DIRECTIONS IN GLOBAL HEALTH

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SPECIAL ISSUE ON Vaccines and immunization

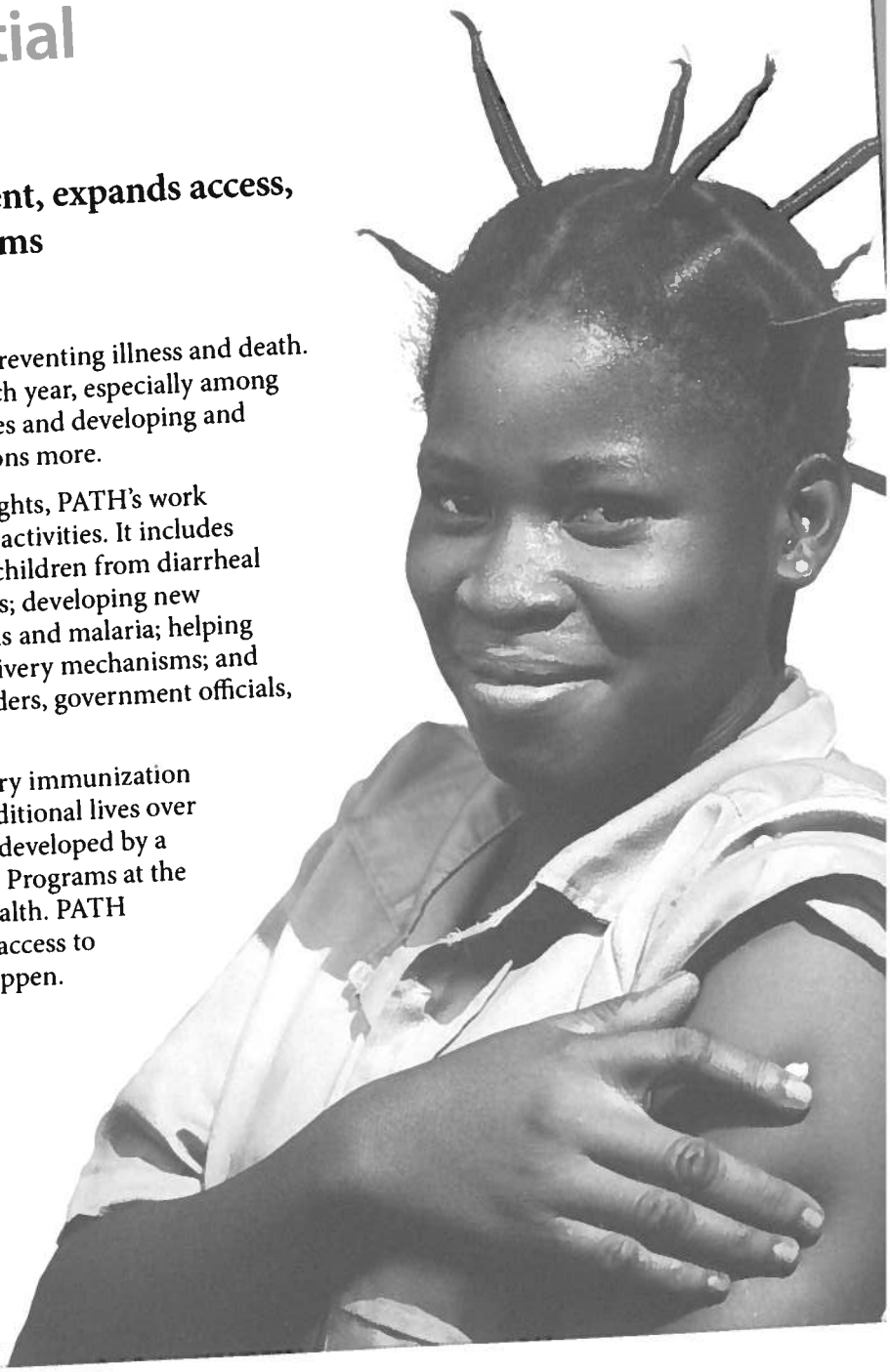
Fulfilling the potential of vaccines

PATH accelerates vaccine development, expands access, and strengthens immunization systems

VACCINES ARE AMONG THE WORLD'S BEST TOOLS for preventing illness and death. Immunization programs save millions of lives each year, especially among young children. Increasing use of existing vaccines and developing and introducing new vaccines promise to spare millions more.

As this issue of *Directions in Global Health* highlights, PATH's work on vaccines and immunization covers a range of activities. It includes increasing access to existing vaccines to protect children from diarrheal disease, Japanese encephalitis, and other illnesses; developing new vaccines against health threats such as meningitis and malaria; helping to improve vaccine distribution systems and delivery mechanisms; and communicating with families, health care providers, government officials, funders, and others to spur action.

Anticipated improvements in developing-country immunization programs may save an estimated 8.7 million additional lives over the next decade, according to a model recently developed by a consortium led by the Institute of International Programs at the Johns Hopkins Bloomberg School of Public Health. PATH and our partners are working to ensure global access to the tools and resources needed to make this happen.



PATH / Gabe Bienczycki

INSIDE

PATH
A catalyst for global health

Product development partnerships

Project name
Meningitis Vaccine Project

Locations
Burkina Faso, Mali, Niger, and other countries in sub-Saharan Africa

Methods
Clinical trials, case-based surveillance, product development partnerships, vaccine development and introduction

Partners
African health ministers, Agence Africaine de Recherche en Santé Humaine, Association pour l'Aide à la Médecine Préventive, DiagnoSearch Life Sciences Pvt. Ltd., GAVI Alliance, International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control, Médecins Sans Frontières, Serum Institute of India Limited, SynCo Bio Partners B.V., UK Health Protection Agency, United Nations Children's Fund (UNICEF), US Centers for Disease Control and Prevention, US Food and Drug Administration's Center for Biologics Evaluation and Research, World Health Organization

Funders
Bill & Melinda Gates Foundation, Michael & Susan Dell Foundation, US Agency for International Development

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To learn more, visit www.path.org/menafrivac/.

