Sharing PATH's experiences with the global health community

DIRECTIONS IN GLOBAL HEALTH

Special issue on VACCINE PARTNERSHIPS

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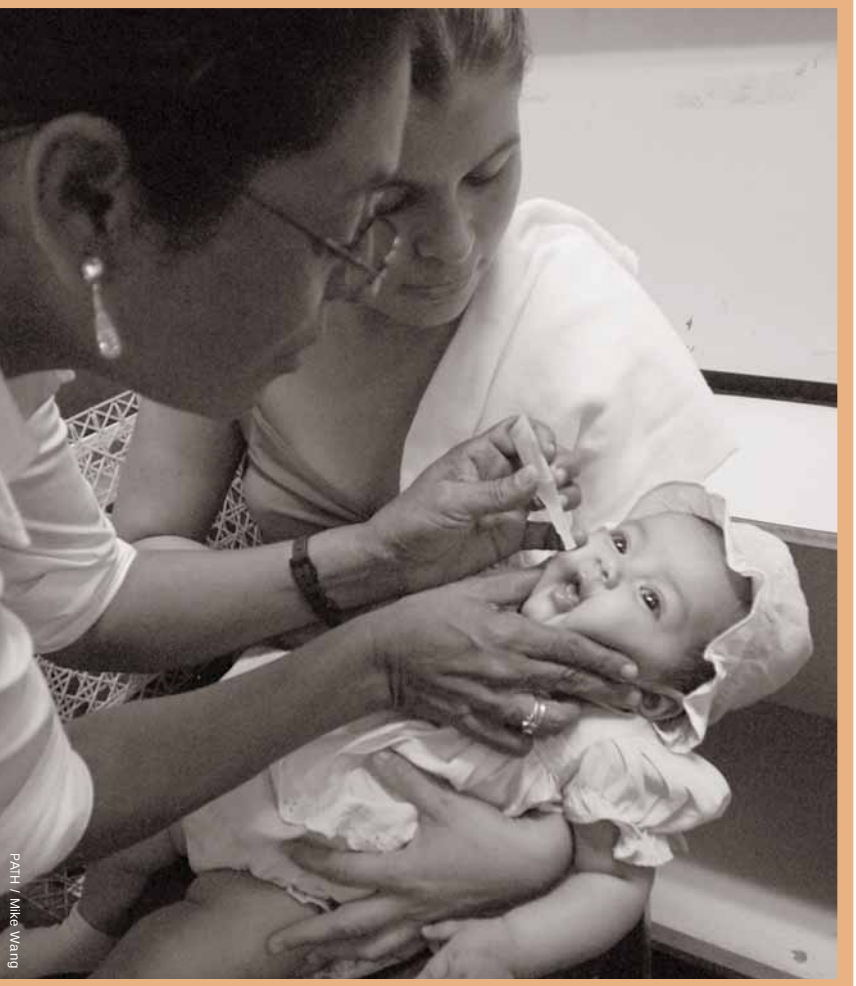

PATH / Mike Wang

Increasing the availability of vaccines

Partnerships advance lifesaving protection

This special issue of *Directions* illustrates how PATH and its partners throughout the global health community are supporting the development, preparation, introduction, and adoption of vaccines for low-resource countries. These partnerships bring together financial, technical, and human resources, increasing the effectiveness of individual efforts and decreasing the amount of time needed to deliver lifesaving vaccines to these countries.

Vaccines for such settings face many obstacles on the way to widespread use: lack of incentive for private-sector investment; absence of information or proven strategies for introduction; weak and overtaxed health systems. Even successful vaccines can take more than a decade to reach low-income countries after licensing.

Through collaboration, PATH and its partners have helped spur the development of vaccines for low-resource settings, speed the introduction of successful vaccine candidates, and provide strategies and technologies that make widespread use possible. Partnerships are essential if poor countries are to one day have access to the same comprehensive, stable immunization programs found in wealthier countries.

INSIDE:

Advancing vaccine research

Collaborating to develop new vaccines

Project names
PATH Malaria Vaccine Initiative (MVI); Pneumococcal vaccine development project (Pneumococcal)

Location
Global

Methods
Vaccine research and development

Vaccine development partners highlighted in this article
MVI: Centro de Investigação em Saude da Manhiça; GlaxoSmithKline Biologicals; Sanaria, Inc.

Pneumococcal: Intercell AG

Funders
MVI: Bill & Melinda Gates Foundation; ExxonMobil Foundation; US Agency for International Development

Pneumococcal: Bill & Melinda Gates Foundation

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Pneumococcal: Please contact Eileen Quinn, senior communications officer, at equinn@path.org.

