to achieve better coverage of hard-to-reach populations in polio eradication efforts.⁵² The success of this new strategy required health worker training on both VVMs and the new policy, but also depended on adoption by the parents of children to be immunized. Many mothers in developing countries know vaccine protocols well and expect vaccines to come directly from the refrigerator. Therefore, some mothers were wary when the OPV vials were transported at room temperature as a result of the new WHO policy.⁵³

In sum, the VVM has led to decreases in vaccine wastage (and reduced costs to governments) and has had a paradigm-shifting impact on the cold chain protocol (resulting in more immunized children in remote areas).⁵⁴ PATH estimates that over the 10-year period of 2005–2015, VVMs will allow health workers to recognize and replace more than 230 million doses of inactive vaccine and to deliver 1.4 billion more doses in remote areas.⁵⁵ The organization believes that using this technology could save more than 140,000 lives and lead to morbidity reductions for many others. In terms of cost savings, UNICEF and WHO estimate that the use of VVMs on basic vaccines can save the global health community US\$5 million per year (based on typical vaccine wastage rates).⁵⁶

Current Challenges

To fully realize the VVM's potential impacts on vaccine wastage, vaccine costs to governments, and vaccine coverage in areas with a fragile cold chain, the device needs to be scaled up on all vaccines used in immunization programs. The major limitation on these impacts has been low adoption of VVMs outside the UNICEF Supply Division. While VVM use is now close to 100% on EPI vaccines procured through UNICEF, the device is underused on vaccines financed by the PAHO Revolving Fund for Vaccine Procurement and on those purchased directly by developing-country government procurement agencies (and not procured through UNICEF). As Stephen Jarrett, deputy director of UNICEF's Supply Division, said, "The uptake of the device on other [non-UNICEF procured] vaccines has been slower than originally anticipated. . . . One of the reasons has been that UNICEF is the only committed buyer of vaccines with VVMs."⁵⁷

The PAHO Fund has never recommended the use of VVMs in its region (North and South America and the Caribbean). At the March 2002 meeting on VVM implementation, a PAHO representative stated that the agency had not adopted VVMs because initially the device was used only for OPV, and polio had already been eradicated in the Americas at the time of VVM introduction. He then explained that the subsequent delay in adopting VVMs had been due to PAHO's desire to introduce VVMs on all vaccines; now that these VVMs were more widely available, PAHO would revisit its decision.⁵⁸ As of November 2006, however, PAHO still had not recommended the use of VVMs to vaccine suppliers or purchasers. While PAHO did contribute to early VVM research, the agency did not support later trials in the region. As a result, there has been no opportunity to evaluate whether the technology would be cost-effective in the region or well received by health workers.⁵⁹ PAHO's resistance to VVMs adds a layer of complexity to the production processes of vaccine producers who

provide vaccines to both the UNICEF Supply Division and the PAHO Fund. These producers require two different types of labels to produce both VVM-labeled and nonlabeled vaccines.

Like the PAHO Fund, many developing-country government procurement agencies have not required VVM use. John Lloyd of PATH asserts that this has led to “a huge proportion of domestically supplied non-polio vaccines in vaccine-producing countries [that] are still being distributed without VVMs.”⁶⁰ Without a government requirement, vaccine producers have little incentive to use VVMs.⁶¹ For them, affordability remains an important problem. Though the VVM is low cost, these vaccine producers are understandably reluctant to pay the additional costs of VVMs in a competitive market where the technology is not requested by the purchaser for all producers, where other producers are not using VVMs, and where the government is not interested in paying the additional costs.