Eliminating epidemic meningitis in Africa

Introduction of a new vaccine in three countries paves the way for wider use

PATH / Gabe Bienczycki

Millions of people in Burkina Faso, Mali, and Niger have already received the new meningitis vaccine.

EPIDEMIC MENINGITIS HAS THREATENED communities in sub-Saharan Africa for more than a century. Most often attacking children and young adults, recurring epidemics have killed 5 to 10 percent of those who become ill. Up to 25 percent of survivors suffer brain damage, profound hearing loss, and other permanent disabilities.[1]

In late 2010, PATH, the World Health Organization (WHO), and other groups helped to introduce a new vaccine against Group A meningococcus, the most common cause of African epidemics. Successful vaccination campaigns in Burkina Faso, Mali, and Niger have paved the way for extending the benefits of MenAfriVac™ to other countries. Widespread use of this affordable, long-lasting vaccine may spare hundreds of thousands from death or disability over the next decade while saving money compared to current management of epidemics.

Meeting needs

About 450 million people in 25 African countries are at risk of epidemic meningitis, which killed 25,000 people in the largest-ever epidemic in 1996 and 1997.[2] These countries form a "meningitis belt" stretching from Senegal to Ethiopia.

Epidemics have devastating social and economic consequences as well as health effects. Fields go untended, markets shut down, workers lose wages, and families use scarce resources to pay for health care. A single case of meningitis can cost a family US$90, equivalent to three or four months of disposable income.[3]

In response to epidemics, countries have previously conducted reactive immunization campaigns using polysaccharide vaccines, which offer only limited protection and can be difficult to obtain quickly. The cost of a reactive campaign can reach

5 percent of a country's annual health budget.

In 2001, PATH and WHO formed the Meningitis Vaccine Project (MVP) to develop an affordable vaccine that could proactively provide long-lasting protection against African epidemics. Because African ministers of health said they could not afford to pay more than $0.50 per dose, the MVP team focused on staying below this cost ceiling.

Partnerships for accelerated vaccine development

MVP staff quickly realized that pharmaceutical companies in industrialized nations could not produce the vaccine at the needed price. After exploring alternatives, the team found a developing-country manufacturer, the Serum Institute of India Ltd., that could meet price targets.

Previous research had shown that chemically linking (conjugating) a protein to a polysaccharide antigen produces a vaccine that works better and provides longer-lasting protection. To acquire the technology needed to make a conjugate vaccine against Group A meningococcus, MVP partnered with the Center for Biologics Evaluation and Research at the US Food and Drug Administration. The US National Institutes of Health then assisted in transferring the technology to the Serum Institute of India at almost no cost. SynCo Bio Partners B.V., a Dutch firm, provided the meningococcal A polysaccharide needed for vaccine production.

To meet the simultaneous challenges of developing the vaccine, meeting regulatory and technical requirements, establishing clinical trials, and strengthening countries' ability to host the trials and administer the vaccine, the MVP team collaborated with three other key groups:

- A panel of pharmaceutical and clinical trial experts oversaw development of the vaccine.
- A group of specialized consultants helped to address specific questions or problems that arose as the vaccine was developed.
- A WHO project advisory group of senior African public health officials advised MVP on trial design and site selection.

This network of experts provided technical know-how and guidance that ultimately allowed MVP to develop the vaccine at a fraction of the typical cost of a new vaccine.

Clinical trials and vaccine introduction

The MVP team conducted clinical trials in meningitis belt countries and in India to test the vaccine's safety and efficacy while strengthening countries' capacity to host clinical trials. Based on the positive results, the vaccine was licensed by the Drugs Controller General of India and then prequalified by WHO for use in Africa.

To ensure successful introduction in Burkina Faso, Mali, and Niger, the MVP team coordinated technical assistance to strengthen disease surveillance and cold chain logistics and enhance laboratory capacity. MVP staff also provided stakeholders with information about the vaccine. In December 2010, the three countries launched immunization campaigns that reached nearly 20 million people by year's end.

Next steps

MVP and its partners are assessing the impact of immunization campaigns to date and preparing to roll out the vaccine to other high-risk countries. If additional funding can be secured, the project team hopes to vaccinate 315 million people over the next five years. An MVP analysis found that widespread vaccination in hyperendemic regions might prevent more than 140,000 deaths and 280,000 disabilities over a decade and save $350 million or more compared to current management of epidemics.

The new vaccine promises sweeping change across the meningitis belt. MVP's innovative partnership model and determination to meet price targets have brought elimination of African meningitis epidemics within reach. ■

Tool helps vaccine decision-makers

To help countries prepare for meningitis vaccine introduction, the Meningitis Vaccine Project developed an e-learning tool for African health program managers. The Advanced Immunization Management (AIM) module, published in both English and French, provides comprehensive information on meningococcal meningitis and the MenAfriVac™ vaccine from basic disease characteristics through immunization session planning.

The tool is part of a series of AIM modules. Others focus on vaccines for rotavirus, hepatitis B, and Japanese encephalitis; immunization financing; and measles control. They are available on CD.