Vaccines are elusive for many of the diseases that hit hardest in the developing world. The vaccine development process is complex and costly, and the delay between development of a new vaccine and introduction into markets for these countries can be decades. Malaria and pneumococcal infection present particular challenges that have slowed the creation of new vaccines.

PATH is partnering with the private sector to develop vaccines for both diseases. We are working with malaria vaccine developers to identify the best candidates as quickly and effectively as possible by offering clinical trial expertise. Our involvement in the development of a pneumococcal vaccine will expand protection against pneumococcal disease to infants and children in low-income countries.

Accelerating malaria vaccine development

Vaccine developers have been working for more than 40 years to produce a malaria vaccine that can protect against the tenacious, mosquito-borne infection. Parasites that cause malaria undergo changes in the human body, making it difficult to target malaria with a single vaccine. Limited resources and a complex biology have caused significant delays.

PATH's Malaria Vaccine Initiative (MVI) works to remove scientific, financial, and policy barriers to developing safe, effective, and affordable malaria vaccines. One strategy MVI has used successfully is partnering with vaccine developers to plan for and execute clinical trials of vaccine candidates. These trials provide the global community with the information necessary to focus resources and attention on the most promising candidates.

RTS,S: a proven partnership

In 2000, MVI began working with GlaxoSmithKline Biologicals (GSK) to validate a new vaccine candidate, RTS,S. Promising early clinical trials for RTS,S prompted MVI to bring together GSK, local health centers, and the Centro de Investigação em Saude da Manhiça for the largest malaria vaccine pediatric trial in Africa. The Phase 2b trial involving 2,000 children aged one to four years proved to be a breakthrough in malaria vaccine development. We also worked with GSK through the process of collecting market data and other information critical for policymaking and aligning the vaccine with the needs of low-resource countries.

The trial showed RTS,S to be effective for at least 18 months in reducing severe malaria by almost 50 percent—an incentive for continued investment in malaria vaccine development. Future positive results for RTS,S could lead to licensure as soon as 2011.

A novel vaccine for an elusive infection

Now MVI is collaborating with the vaccine company Sanaria, Inc., to move forward a novel malaria vaccine candidate that uses a live, weakened *Plasmodium falciparum* parasite (which causes the most deadly form of malaria) in its entirety, instead of using only parasite components, promising high levels of protection. The MVI–Sanaria partnership works in three essential ways:

- **Cost-sharing.** MVI is providing a small amount of funding for new vaccine trials to expedite initiation of additional trials.

- **Expertise.** MVI is designing studies to evaluate the safety of the vaccine in animals before its use in humans and will manage the timeline for subsequent clinical trials.
- **Connections.** MVI's extensive partner network is bringing together experts in malaria control, clinicians from future trial sites, and scientists from Sanaria to create a clinical development plan and other vaccine development guidelines.

A clinical trial to measure the efficacy of the Sanaria vaccine is scheduled to begin in late 2008.

Opening new markets for a pneumococcal vaccine

Nearly one million children die every year from pneumonia caused by the pneumococcus bacterium. The current pneumococcal conjugate vaccine, which includes the seven serotypes most common in the United States, could soon provide substantial protection to children in other parts of the world. Because pneumococcal strains differ regionally and the conjugate vaccine is expensive, new vaccines are also needed to broaden the strain coverage and make protection available to children in low-income countries.

A vaccine with worldwide application

PATH is partnering with Intercell AG, an Austrian biotechnology firm, on the development of a pneumococcal vaccine that contains proteins common to all pneumococcus strains. Intercell is in the early stages of developing such a vaccine, with an intended market of elderly individuals in Europe and the United States. PATH's involvement may help expand this target market to include another vulnerable segment of the global population: children in poor countries.

Reduced risk and developing-world expertise

PATH's contributions are twofold: financial support and technical expertise. The partners have agreed on a work plan for determining what type of vaccine will be effective in low-resource countries and then producing such a vaccine, and each partner covers approximately half of the costs. Funding from PATH reduces the risk Intercell incurs by investing in a vaccine for uncertain markets in poor countries.

In addition, PATH offers expertise in downstream development—planning for clinical trials, manufacturing, and vaccine introduction. Over the next year, PATH will begin work on a pneumococcal strain and serum repository, providing companies like Intercell with a range of reagents useful for characterizing their vaccine antigens and producing vaccines with global, rather than local, impact.