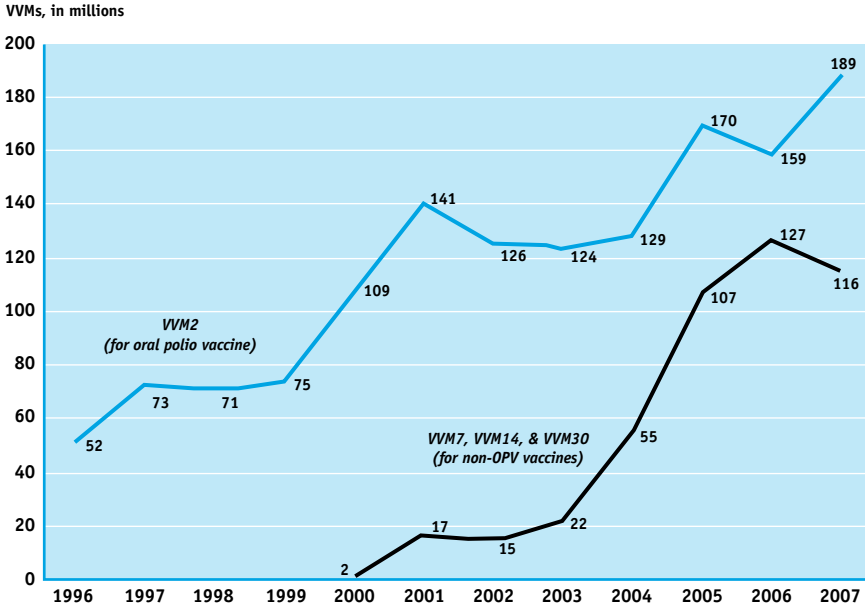
In 2007, WHO and UNICEF issued a joint statement requesting countries to include VVMs among the minimum requirements for vaccine purchasing agreements with all producers.⁶² The government procurement agencies in two countries, Indonesia and India, now require VVMs on all vaccines. WHO has had discussions with other government procurement agencies and national vaccine producers about using VVMs, but with limited success. While there is a potential cost savings to immunization programs that use VVMs (through decreased vaccine wastage), and the device can also help increase vaccine coverage in remote areas, most governments have been slow to require the product. Debra Kristensen of PATH explains that one model that has been successful in getting national producers to adopt VVMs is the use of an advocate/consultant with a mandate from the government and some funding.⁶³ In India, for example, the United Kingdom Department for International Development (DFID) gave money to the Indian government in the mid-1990s to scale up VVMs on all OPV in the country, including vaccines supplied by national manufacturers. DFID also provided financing and technical assistance to manufacturers for VVM implementation and paid for a one-time procurement of OPV from each of the manufacturers. This project succeeded because there was both sufficient funding and a concerted effort, led by an advocate, to include the government and all producers in the country. But PATH currently has no funding dedicated to support VVM adoption in developing countries. While PATH continues to provide technical assistance to WHO on VVMs, its focus has moved to other new technologies. As a result, the architecture steering the adoption process for VVMs by individual developing countries has stalled.

Conclusions

The VVM story, spanning 27 years and still ongoing, demonstrates that bringing new technologies through product development, introduction, and scaling up is a “long and arduous journey.”⁶⁴ The process requires focused effort by public and private agencies, plus sufficient financing and patience. Each access phase for VVMs required years of concerted effort: twelve years for product development, six years for the first introduction on oral polio vaccine, and nine years for scaling up to EPI vaccines supplied by WHO prequalified producers. Data are not available for VVM coverage on vaccines delivered in developing-country immunization programs, but sales data from Temptime show a marked increase in VVM uptake over time. Between 1996 and 2007, Temptime’s sales of VVMs for oral polio vaccine rose more than three-fold to nearly 200 million vials per year and for other EPI vaccines sales rose from nothing to over 100 million vials per year (see Figure 7.1). By the end of 2005, close to 100% of WHO-prequalified vaccine producers used the technology. Significant challenges, however, still remain in expanding VVM access in the PAHO region and in developing-country vaccine markets.

Efforts to promote access to VVMs encountered barriers (as shown in Table 7.3)—particularly adoption problems—and these differed in the introduction and scaling-up phases. When VVMs were first introduced on OPV, the technology was new and the most pressing needs were to demonstrate the effectiveness of VVMs on OPV and to require their use through policy development. The primary barriers involved a number of vaccine producers’ concerns that were eventually addressed through open discussion in meetings, technical changes, and validation studies. In the scaling-up phase to all EPI vaccines, the number of vaccine producers that became potential VVM users increased significantly. As the number of actors multiplied, so too did the number of barriers encountered in trying to achieve adoption by vaccine producers. To address these blockages, WHO and PATH held a series of technical meetings with vaccine producers and Temptime, UNICEF specified and enforced VVM requirements in vaccine tenders, and Temptime modified the technology and worked with vaccine producers to develop new labeling processes.