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Cancer prevention

Stopping cervical cancer before it starts

HPV vaccine and other interventions make prevention possible in developing countries

Project names
HPV Vaccines: Evidence for Impact; Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention—Utility and Program Planning (START-UP)

Locations
India, Nicaragua, Peru, Uganda, Vietnam

Methods
Capacity-building, demonstration projects, public-private partnerships, vaccine introduction

Partners
Alliance for Cervical Cancer Prevention; Arbor Vita Corporation; Cancer Institute and Hospital, Chinese Academy of Medical Sciences; Cervical Cancer Action Coalition; governments of India, Nicaragua, Peru, Uganda, and Vietnam; International Agency for Research on Cancer; Jhpiego; QIAGEN; Tata Memorial Hospital (Mumbai, India); World Health Organization

Funder
Bill & Melinda Gates Foundation

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For more information on cervical cancer programs in the developing world, download PATH's May 2010 *Outlook* newsletter, available at http://www.path.org/publications/detail.php?i=1800.

Another good source of information is PATH's website on cervical cancer, www.rho.org/.

NEW EVIDENCE FROM PATH'S WORK in Latin America, Asia, and Africa shows that vaccinating girls to prevent human papillomavirus (HPV) infection is feasible through the public sector in developing countries. Because HPV is the primary cause of cervical cancer, future large-scale immunization programs may substantially reduce the global burden of this disease.

Cervical cancer kills about 275,000 women each year, with more than 88 percent of deaths occurring in developing countries.[1] The World Health Organization projects that the number of deaths may increase by 30 percent over the next decade unless prompt action is taken.[1]

Prompt action is needed to avert a projected 30 percent increase in cervical cancer deaths over the next decade.

Two vaccines are available to protect girls from cervical cancer—Gardasil® by Merck & Co., Inc., and Cervarix® by GlaxoSmithKline. Although these vaccines are extremely effective at protecting against the types of HPV that cause 70 percent of cervical cancer cases and are widely used in industrialized countries, they have been out of reach for most girls in developing nations. The cost of vaccine, which can be several hundred dollars per person, has been considered a major barrier to introduction. Even with the rapid decline in prices recently seen in developing countries, further price reductions will be needed before routine vaccination of girls and effective screening and treatment programs for adult women may reduce mortality in developing countries to the low levels seen in wealthy nations.[2]

Evaluating HPV vaccination strategies in four countries

PATH conducted studies in India, Peru, Uganda, and Vietnam to evaluate the most promising and cost-effective ways to reach girls 9 to 13 years old with HPV vaccine. Girls received three doses of donated vaccine over six months through programs at schools, health facilities, and community centers. More than 57,000 girls were vaccinated—or about 80 to 90 percent of those eligible in the demonstration areas. The vaccination campaigns united stakeholders from across the public health and education sectors, including teachers, health workers, and local and national leaders.

In all four countries, PATH learned that people generally believe in immunization and are motivated by fear of cancer. Once informed about cervical cancer and how it can be prevented, families embraced HPV vaccination.

Building on the project results, PATH developed helpful lessons for policymakers and program managers looking to shape their own HPV vaccination programs. The lessons cover a range of program topics, such as identifying venues

for vaccination, recruiting eligible girls, training health workers and teachers, and communicating with communities and families. Examples of lessons learned include:

- Delivering HPV vaccine through schools can achieve high coverage levels at reasonable incremental program costs.
- A vaccination program protocol can help to maintain quality, facilitate training, standardize delivery, and engender community trust.
- Visible endorsement by national and district government leaders is critical to community acceptance.

Reports on project results are available through www.rho.org/, a website on cervical cancer established by PATH.

Working to improve access to vaccines

Because HPV vaccines have previously been unaffordable for developing-country health systems, GlaxoSmithKline and Merck have pledged to offer their vaccines to low-income countries at significantly reduced prices. The GAVI Alliance has added both products to its list of priority vaccines, though it has not yet subsidized them because of ongoing budget deficits. The Pan American Health Organization (PAHO) has worked to make the vaccines much more affordable (less than $17 per dose in 2010) by engaging with vaccine suppliers and other stakeholders and purchasing vaccine in bulk through the PAHO Expanded Program on Immunization Revolving Fund.

PATH has actively advocated for cost-effective ways to bring HPV vaccines to developing countries. In addition, we have searched for low-cost solutions on a complementary and equally important front: development and use of new screening and treatment technologies.

Vaccines are not enough

Women who are already sexually active are less likely to benefit from HPV vaccination. After 30 years of age, women need to be screened and treated for pre-cancer or cancer. Even girls who are immunized need to be screened later in life because currently available vaccines do not protect against all cancer-causing HPV types.

In industrialized countries, the use of Pap tests has greatly helped to curb deaths from cervical cancer. In low-income countries, however, routine use of Pap tests has been problematic and unsustainable. For the past 15 years, PATH and our partners have assessed simpler, less expensive screening methods, such as visual inspection with acetic acid.

PATH has also explored the use of new, high-tech, and much more sensitive molecular tests—such as *care*HPV™, which provides results in about three hours. In addition to training health workers to use these tests, PATH has evaluated an approach that will allow women to collect vaginal samples in the privacy of their homes or in the clinic, without the need for a health professional or speculum exam. The results so far have been promising.

Ramping up the effort

Many people in developing countries have seen their mothers, grandmothers, aunts, and sisters suffer terribly from cervical cancer. Through demonstration projects, PATH has shown that girls who are properly informed will line up to receive a vaccine that can prevent the disease.