Partnering to save lives

The partnership has a shared goal of bringing an Intercell vaccine to Phase 1 clinical trials by mid-2008. PATH's early involvement means that the development of an Intercell vaccine for elderly individuals and a developing-country counterpart is shared, accelerating the process. If Phase 1 results are encouraging, Intercell and PATH will work together on Phase 2/3 trials.

Shared goal drives the process

Collaboration across sectors can alleviate the difficulty of designing, refining, and bringing to market vaccines for some of the world's most challenging diseases. Leveraging the resources of each partner ensures the development and broadens the reach of important new vaccines. Early involvement is helping PATH remove obstacles in the development of malaria and pneumococcal vaccines, bringing partners closer to a shared goal of producing vaccines for low-resource countries. ■

PATH is collaborating with private-sector partners to develop a vaccine against malaria and against pneumococcal disease.

Preparing the way for a meningitis vaccine

Partnership sets the stage for vaccine adoption

Project name
Meningitis Vaccine Project

Location
Sub-Saharan Africa

Methods
Vaccine research and development, capacity building, surveillance

Partners
Agence Africaine pour la Recherche en Santé Humaine, Centre pour le Développement des Vaccins–Mali, Serum Institute of India Limited, Health Protection Agency, iGATE Clinical Research International, Medical Research Council Laboratories, National Institute for Biological Standards and Control, National Institutes of Health, US Food and Drug Administration, US Centers for Disease Control and Prevention

Funder
Bill & Melinda Gates Foundation

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Among the many bacteria that cause meningitis, none is more deadly than group A meningococcus (Men A), which causes 85 percent of epidemics and approximately one-half of endemic meningitis disease in Africa. Between 1995 and 2004, meningitis outbreaks resulted in close to 700,000 cases of illness and 60,000 deaths. Young adults, adolescents, and children are most affected, and long-term neurological sequelae affect up to one-quarter of survivors.[1]

Created in 2001, the Meningitis Vaccine Project (MVP)—a partnership between the World Health Organization (WHO) and PATH—is working to eliminate meningitis epidemics in sub-Saharan Africa by advancing the development, testing, licensure, and introduction of conjugate meningococcal vaccine. The polysaccharide vaccines that are currently being used have limitations that make conjugate vaccines better suited for preventing epidemics in Africa. For example, the new Men A conjugate vaccine being developed by MVP will provide longer-lasting protection while decreasing carriage of the bacteria in the population.

The new vaccine will be available for use as early as 2008. MVP is preparing the way for adoption by addressing acceptability, affordability, and public health capacity through training and partnerships and by improving knowledge through communication and advocacy.

An affordable conjugate vaccine

The MVP model encourages international partnerships that are focused on addressing a well-defined public health goal within the context of the financial realities of the end users—countries with scarce public health resources. To ensure positive public health impact with the Men A vaccine, early in the project MVP sought advice from African public health leaders, who emphasized the need for a low-cost vaccine—less than US$0.50 per dose—for use in mass campaigns. This information prompted MVP's innovative strategy for vaccine development—a consortium where the raw materials come from one source, the technology from another, and the manufacturing facility from another.

MVP's vaccine development strategy and major improvements in global vaccine manufacturing capacity have allowed MVP to succeed in developing a conjugate meningococcal vaccine at an affordable price. The Serum Institute of India Limited (SIIL) has agreed to manufacture a Men A conjugate vaccine at a target price of US$0.40 per dose, which meets the requirements cited by African public health officials. MVP has completed a cost–benefit analysis showing that preventive use of a vaccine at this price will cost less than current expenditures to control meningitis in hyperendemic countries—even before lost livelihood income and disability savings are taken into account.

Building country capacity

Beginning in 2002, MVP established a collaboration with WHO's Multi-Disease Surveillance Center in Ouagadougou, Burkina Faso. This team promoted enhanced surveillance in countries hit hardest by meningitis through training for national surveillance personnel in epidemiology, data management and analysis, and strengthening laboratory capacity. Accurate laboratory data provide up-to-date information about the strains responsible for meningitis outbreaks. Weekly surveillance data from 14 countries now alert health authorities to the early stages of an epidemic, thereby improving epidemic control, and providing evidence to support vaccine introduction.

Supporting clinical trials

MVP collaborated with African country partners to build a solid infrastructure for clinical studies. Providing staff training and capacity development for clinical trial sites ensures effective study implementation and also meets MVP's objective of strengthening health systems in Africa.