This chapter shows how actors can have widely diverging views of new health technologies, affecting product adoption. For example, for WHO staff and health workers, the technology meant improvements to the functioning of the cold chain and decreases in vaccine wastage. For the UNICEF Supply Division, VVMs challenged their policy on sole suppliers and created stress in their relationships with vaccine producers. For vaccine producers, attaching VVMs to their vaccines sold

Figure 7.1 | Sale of Temptime's VVM products, 1996-2007

Note. Temptime has four categories of VVMs. The first is the VVM2 (for the least stable vaccines) that is used for the oral polio vaccine. The other three categories are the VVM7 (for moderate stability vaccines), VVM14 (for medium stability vaccines), and VVM30 (for high stability vaccines). The VVM7, VVM14, and VVM30 are used for EPI vaccines other than the oral polio vaccine. From *Implementation Update on VVM* by Temptime Corporation, 2005, Morris Plains, NJ. Adapted with permission.

to UNICEF meant a number of legal, logistical, and commercial challenges to their business. Providing access for VVMs required a concerted effort—and a significant amount of time—to bring these diverse groups together. VVM product champions in WHO and PATH steered the process step by step from initial development to introduction on OPV to scaling up to other EPI vaccines. WHO and PATH staff members worked together in an informal partnership on VVM-related activities (testing, impact studies, meetings with vaccine producers) and also had separate responsibilities (WHO was responsible for training, PATH provided technical support to Temptime). WHO served as the coordinating body for VVM access, though once vaccine producers began to use VVMs, the time WHO staff spent in coordination diminished. PATH's role has been one of providing technical expertise to WHO and the VVM manufacturer. Kartoglu, the project manager for VVMs at WHO, stated that since he arrived at WHO in 2001,

PATH staff provided mentoring and other crucial support throughout the VVM access process.⁶⁵ PATH and WHO, together with the UNICEF Supply Division, created an effective architecture for VVM access; the focused effort and time commitment given by staff in these organizations were critical factors in assuring VVM implementation on vaccines procured through UNICEF.

VVM product champions, especially PATH, worked hard to create a close relationship with Temptime as a central part of the architecture for VVM access. PATH established a relationship with Temptime early in the access process by encouraging the company to develop the product. PATH provided continuing support to Temptime, urging the company to continue working on the VVM product from an early stage when the company questioned whether to move forward. For Temptime, PATH staff gave the company the end-user's point of view and a vision for the overall program.⁶⁶ Temptime invested more than \$10 million to develop the VVM⁶⁷ and did not begin to make a profit on the product until 2001.⁶⁸ The company responded to repeated requests to modify the original VVM technology according to evolving WHO specifications and the needs of particular vaccine producers. Importantly, Temptime relied on product champions PATH and WHO to market the technology, rather than carrying out these activities on its own. As a midsized company with no background in public-sector or global health work, Temptime was unprepared to market the VVM and required the support and guidance of WHO and PATH staff in this realm.

The champions for VVMs gave special attention to product adoption by different groups. For example, PATH provided loans that facilitated Temptime's purchase of custom labeling equipment so that vaccine producers could begin using VVMs on OPV. Product champions also tried to find other manufacturers for VVMs in order to address concerns among vaccine producers and UNICEF about Temptime's role as sole manufacturer—but without success. As a result, this issue continues.

Product champions also worked to convince procurement agencies of the need for VVMs on all EPI vaccines. These relationships represented important components of the VVM architecture. Requiring VVMs in UNICEF tender specifications for vaccines and enforcing these requirements was vital to achieving adoption by vaccine producers.⁶⁹ UNICEF enforced the VVM requirements gradually over time, due in part to the limited supply of some vaccines and the organization's need to purchase all available products, regardless of whether they had VVMs. A continuing problem has been the resistance to VVMs by PAHO and many developing-country government procurement agencies. The lack of adoption by these groups has limited

access to VVMs in the PAHO region and in countries that procure their own vaccines (often from domestic sources) but do not require VVMs on all vaccines.

The work of VVM product champions depended on adequate financing. For VVMs, these funds came to PATH mainly through USAID's HealthTech Program. USAID's willingness to provide long-term funding for HealthTech (1987–2006) was particularly important. This gave PATH the unusual opportunity of providing long-term support to WHO, Temptime, and other groups. In addition to USAID funds, PATH financed its VVM work through other sources, such as its Loan Fund, the U.S. Centers for Disease Control and Prevention, and other donors.