By cataloging and disseminating tools, results, and lessons learned, PATH is helping many countries ramp up efforts to prevent cervical cancer. We are also pushing commercial firms and other stakeholders to provide all elements of effective control programs—vaccines, screening, and treatment—at an affordable cost to women who need them most. ■

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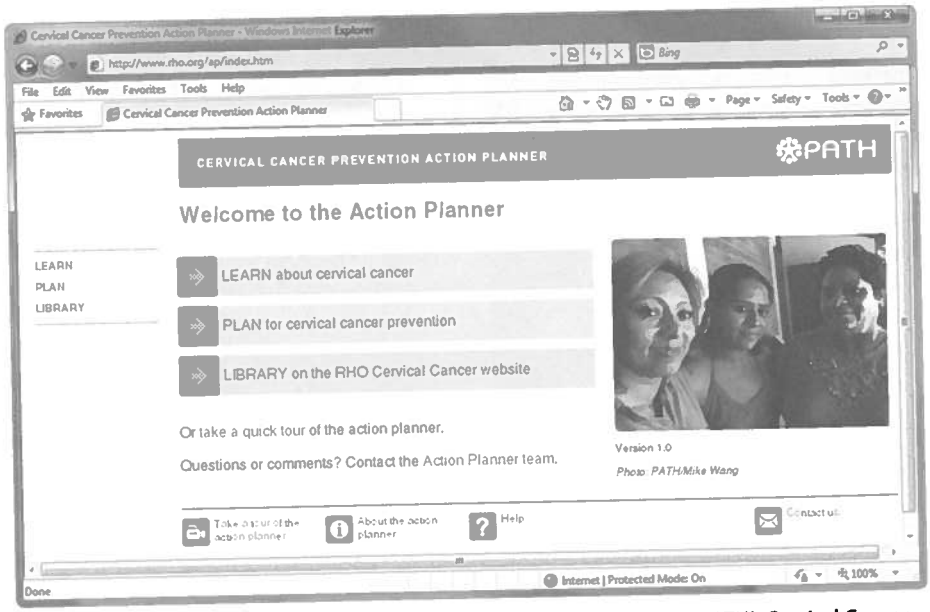

Public health officials can begin designing prevention programs by using PATH's Cervical Cancer Prevention Action Planner, available at www.rho.org/ap/. The Action Planner is an interactive tool that includes videos, mini-lectures, films, impact models, and other information and resources.

Transforming vaccine distribution

Project Optimize helps to redesign systems for a new era of opportunities and challenges

Project name
Optimize

Locations
Global

Methods
Advocacy, capacity-building, demonstration projects, health systems strengthening, operations research, procurement, technology development and introduction

Partner
World Health Organization

Funder
Bill & Melinda Gates Foundation

For more information

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The ultimate goal is to extend the benefits of vaccination to more people, especially in geographically remote areas.

FOR MORE THAN THREE DECADES, immunization programs around the world have dramatically reduced the burden of diseases such as polio and measles. Limitations of vaccine distribution systems, however, now hinder further expansion of these programs to save even more lives.

Project Optimize, a collaboration between PATH and the World Health Organization (WHO), is helping countries redesign distribution systems to meet growing needs. Project staff are working with health officials in several countries to test promising methods to improve supply and information systems. They are also exploring the potential for easing temperature requirements for vaccine storage and transport in some circumstances. The ultimate goal is to extend the benefits of vaccination to more people, especially in geographically remote areas.

Improving supply chains

Although immunization programs save more than 2.5 million lives each year, about 1.7 million children still die annually from vaccine-preventable diseases.[1] To further reduce the death toll, the world has invested heavily in new vaccines against rotavirus, pneumococcus, and other threats. Existing vaccine supply chains, however, were not designed to handle the growing number of vaccines, many of which are expensive and require substantial storage space. Also, the need to keep vaccines cold during storage and transport (in the "cold chain") has made it more difficult to use them in remote locations.

To improve vaccine supply chains, Optimize is working with government partners in several countries to test new approaches. In Senegal, for example, Optimize is collaborating with the Ministry of Health to integrate previously separate vaccine and medical supply chains and implement a "moving warehouse" system in the Saint-Louis region. Each month, workers use a large truck and a pickup to distribute supplies directly from regional facilities to peripheral health centers. Each vehicle has a web-enabled computer connected to a logistics management information system for sharing information in real time with multiple levels of the health system. Workers also maintain refrigerators at health centers and collect data on use of vaccines and supplies.

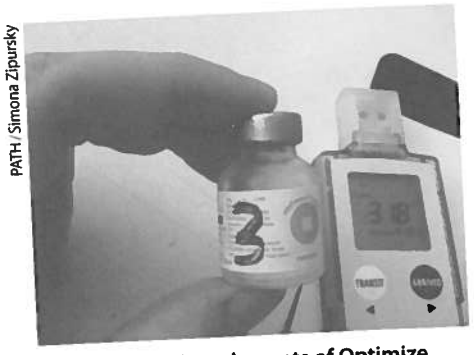
Introducing reliable, alternative sources of energy

Because high energy costs and unreliable power supplies are major problems for many immunization programs, the Optimize team is exploring use of alternative energy sources for vaccine distribution. In Tunisia, the team is piloting use of solar panels at regional and district stores to produce enough energy for storing vaccine and for charging an electric vehicle.

In Senegal, Optimize is testing use of battery-free solar refrigerators at outlying health centers and retrofitting regional vaccine storage facilities with solar technology. And in Vietnam, the project team is piloting use of new small-volume passive cooling devices, which may be especially suitable


M. Dorgabekova


WHO/Olivier Ronveaux


PATH/Simona Zipursky

Improving transportation of vaccines under tough conditions and monitoring temperatures in the cold chain are key elements of Optimize.

for short-term vaccine storage at commune health centers.