In November 2006, MVP launched a Phase 2 study of the Men A vaccine to provide information on safety and immunogenicity among toddlers 12 to 23 months old in Mali and The Gambia. Phase 2/3 studies begin this year. MVP and SIIL will then seek licensure in India and will apply for WHO prequalification, which will put the vaccine on the list of drugs that can be purchased by United Nations agencies. MVP is already collaborating with African public health officials to prepare for broad introduction once the vaccine is available, on the basis of country disease burden and the ability of countries to deliver comprehensive mass vaccination campaigns.

Information sharing

MVP advocacy and communication efforts focus on disseminating information in Africa that will lead to widespread uptake of the vaccine. For example, the team is providing comprehensive, interactive information on meningococcal meningitis through the Advanced Immunization Management e-Learning tool, an online tool for immunization managers in developing countries (http://aim.path.org). In addition, MVP is reaching hyperendemic areas with appropriate and accessible information and training for journalists, national officials, health workers, and communities.

Promising model

If successful, MVP's model will be the first instance where public, private, and nongovernmental organizations have come together to develop a vaccine that is critically needed in Africa but would not have otherwise been made by the private sector. Through this unique model and activities supporting eventual adoption of a better meningitis vaccine, MVP's approach may one day prove useful for developing other orphan vaccines and drugs for which the primary markets are low-income countries. ■

REFERENCE

1. World Health Organization (WHO). Enhanced surveillance of epidemic meningococcal meningitis in Africa: a three-year experience. *Weekly Epidemiological Record*. 2005;80(37): 313–320.




BBC's *Kill or Cure?* series to highlight meningitis

The Meningitis Vaccine Project (MVP) recently partnered with Rockhopper TV to develop a documentary on meningococcal meningitis for the BBC's *Kill or Cure?* series.

Filmed during the 2007 epidemic in Burkina Faso, the documentary offers a poignant and revealing account of the devastating impact meningitis epidemics have on individuals, families, and communities. The documentary also takes viewers to Mali, where MVP and the Serum Institute of India Limited are testing a new vaccine that offers hope for eliminating epidemic meningitis as a public health problem in sub-Saharan Africa.

The film will be broadcast on BCC World on June 8 through 13, 2007, and later will be available on DVD and the MVP website, www.meningvax.org. For more information on the film, contact info@meningvax.org.

Introducing vaccines against cervical cancer

New strategies needed to reach adolescents

Project name
Cervical cancer vaccine project

Locations
India, Peru, Uganda, and Vietnam

Methods
Advocacy, formative research, operations research

Partners
GlaxoSmithKline; Harvard University; International Agency for Research on Cancer; Merck & Co., Inc.; ministries of health and research institutes in the four demonstration countries; World Health Organization Initiative for Vaccine Research

Funder
Bill & Melinda Gates Foundation

For more information
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New vaccines against the human papillomavirus (HPV) promise to sharply reduce cervical cancer rates during the next several decades—especially in developing countries, where women rarely receive routine screenings for early cancer detection. Various sectors of the global health community, including women's rights advocates, adolescent and reproductive health experts, and the vaccine community, are joining forces to ensure that HPV vaccines reach developing countries without delay.

Drawing on experience in both cervical cancer prevention and vaccine introduction, PATH is collaborating with these groups to find effective ways to reach adolescent girls with the vaccine, assess vaccine demand (in the hopes of influencing supply and price), and communicate the results of research and lessons learned to decision-makers and global health colleagues around the world.

Finding what works

HPV vaccines pose unique introduction challenges. The vaccines are effective if given before girls are infected with HPV. Because infection usually results within a year or two of sexual debut, it is important to protect girls early—between the ages of 9 and 16 years. But young girls in poor countries rarely access health services, unless there is an emergency; therefore, the global health community needs new strategies to reach these youth. Cultural norms and beliefs present additional barriers for HPV vaccine introduction. Some communities may oppose vaccinating young girls against a sexually transmitted infection, and others may be suspicious of a vaccine offered only to girls.

Working closely with the World Health Organization, ministries of health, vaccine manufacturers, and in-country partners, PATH is planning demonstration projects to introduce the HPV vaccine in India, Peru, Uganda, and Vietnam. These countries are committed to preventing cervical cancer through their strong vaccination programs and are willing to expand successful projects. To prepare for the demonstration projects, PATH is supporting formative research to answer the following questions:

- What societal attitudes will influence the acceptability of HPV vaccine?
- How can HPV vaccines be integrated into existing health systems—and delivered most efficiently and effectively to adolescent girls?
- What are the cost implications of HPV vaccine programs, including the ultimate public-sector price for a vaccine?
- What combination of program activities, including cervical cancer screening and treatment services for older women who may already have been infected, could have the greatest impact on cervical cancer rates?