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 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.

Table 7.3 | Vaccine vial monitors access table

	BARRIER	STRATEGY	SPECIFIC ACTION
ARCHITECTURE	Need for a global champion for VVMs	Identify effective leadership and design partnerships for the technology	PATH used funds from USAID and other sources to work with WHO as product champions and collaborated with Temptime to develop the technology and push it through product development, introduction, and scaling up
ADOPTION	Concerns by vaccine producers about lack of independent validation, labeling process, sole VVM supplier, and liability (vaccine producer adoption)	Assure adequate quality and quantity of the product to persuade producers to adopt the technology	WHO funded an independent validation of VVMs to demonstrate its effectiveness; PATH worked with Temptime to modify the technology to meet WHO specifications, develop new labeling processes and address concerns of individual vaccine producers; UNICEF addressed liability and sole supplier issues in contracts with vaccine suppliers; WHO and PATH held technical meetings with Temptime and vaccine producers
	Concerns of UNICEF Supply Division about sole VVM supplier and the limited global vaccine supply (UNICEF adoption)	Produce acceptance of the technology at the global level	PATH and WHO worked to assure adoption by UNICEF Supply Division
	PAHO has not required VVM use (PAHO adoption)	Produce acceptance of the technology at the global/regional levels	WHO conducted impact studies to demonstrate how VVMs reduced vaccine wastage in developing country settings, but PAHO has resisted adoption
	Many developing countries have not required national vaccine producers to use VVMs (national adoption)	Produce acceptance of the technology at the national levels	This problem has not been adequately addressed, in part because PATH has lacked funding to work with governments and producers in developing countries to facilitate national adoption

Table 7.3 | Vaccine vial monitors access table (continued)

	BARRIER	STRATEGY	SPECIFIC ACTION
AFFORDABILITY	Concerns by producers that VVM labeling process would require new equipment (and costs)	Assure vaccine producers that the technology will not impose major additional costs	Temptime developed a new labeling process that did not require vaccine producers of liquid vaccines to purchase new labeling equipment; producers of freeze-dried vaccines do require additional equipment to apply the VVM, but Temptime agreed to work with each company to tailor the VVM to its particular labeling system
AVAILABILITY	Concerns of UNICEF and vaccine producers that Temptime was the sole supplier of VVMs.	Assure adequate quantity of production	PATH and WHO encouraged and funded other companies to develop competitive products, but none were successful; UNICEF addressed sole supplier issue in contracts with vaccine producers, and WHO and PATH held technical meetings with Temptime and vaccine producers

Endnotes

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- ² GAVI, *GAVI Sixth Board Report* (Ottawa, Canada: GAVI, 2001).
- ³ PATH, *HealthTech Historical Profile: Vaccine Vial Monitors* (Seattle: PATH, 2005). Other temperature indicators for vaccines are temperature data loggers (monitoring international transport), Cold Chain Monitor cards (monitoring transport between levels), and Stop!Watch (monitoring refrigerator temperatures). The VVM is the only tool that is available at all times during distribution and delivery.
- ⁴ PATH.
- ⁵ Ray Baughman (Robert A. Welch Professor of Chemistry and Director of Alan G. MacDiarmid NanoTech Institute, University of Texas in Dallas), interview by author (Laura Frost), August 19, 2005.
- ⁶ PATH.
- ⁷ PATH.