Upgrading information systems

Improving information systems is a critical part of the effort. In Albania, for example, the team is helping selected areas transition from paper-based, decentralized immunization registries to computerized, web-based records. Health workers in remote villages without Internet access can use mobile phones to connect. Potential benefits of the new system include:

- Accurate forecasts of vaccine demand.
- Ability to track each vaccine dose back to a vaccine lot in the case of a recall.
- Improved analysis of immunization coverage.
- Ability to send automated reminders to increase immunization rates.
- Potential for improved reporting of adverse events following immunization.

In Vietnam, vaccine refrigerators at all levels are being equipped with a communications device to improve tracking and tracing of vaccine lots. The device allows easy data entry through a barcode reader and keypad, and it uses mobile phone technology to communicate with a central server. Knowing the whereabouts of each vaccine lot helps program managers improve distribution planning and makes it easier to recall a lot when necessary.

Exploring temperature requirements

Although some vaccines lose potency when outside the cold chain for even short periods, others do not. Allowing heat-stable vaccines to spend time outside the cold chain under controlled temperatures for specific periods may have a number of benefits. These include facilitating outreach to hard-to-reach areas, freeing up valuable space in refrigerators, delivering vaccines exactly when needed (for example, hepatitis B vaccine dose at birth), and reducing risk of freeze damage when vulnerable vaccines are transported in ice.

Optimize is developing evidence for countries that want to explore use of a "controlled temperature chain" for some vaccines. In Mali, for instance, Optimize documented practices during an oral polio vaccine campaign in which vaccine was transported without icepacks. Even though the vaccine was out of the cold chain for up to seven hours, vaccine vial monitors (which indicate heat exposure over time) showed that all vaccine remained potent at the time of use.[2]

A study in Chad likewise found that vaccine vial monitors could reliably assess potency of oral polio vaccine kept out of the cold chain for up to 87 hours. In Papua New Guinea, a case study found that a birth dose of hepatitis B vaccine could be delivered more reliably when community health workers and volunteers could transport the vaccine without icepacks for short periods.

Optimize is also working to define a regulatory pathway to relabel specific, suitable vaccines for use in a controlled temperature chain. Staff are conducting laboratory-based research to gather necessary scientific evidence on the practice, in collaboration with manufacturers and WHO's Quality, Safety, and Standards team.

Shaping the future

By improving supply systems and investigating how to take full advantage of current information and communications technologies and vaccines' heat-stability profiles, Optimize is helping to model the vaccine distribution systems of the future. It is also empowering policymakers with information to guide national decision-making. More effective and efficient vaccine distribution systems will help to prevent millions of needless deaths by expanding the reach and scope of immunization programs around the world. ■

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Expanding the reach of rotavirus vaccines

Improving access to current and future tools to prevent diarrheal disease

Project names
Accelerated Vaccine Introduction Initiative, Advancing Rotavirus Vaccine Development Project, Rotavirus Vaccine Program

Locations
Australia, Bangladesh, China, Ghana, India, Indonesia, Kenya, Malawi, Mali, Mexico, Nicaragua, South Africa, Vietnam

Methods
Advocacy, clinical trials, public-private partnerships, vaccine development and introduction

Partners
Bharat Biotech International Ltd., China National Biotec Group's Wuhan Institute of Biological Products, GAVI Alliance, Johns Hopkins Bloomberg School of Public Health, Murdoch Childrens Research Institute, UNICEF, US Centers for Disease Control and Prevention, World Health Organization

Funders
Bill & Melinda Gates Foundation, GAVI Alliance, UK Department for International Development

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INFECTION WITH ROTAVIRUS is the leading cause of severe and fatal diarrhea among young children around the world. Each year, more than 500,000 children under five years of age die from diarrheal disease caused by rotavirus, and millions more are hospitalized. Most deaths occur in developing countries.[1]

Rotavirus is highly contagious and resilient, and improvements in water quality and sanitation that stop many diarrhea-causing bacteria and parasites do not adequately prevent its transmission. Two commercially available rotavirus vaccines—one manufactured by GlaxoSmithKline and one by Merck & Co., Inc.—are currently the most effective tools for defending young children from serious illness.

For the past decade, PATH has worked with the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), the GAVI Alliance, and other groups to study the performance of rotavirus vaccines and speed their delivery to resource-poor settings. We have also supported development of new vaccines to overcome limitations of currently available products related to manufacturing capacity and cost. Used as part of a comprehensive approach to preventing diarrheal disease, rotavirus vaccines will help many more children in developing countries reach their fifth birthday.

Increasing access to existing vaccines

By assessing the burden of diarrheal disease caused by rotavirus and conducting clinical trials and epidemiological studies in low-resource settings, PATH and our partners have built an evidence base to support rapid introduction of existing vaccines in the developing world. In 2006, we helped Nicaragua become the first developing country to introduce rotavirus vaccine. With more than 80 percent of young children vaccinated in the year after the vaccine was introduced, Nicaragua's hospital beds are now virtually empty of rotavirus cases. In low-resource settings in Africa where rotavirus burden is very high, clinical trials of rotavirus vaccines by PATH, WHO, and the CDC demonstrated their lifesaving potential, with the vaccines significantly reducing the incidence of severe rotavirus among infants.[2]

After evaluating evidence from these and other studies, WHO recommended including rotavirus vaccines in all national immunization programs. Although more than 20 middle- and higher-income countries have introduced the vaccines through the public sector, the cost has put these vaccines out of reach for most children in low-income nations. Currently, rotavirus vaccines have been introduced in four low-income countries: Bolivia, Guyana, Honduras, and Nicaragua.