The information gained will help PATH tailor introduction approaches in each of the four countries. Demonstration projects are scheduled to begin in 2008.

Translating global demand into global supply

New vaccines are expensive and out of reach for many countries without significant financial assistance. Accurate vaccine demand estimates are needed nationally, regionally, and globally to ensure a sufficient supply of vaccines and to support an affordable price for health systems in low-income countries.

Building on formative research and conversations with governments and donors, PATH is developing a global demand estimate for the HPV vaccine to guide manufacturers' supply and pricing decisions. This information will help the GAVI Alliance, UNICEF, and manufacturing partners negotiate the best possible price for public health programs in low-resource countries.

Countries choosing to introduce HPV vaccines will have access to data from the demonstration projects to guide approaches for reaching adolescent girls and improve health for generations of women. Their experience introducing HPV vaccines will, in turn, guide strategies for introducing future vaccines for sexually transmitted infections. ■

Advocacy at the international level

As information comes to light, PATH will rapidly synthesize and disseminate findings to inform HPV vaccine policy, programming, and funding decisions made by national, regional, and global organizations. PATH will tailor its communications to various audiences, sharing results in peer-reviewed journals and producing interactive online tools for decision-makers and program managers, resources for health workers and nurses who provide screening services, and media support materials to help raise global public awareness of the need for HPV vaccine.

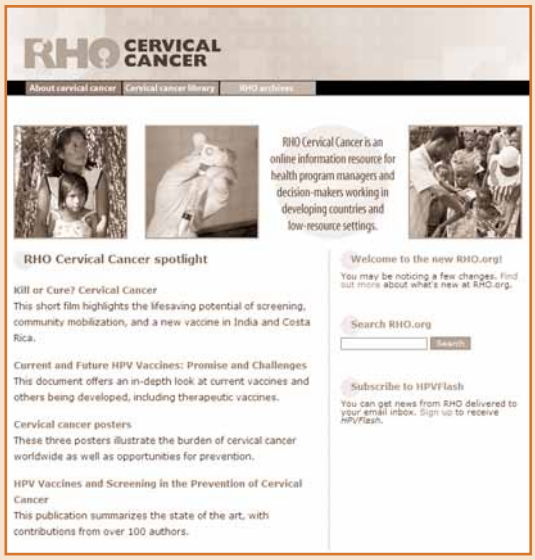
PATH also maintains a comprehensive library of resources for general cervical cancer prevention: www.rho.org. The library contains science-based cervical cancer information to ensure health officials and health workers around the world have prompt access to the accurate and up-to-date information they need.

Informed decisions, tailored approaches

Decision-makers in low-resource countries have the daunting task of prioritizing and allocating scarce resources. Information and lessons learned from PATH's formative research, demonstration projects, awareness-raising on cervical cancer prevention, and work on the demand–supply equation will help them make informed decisions for their situations—whether it be introducing the vaccine, improving screening services, or a combination of both.

Building awareness about cervical cancer

Part of PATH's role in introducing vaccines against human papillomavirus (HPV) is ensuring that governments and collaborators have the most up-to-date information at hand. We recently made two new resources available.



The May 2007 issue of PATH's *Outlook* newsletter provides evidence-based information about cervical cancer. It summarizes key issues related to HPV transmission, new HPV vaccines, and strategies for introduction in low-resource countries. The issue also identifies new methods for early detection and treatment of cervical cancer. Download *Outlook* from PATH's online publications catalog at www.path.org.

Since 1998, PATH's Reproductive Health Outlook has served as an online resource for health managers in low-resource settings. Now PATH has revamped the site to serve as a clearing house for cervical cancer resources. RHO Cervical Cancer (www.rho.org) offers research, films, and many publications from the world's leading experts and organizations, including the Alliance for Cervical Cancer Prevention, the American Cancer Society, and the World Health Organization.

Accelerating the availability of rotavirus vaccine

Flexible approaches meet unique needs

Project name
Rotavirus Vaccine Program

Locations
Africa, Asia, Eastern Europe, Latin America

Methods
Modeling, surveillance, country-specific assessment and planning, clinical trials, public-private partnerships

Partners
GlaxoSmithKline; Merck & Co., Inc.; US Centers for Disease Control and Prevention; World Health Organization

Funder
GAVI Alliance

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Rotavirus kills more than half a million children annually, the vast majority in poor countries. Newly licensed vaccines against rotavirus are the most promising intervention for preventing this most common cause of acute diarrheal disease. PATH's Rotavirus Vaccine Program is working to bring these vaccines to children in developing countries as quickly as possible by providing governments and manufacturers with information that can accelerate introduction.