- ⁸ PATH.
- ⁹ Ümit Kartoglu (Scientist, World Health Organization), interview by author (Laura Frost), August 17, 2005.
- ¹⁰ Baughman interview.
- ¹¹ PATH.
- ¹² PATH; and Ted Prusik (Senior Vice President, Temptime Corporation) and Chris Caulfield (Director of Sales, Temptime Corporation), interview by author (Laura Frost), August 3, 2005.
- ¹³ CliniSense Corporation has developed an electronic time-temperature indicator called LifeTrack for monitoring both vaccine heat exposure and freezing. This indicator, however, costs \$3.00–5.00 at high production volumes and is therefore too expensive to attach to each vaccine vial. See: Stephen E. Zweig, “Advances in Vaccine Stability Monitoring Technology,” *Vaccine* 24 (2006): 5977–5985.
- ¹⁴ PATH.
- ¹⁵ PATH.
- ¹⁶ Debra Kristensen (Senior Technical Officer, PATH), interview by author (Laura Frost), August 16, 2005.
- ¹⁷ Oya Zeren Asfar and Birhan Altay, *Vaccine Vial Monitors Impact Study During 1997 National Immunization Days in Turkey* (Geneva: World Health Organization, 1998, WHO/EPI/TECHNET.98/WP.23).
- ¹⁸ Asfar and Altay.
- ¹⁹ PATH, Kingdom of Bhutan, and World Health Organization, *Vaccine Vial Monitor Impact Study Results: Kingdom of Bhutan* (Seattle: PATH, 1999).
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- ²¹ Kristensen interview.
- ²² PATH, Kingdom of Bhutan, and World Health Organization.
- ²³ The Consumer Association Research and Testing Centre (UK) carried out a conformity test of VVM2 samples, and Precision Measurements and Instruments Corporation (U.S.) carried out conformity tests of VVM7, VVM14, and VVM30 under a WHO contract.
- ²⁴ Interview by author (Laura Frost) with anonymous source, September 29, 2005.
- ²⁵ Kristensen interview.
- ²⁶ PATH.
- ²⁷ Kristensen interview.
- ²⁸ World Health Organization-UNICEF, *Quality of the Cold Chain*.
- ²⁹ PATH.

- ³⁰ World Health Organization, *Technical Review of Vaccine Vial Monitor Implementation* (Geneva: WHO, 2002).
- ³¹ World Health Organization, *Q&A: Technical Session on Vaccine Vial Monitors* (Geneva: WHO, 2002).
- ³² Kristensen interview.
- ³³ Kartoglu interview; and World Health Organization, *Technical Review*.
- ³⁴ World Health Organization, *Technical Review*.
- ³⁵ World Health Organization, *Q&A*.
- ³⁶ World Health Organization, *Q&A*.
- ³⁷ Prusik and Caulfield interview.
- ³⁸ World Health Organization, *Technical Review*.
- ³⁹ World Health Organization, *Technical Review*, 20.
- ⁴⁰ World Health Organization, *Technical Review*.
- ⁴¹ GAVI, “VVM Uptake: Accelerating in International Markets,” *Vaccine Forum* 1 (2004): 1–3.
- ⁴² PATH.
- ⁴³ Kartoglu interview.
- ⁴⁴ The policy applies to multidose vials of the following vaccines: oral polio, diphtheria-tetanus-pertussis, tetanus toxoid, diphtheria-tetanus, hepatitis B and liquid formulations of *Haemophilus influenzae* type b vaccine. It does not apply to the vaccines that are reconstituted—Bacillus Calmette-Guérin, measles, yellow fever, and some formulations of *Haemophilus influenzae* type b vaccine. See: World Health Organization, *WHO Policy Statement: The Use of Opened Multi Dose Vials in Subsequent Immunization Sessions* (Geneva: WHO, 2000, WHO/V&B/99.18).
- ⁴⁵ World Health Organization, *WHO Policy Statement*.
- ⁴⁶ World Health Organization, *WHO Policy Statement*.
- ⁴⁷ Asfar and Altay.
- ⁴⁸ Asfar and Altay, 7.
- ⁴⁹ PATH.
- ⁵⁰ Carib M. Nelson, Hariadi Wibisono, Hary Purwanto, Isa Mansyur, Vanda Moniaga, and Anton Widjaya, “Hepatitis B Vaccine Freezing in the Indonesian Cold Chain: Evidence and Solutions,” *Bulletin of the World Health Organization*, 82 (2004): 99–105.
- ⁵¹ PATH.
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- ⁵³ Prusik and Caulfield interview.
- ⁵⁴ PATH, 10.
- ⁵⁵ PATH.

- ⁵⁶ World Health Organization-UNICEF, *Quality of the Cold Chain*.
- ⁵⁷ GAVI, “VVM uptake,” 1.
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- ⁵⁹ Kristensen interview.
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- ⁶⁴ Kristensen interview.
- ⁶⁵ Kartoglu interview.
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- ⁶⁷ Temptime Corporation, *Implementation Update on VVM* (Morris Plains, NJ: Temptime Corporation, 2005).
- ⁶⁸ Prusik and Caulfield interview.
- ⁶⁹ PATH.