To make rotavirus vaccines available to all children, GAVI launched the Accelerated Vaccine Introduction Initiative in 2009. Led by WHO and UNICEF, the initiative aims to speed and expand access to rotavirus vaccines (as well as pneumococcal vaccines) and to create a platform

for introducing other new vaccines. Project partners include PATH, the CDC, and the Johns Hopkins Bloomberg School of Public Health.

Existing vaccines, however, are insufficient to solve the global problem of diarrheal disease due to rotavirus. Even if these vaccines can be made more affordable, they may be less effective in settings where children are malnourished or fighting other pathogens.[2] Also, the manufacturers of currently available vaccines have limited capacity to meet potential global demand.

Support for new solutions

PATH is addressing limitations of existing vaccines by evaluating ways to improve upon them and supporting development of new vaccines from emerging-country manufacturers. The goal is to ensure adequate supply of vaccine and affordability in high-burden, low-resource settings.

One promising rotavirus vaccine candidate is 116E, being developed by Indian manufacturer Bharat Biotech International Ltd. Since 2001, PATH has been a part of a collaborative effort to evaluate 116E, moving it through early and advanced-stage clinical trials.

PATH is also helping to advance a bovine-human reassortant vaccine developed by the US National Institutes of Health. We are offering a "shared technology platform" to emerging-country manufacturers actively developing the vaccine so they can cost-effectively share technologies, training tools, methodologies, and other materials.

A third live vaccine supported by PATH is RV3, which is being developed by Murdoch Childrens Research Institute in Australia. Unlike the other rotavirus vaccines and vaccine candidates, which are first administered to infants between six and eight weeks of age, RV3 is being designed for initial administration at birth. Because newborns are especially vulnerable to infection, very early vaccination may be helpful for preventing deaths.

Further down the road, nonreplicating rotavirus vaccine (NRRV) candidates may be added to the global portfolio, potentially overcoming the efficacy limitations that live, oral vaccines encounter in developing countries. Although several organizations have been developing NRRVs, none of these vaccine candidates has been evaluated in humans. PATH has identified four candidates for possible advancement to proof-of-concept clinical studies and is now working to move them toward early clinical development.

Comprehensive control

Although rotavirus is the most common cause of fatal diarrhea, 60 percent of deaths from diarrhea are not attributable to rotavirus and are associated with unsanitary living conditions and unsafe drinking water. PATH frames all of our rotavirus work in the context of comprehensive control of diarrheal disease and pursues an advocacy strategy that shows how the vaccines can fit into a larger set of prevention and treatment interventions. These interventions include hand-washing, sanitation, breastfeeding, oral rehydration therapies, zinc, and vitamin A supplementation.

PATH will continue to work with global health stakeholders to bring rotavirus vaccines to more children in the world's poorest regions. The end goal is not just to prevent deaths from rotavirus but to defeat diarrhea as a major killer in developing countries. ■

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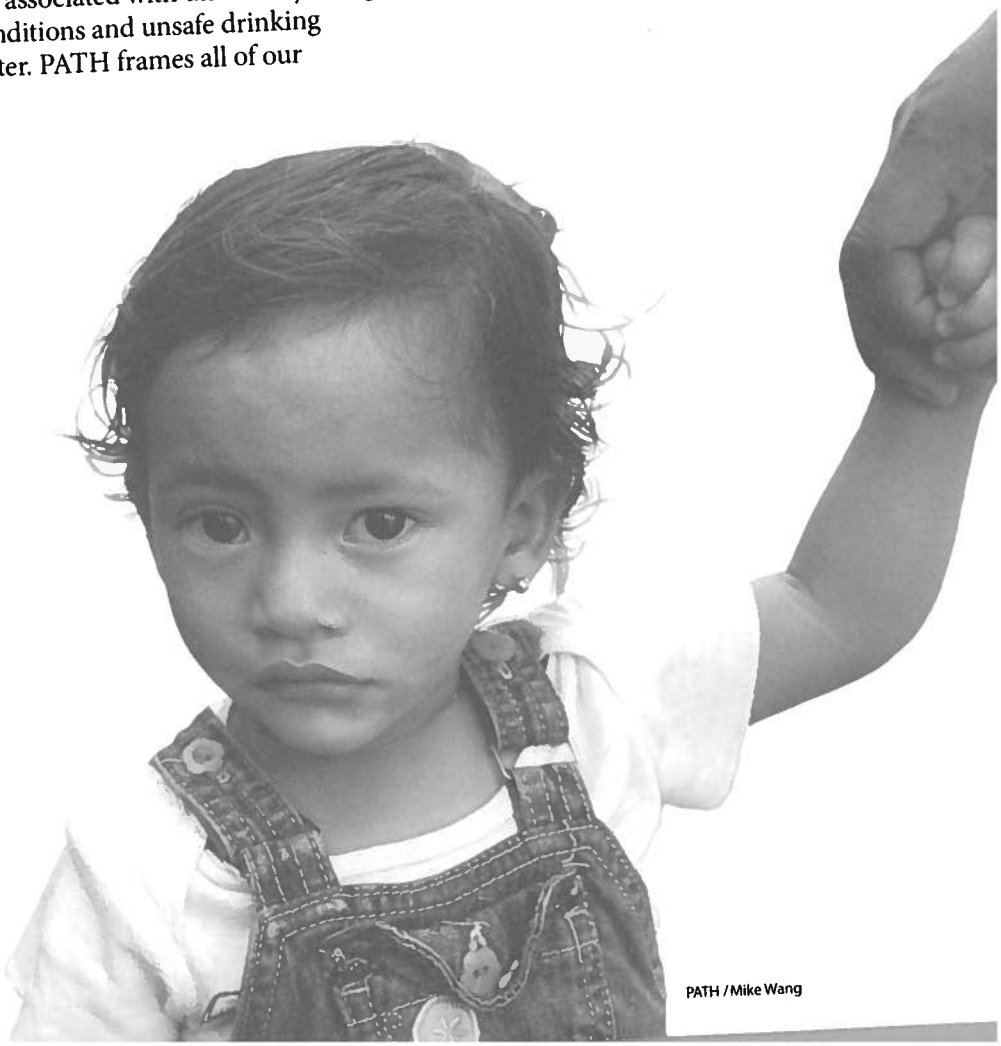