PATH uses sophisticated models to estimate the demand for rotavirus vaccine and predict the impact of introduction. However, these models cannot fully capture countries' awareness of the disease burden or health priorities. On-the-ground research and conversations with government stakeholders and public health professionals are bridging the gap between modeling and reality—and helping countries develop introduction strategies tailored to their unique needs.

Estimating global demand

In collaboration with the US Centers for Disease Control and Prevention and the World Health Organization (WHO), PATH is estimating the global demand for vaccines through surveillance activities, modeling, and cost-effectiveness studies. Demand estimates are essential to conversations about supply and price with donors and vaccine manufacturers.

To refine these estimates, PATH has been engaging low-resource countries in all regions of the world. PATH is sharing data, raising awareness of rotavirus disease burden, and convening conversations about rotavirus vaccine introduction at national, regional, and international levels through conferences and in-person meetings.

A comprehensive approach in Latin America

Beginning to build a strategy for rotavirus vaccine introduction in Latin America, PATH and its partners met with country leaders and ministers of health in several countries. During these conversations, PATH learned that health officials in the region were most concerned with addressing the broader issue of diarrheal disease. Rotavirus vaccines would protect against approximately 40 percent of acute diarrhea cases, but health workers wanted options for preventing or treating the full spectrum of disease.

In response, PATH and UNICEF developed a comprehensive approach to controlling diarrheal disease that incorporates new health interventions, such as vaccination and zinc supplementation for acute diarrhea episodes, along with proven methods, such as sanitation, breastfeeding, and oral rehydration. Governments and local organizations embraced the approach, dubbed the "Enhanced Diarrheal Disease Control Initiative," and welcomed the vaccine as a central component. A website on this initiative provides information and guidelines, in multiple languages, on new and existing interventions for diarrhea control (www.eddcontrol.org).

Earlier this year, Nicaraguan health officials made history when they worked with Merck & Co., Inc., to introduce the RotaTeq® vaccine: it was the first time that a low-resource country began using a new vaccine the same year it was introduced in the United States. Other countries in Latin America are following suit. Middle-income countries Brazil, El Salvador, Panama, and Venezuela have also adopted the vaccine, and the region's poorest nations, including Bolivia, Guyana, and

Honduras, top the list to receive purchasing support from the GAVI Alliance.

Focusing on the vaccine in Eastern Europe

Diarrheal disease was the priority in Latin America, but health leaders in Eastern Europe preferred a targeted approach to control diarrheal disease and expressed interest primarily in the new rotavirus vaccines. PATH worked with health officials to characterize the rotavirus burden in the region and estimate the potential health and economic benefits and costs associated with vaccine introduction. Eastern Europe may be next to introduce the vaccine.

Clinical trials in Africa and Asia

Although extensive clinical trials have demonstrated the safety and efficacy of rotavirus vaccines in Europe, Latin America, and the United States, additional trials are needed in Africa and Asia because orally administered enteric vaccines like those for rotavirus can perform differently by region. PATH is collaborating with vaccine manufacturers to conduct Phase 3 clinical trials in these regions.

The search for crucial data will slightly delay vaccine availability in Africa and Asia, but the regions will benefit from clearer evidence of the vaccines' performance. In addition, the experience of vaccine introduction in Latin America will inform decisions in other regions by demonstrating the real-world impact of the vaccines in terms of health outcomes and economic indicators.

Toward an ample supply

While demand for rotavirus vaccine grows, PATH is working to ensure an affordable supply. Considering surveillance data in the context of consultations with country leaders, PATH drafted an investment case for rotavirus vaccines. In November 2006, the GAVI Alliance accepted PATH's recommendation to phase in financial support for rotavirus vaccine introduction—beginning next year in Latin America and Eastern Europe, with the goal of extending support to countries in Africa and Asia around 2010, once clinical trials are complete.

In addition, the Rotarix® vaccine manufactured by GlaxoSmithKline became the first-ever WHO-prequalified rotavirus vaccine, moving interested countries one step closer to introduction. WHO prequalification puts the vaccine on the list of drugs available for purchase by United Nations agencies such as UNICEF and the Pan American Health Organization. Merck has also applied to WHO for prequalification of its RotaTeq® vaccine.

At an event to launch nationwide rotavirus immunization, Nicaragua's president, Enrique Bolaños, administers the RotaTeq® vaccine manufactured by Merck & Co., Inc. The 2006 event marked the first time in history that a vaccine was introduced in a GAVI-eligible country during the same year it was introduced in the United States.

The WHO prequalification and the GAVI Alliance's acceptance of the investment case and pledge of support are important signals to vaccine manufacturers to increase supply. Sequencing the vaccine introduction over several years allows time for current manufacturers to expand production capacity. New suppliers will also likely enter the market, boosting supply and lowering price.

Looking ahead

This approach to vaccine introduction—focused on creating a predictable demand for vaccine and a corresponding supply, and on engaging countries early, even as data on disease burden and clinical trials are still being collected—should overcome some of the barriers that have delayed the introduction of new vaccines in low-resource countries. Over the next few years, PATH will continue to work with countries, donors, WHO, and vaccine manufacturers to accelerate introduction of rotavirus vaccine. ■

Introducing a vaccine technology

Successful introduction and adoption of the vaccine vial monitor

Project name
Vaccine vial monitor

Location
Global

Methods
Technology development and introduction

Partners
TEMPTIME Corporation (formerly LifeLines Technology, Inc.), World Health Organization

Funder
US Agency for International Development, under the HealthTech program

For more information
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In 1992, PATH and TEMPTIME Corporation completed the development of a new technology that would flag when vaccines were overexposed to heat. By 1996, the technology, vaccine vial monitor (VVM), was on every vial of oral polio vaccine (OPV) distributed by UNICEF. Today, VVMs are available for all vaccines used in immunization programs in low-resource countries, and UNICEF requires them on all vaccines they purchase.

Moving health technologies for the developing world quickly into widespread use is essential to their effectiveness. Technologies that remain too long in the product introduction pipeline risk stalling there permanently—or becoming obsolete before they emerge. To make the VVM available to health workers worldwide, PATH nurtured partnerships with the private sector, developing-country governments, and global health giants like UNICEF and the World Health Organization (WHO). This year marks the tenth anniversary of the VVM and one of PATH's most successful collaborations.

Vaccine vial monitors indicate heat exposure.

The birth of the VVM

The "cold chain" of continuous refrigeration allows even extremely heat-sensitive vaccines to travel successfully from manufacturers to remote villages in the developing world and elsewhere. However, the chain is not perfect. At many points along the way, vaccines may be exposed to heat—and health workers at the other end of the line must decide whether to use potentially damaged vaccines or discard expensive vaccine that may still be usable. In the late 1970s, with funding from a number of partners, particularly the US Agency for International Development, PATH began working with WHO on an indicator that would flag vaccine that had been overexposed to heat—to turn the idea of a VVM into reality.

PATH searched various industries to identify a chemical that could be used to monitor the heat exposure of sensitive vaccines. After rigorously evaluating the first promising candidate, which PATH produced and refined, in more than 20 countries, we discovered a food industry technology manufactured by the TEMPTIME Corporation that could be applied to a broader range of vaccines, including the very heat-sensitive OPV. In 1989, we began working with TEMPTIME to adapt and produce VVMs with their HEATmarker™ technology.

From 1990 through 1992, we conducted studies with HEATmarker prototypes in eight countries. We worked with Zimbabwe's Ministry of Health to analyze the impact of VVMs on the discard rates for measles vaccine. Based on positive results, PATH, WHO, and other partners continued to refine the VVM specifications and address the feasibility of integrating VVM labels into vaccine products.

Assessing the market

The goal was for VVMs to be adopted by vaccine producers that supply United Nations agencies with vaccine for use in national immunization programs throughout the world. With this in mind, PATH and our partners worked with these agencies to quantify annual supply needs. PATH and WHO began approaching other potential VVM manufacturers, meeting and working with

more than a half-dozen companies to create market competition.

Ultimately, only one manufacturer—TEMPTIME—proved able to manufacture the product at a price that was affordable for the developing world. PATH addressed concerns about designating a sole supplier by helping TEMPTIME procure a low-interest loan to create back-up production lines. We also spoke with United Nations agencies about ways to address supply issues in vaccine procurement contracts.

Early introduction in selected countries

In 1995, WHO and ministries of health in Tanzania and Vietnam began pilot introduction of VVMs for OPV, an extremely heat-sensitive vaccine that was the centerpiece of global polio eradication efforts. These "early adopter" countries were crucial, providing data for policy- and decision-makers on the positive impact of VVMs and helping refine the introduction strategy.