PATH / Mike Wang

Advancing vaccine technologies

PATH explores innovations to enhance safety, effectiveness, and ease of use

Primary project names
Disposable-Syringe Jet Injectors, Enteric Vaccine Initiative, Mucosal Immunization Technologies

Locations
Global

Methods
Research, technology development

Partners
Oregon Freeze Dry, Inc., Bioject Medical Technologies Inc., PharmaJet

Funders
Bill & Melinda Gates Foundation, Global Polio Eradication Initiative, Health Innovation Portfolio at PATH, World Health Organization

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PATH/Patrick McKern

Fast-dissolving tablets may be an especially good way to administer some vaccines.

DEVELOPING TECHNOLOGIES to make delivery of vaccines and other medicines safer, more effective, and more convenient has been a critical area of focus for PATH and our partners since the 1980s. Recently, we have worked to develop promising new vaccine formats to enable vaccinations without the use of needles and syringes—minimizing the pain of administration as well as the biosafety risks and disposal issues associated with the use of sharps. These novel formats include two methods to successfully deliver vaccine through mucosal, oral routes.

We are also advancing novel needle-free devices to enable intradermal vaccine delivery (see sidebar on page 11). In addition, we are developing formulation and processing methods to improve the ability of vaccines to withstand exposures to temperature extremes during storage and transport (featured in the May 2008 issue of this newsletter).

Addressing barriers to mucosal immunization

AIDS, tuberculosis, acute respiratory-tract infections, and diarrheal diseases account for millions of deaths each year. All are caused by pathogens that enter the body through mucosal tissues, the moist tissues lining the respiratory, gastrointestinal, and reproductive tracts. Vaccines that can be administered via the mucosa hold great promise because the mucosa is home to key antibodies and cells that can be activated to enhance the body's defense against pathogens.[1] Because they are delivered without needles, oral mucosal vaccine products will also likely be easier to administer and transport than traditional injectable vaccine products.

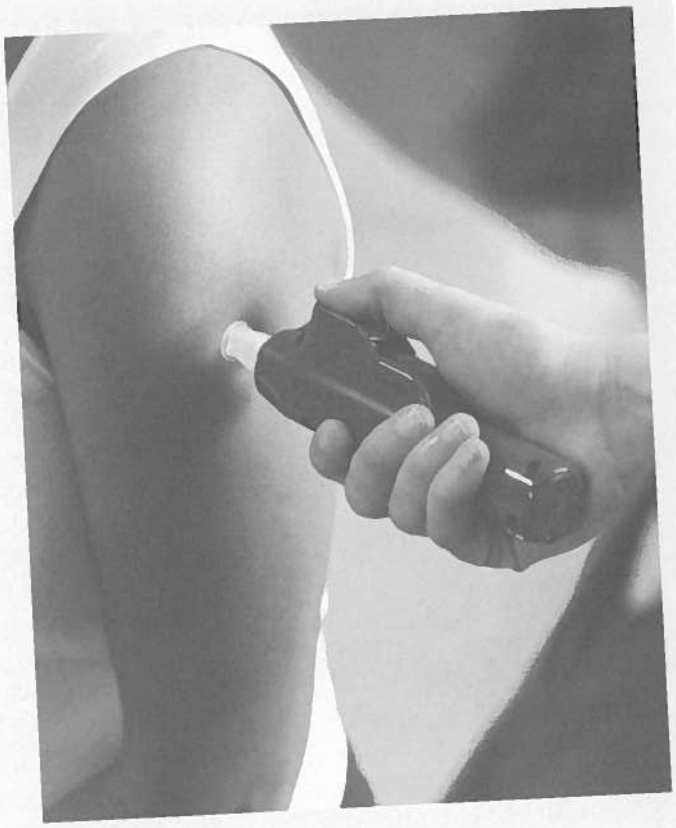
PATH recently set out to solve a number of technical challenges associated with previous attempts at mucosal immunization. We developed a technology platform—viable in two formats—to enable the efficient administration of certain vaccines via the mucosal surfaces under the tongue. Both formats contain a thermoresponsive polymer, a penetration enhancer, a muco-adhesive agent, and a safe as well as potent adjuvant that helps prevent rapid clearance by salivation or swallowing, which together help to induce a strong immune response.

The first format is a liquid solution at room temperature that instantly transforms into a gel at human body temperature, enabling it to adhere to mucosal surfaces. Its gel matrix protects the vaccine antigen from degradation caused by salivary enzymes. The second format is a fast-dissolving tablet that disintegrates instantly in a small amount of liquid. Evaluations using *in vitro* assays and animal models suggest that both formats may be applicable to a number of vaccines that prevent infections of the respiratory, gastrointestinal, and reproductive tracts.