The following year, VVMs began to be integrated more broadly into global and country immunization programs. WHO completed VVM impact studies in four countries: Kenya, Nepal, Tanzania, and Turkey. India imported OPV with VVMs for national immunization days and later issued an official request for WHO assistance in supplying VVMs on locally produced OPV.

Targeted activities were essential to making VVMs available in these national or special programs. To ensure that information about VVMs was widely available, PATH created and published training documents at WHO's request; assisted with in-country vaccine management training; and provided information to policymakers, industry collaborators, and other immunization professionals.

Paving the way with the private sector

PATH also worked with vaccine producers to remove obstacles to their adoption of VVMs. We facilitated the provision of technical information to vaccine producers that responded to their requirements for handling and performance of the VVM. Manufacturers started to comply with new UNICEF requirements that VVMs be included on all UNICEF-procured vaccines. WHO support was essential to this effort, as was the GAVI Alliance's requirement that new vaccines funded by the Vaccine Fund be labeled with VVMs.

Integrating VVMs into health systems

PATH estimates that, over the next ten years, VVMs will allow health workers to recognize and replace more than 230 million doses of inactive vaccine and deliver 1.4 billion more doses in remote settings—actions that could save more than 140,000 lives and reduce morbidity for countless others. Thanks to the presence of VVMs, WHO was able to revise its policies to allow open vials of liquid vaccine to be used for more than a single day. That alone has saved immunization programs around the world millions of dollars. UNICEF and WHO have estimated that the use of VVMs, even if only on basic vaccines, could save the global health community US$5 million per year.

New framework for product introduction

Productive collaborations with public and private institutions are essential to PATH's approach to developing, adapting, transferring, and introducing technologies like the vaccine vial monitor. *PATH's framework for product introduction* outlines our process for using such collaborations to reach underserved populations and improve global health. The framework is available for download from PATH's online publications catalog available at www.path.org.

The successful introduction of the VVM was the result of collaboration between entities from all spheres—the public sector, the private sector, and policymakers at the global, national, and local levels. Relying on strategic planning at every stage of the product lifecycle, from development to initial introduction to regulation and widespread integration, PATH and its partners made sure this promising technology will have a sustained impact on the health of people around the world. ■

HEATmarker is a trademark of TEMPTIME Corporation.

CASE STUDY

Guidelines for successful partnerships with the private sector

PATH was an early innovator in partnerships between the public sector and the private sector. Our first project in the 1970s—helping manufacturers in China set up facilities for making high-quality condoms and other contraceptives—set a standard for strong and ethical relationships with business.

Partnerships are vital to our work in advancing technologies for the developing world at all stages of the process, from development to introduction to widespread use. They harness the strengths of the private sector in research, manufacturing, and distribution toward public health goals that might otherwise not be prioritized.

To make sure that our collaborations with vaccine developers and others in the private sector result in appropriate, effective, and sustainable outcomes and are conducted responsibly and ethically, we have developed a set of guidelines: the *Guiding Principles for Private-Sector Collaboration*. These principles call for:

- A clear link to PATH's mission, balanced by recognition of private-sector needs.
- Clear definition of roles, responsibilities, and expectations.
- Transparent collaboration.
- Appropriate selection of collaborators and management of risk.
- Dissemination of results to those who can use them to further global health goals—with appropriate protection of the intellectual property of private-sector partners.
- Awareness of potential conflicts of interest and adherence to the highest quality and ethical standards.

Refined through three decades of productive collaboration, our *Guiding Principles* acknowledge the points at which the goals of the nonprofit and for-profit sectors diverge and provide a roadmap for achieving the greatest possible health impact. To download a copy, visit PATH's online publications catalog at www.path.org.

Celebrating 30 years

This year, PATH is celebrating an important milestone in our efforts to improve the health of people around the world: 30 years of innovation. We began our work in a single country with support from a single funder. Today, our projects reach more than 65 countries, extending to the areas of health technologies; maternal and child health; reproductive health; vaccines and immunization; and emerging and epidemic diseases.

More than 500 partners throughout the world—individuals, foundations, governments, businesses, global health colleagues, ministries of health, and local community groups—share our vision: a world where innovation ensures that health is within reach for everyone. It is through these collaborations that, on our 30th anniversary, we are closer than ever to seeing that vision come alive.

PATH is an international, nonprofit organization that creates sustainable, culturally relevant solutions that enable communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, we help provide appropriate health technologies and vital strategies that change the way people think and act. Our work improves global health and well-being.

Directions in Global Health shares information about PATH's programmatic experiences with colleagues around the world. Produced three times per year, *Directions* is available free of charge. To subscribe, please send your contact information to:

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