Advancing intradermal vaccine delivery with needle-free jet injectors

Intradermal (ID) delivery of some vaccines can provide full immunity while using up to 80 percent less vaccine than is needed for subcutaneous or intramuscular injection. Devices that facilitate ID delivery may someday help immunization programs stretch limited vaccine supplies across a larger number of people, potentially reducing costs. Because it is difficult to ensure accurate ID delivery with a traditional needle and syringe, PATH is researching novel technologies to improve the reliability and effectiveness of this method.

In collaboration with the World Health Organization and the Global Polio Eradication Initiative, PATH and Bioject Medical Technologies Inc. are advancing research on Bioject's ID Pen, a spring-powered, needle-free jet injector to improve the safety and ease of ID delivery for polio vaccine. PATH is also helping to demonstrate the acceptability, sustainability, and cost-effectiveness of jet injectors—plus the feasibility of using them for ID vaccine delivery—in a number of settings. PATH partner PharmaJet recently received US Food and Drug Administration clearance for its jet injector for ID delivery, paving the way for needle-free ID delivery and product commercialization worldwide.



PATH/Scott Areman

Exploring use of fast-dissolving tablets to prevent diarrheal disease

Infants and young children in some low-resource settings are particularly vulnerable to enterotoxigenic *Escherichia coli* (ETEC). These bacteria can cause severe diarrhea and dehydration, leading to 300,000 to 500,000 deaths each year.[2] Although no vaccine has been approved to target these bacteria, PATH is advancing the development of ACE527, a promising candidate for immunization of children in ETEC-endemic countries.

PATH scientists have recently investigated use of the fast-dissolving tablet (FDT) technology platform—which employs a standard lyophilization (freeze-drying) process—as an inexpensive, scalable, and easy-to-use product presentation for ACE527 and other vaccines. Packaged in unit-dose foil blisters that better protect the product from moisture, the FDTs may help to reduce the overall bulk volume of vaccine during storage and transport.

After evaluating a series of formulations and optimizing the freeze-drying process parameters, PATH identified a lead FDT formulation with desired properties, including rapid disintegration in less than 10 seconds. This formulation also has excellent storage stability at 4°C, with no appreciable loss of viability over six months. After rapid reconstitution with a buffer, the vaccine dose could potentially be orally delivered to children with a liquid dropper. PATH researchers are also exploring whether ACE527 FDTs can be designed to dissolve instantly in a small amount of saliva—which would further ease administration by eliminating the need for reconstitution.

Looking ahead

PATH has advanced many technologies that have enhanced the effectiveness, efficiency, and safety of immunization programs around the world. Our current portfolio of vaccine technologies—in various stages of product development and commercialization—holds promise for further improving delivery of vaccines, helping to safeguard even more lives in the years ahead. ■

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1. Neutra MR, Kozlowski PA. Mucosal vaccines: the promise and the challenge. *Nature Reviews Immunology*. 2006;6(2):148–158.
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News and notes

APHIA*plus* project highlighted in report and video

A report by the Center for Strategic and International Studies' Global Health Policy Center and a related video highlight the PATH-led APHIA*plus* project as an example of how to integrate health services to better meet developing-country needs. The report and video are featured on the US Global Health Initiative's new website (www.ghi.gov/) and are based on a visit to Kenya by Dr. Christopher J. Elias, PATH's president and CEO, and three Global Health Policy Center members.

Decade of Vaccines Collaboration launched

To fully realize the lifesaving potential of vaccines, the World Health Organization, UNICEF, the US National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation launched the Decade of Vaccines Collaboration in late 2010. The group is coordinating work across the international community to create a global vaccine action plan, to be completed in 2012. PATH president and CEO Dr. Christopher J. Elias serves as co-chair of the Decade of Vaccines Collaboration steering committee and secretariat.

Chinese manufacturers to produce water treatment devices based on PATH prototype

PATH's Safe Water Project finalized agreements with three Chinese manufacturers that will develop, produce, and sell gravity-fed household water treatment devices based on a PATH prototype. To create a competitive market, each manufacturer will alter the product design based on its market knowledge. Designed for use in low-income households, the products will be sold to distributors and retailers who will then brand and sell them in neighboring countries. For more information on PATH's Safe Water Project, see www.path.org/projects/safe_water.php.

PATH/Patrick McKern

PATH developed a prototype household water treatment device by applying principles of user-centered design.

Phase 2 pneumococcal vaccine trial begins in The Gambia

PATH and our partners in a pneumococcal vaccine project launched a two-stage phase 2 clinical trial of a vaccine against *Streptococcus pneumoniae* in Fajikunda, The Gambia. The vaccine, which employs an innovative combination of protein and conjugate vaccine technologies, is designed to protect against a broader range of pneumococcal serotypes than do currently licensed vaccines. For more information on the project, see www.path.org/projects/pneumococcal_protein_vaccine_project.php.

New resources on vaccines and immunization

PATH and BIO Ventures for Global Health recently published a report, *The Case for Investment in Enterotoxigenic* Escherichia coli *Vaccines*, that highlights potential markets for vaccines against one of the leading bacterial causes of diarrhea. Another report, *Immunization Logistics and Supply Systems: From Vision to Action*, describes how PATH and the World Health Organization convened stakeholders to discuss the needs of developing-country immunization programs. Both documents are available through PATH's online publications catalog at www.path.org/publications/.

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. For more information, please visit www.path.org.

Directions in Global Health shares information about PATH's programmatic work with colleagues around the world. To subscribe, please send your contact information to publications@path.org. To learn more about PATH's work, visit the PATH website or subscribe to one or more of our electronic newsletters. These include *News From PATH* and several topic-specific e-newsletters. To subscribe, go to www.path.org/sign-up.php#news.

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