Cervical Cancer Prevention Initiatives at PATH

Two decades of progress toward a world free of HPV-related cancers

PATH
A catalyst for global health

PATH first began to focus on the problem of cervical cancer in 1991, supported by a small amount of seed funding from the World Bank. Over nearly two decades our portfolio has grown tremendously, with the most rapid expansion since 1998 and thanks in large part to grants from the Bill & Melinda Gates Foundation. Our four key areas of interest are summarized in the box at right, and are described in depth later in this report.

Background: cervical cancer and HPV

Human papillomavirus, or HPV, is the primary cause of cervical cancer. HPV is a common sexually transmitted infection (STI) that many women acquire at some point in their lives, although most will not develop cervical cancer as a result. Two new vaccines can prevent infection with HPV types 16 and 18, which account for 70 percent of cervical cancer cases worldwide. The vaccines have been proven at least 90 percent effective in safely preventing these two types when administered prior to onset of sexual activity.

In industrialized countries, even before the vaccines were developed, screening programs (traditionally using Pap smears) helped detect and treat the precursors of cervical cancer, saving countless lives. Routine Pap screening (cytology) continues to be a powerful tool in those places where it can be used effectively. But low-resource countries do not have the laboratories and trained technicians necessary to implement effective cytology-based programs, with the result that the vast majority of women cannot access screening or treatment. Of the estimated 270,000 annual cervical cancer deaths worldwide, 85 percent occur in developing countries (see box on page 2). The loss of these productive adult women rends the fabric of their families, villages, and nations.

PATH/Amynah Janmohamed

School girls in Piura, Peru.

PATH cervical cancer prevention initiatives

- **HPV vaccination**—operations research exploring a variety of strategies for effectively delivering vaccine to girls in the developing world, plus analysis and computer modeling of supply and demand scenarios necessary to build a comprehensive evidence-base for national and global decision-making (page 1).
- **Innovative approaches to screening in low-resource settings**—low-cost solutions for situations where cytological (Pap smear) screening has not proven feasible, such as visual inspection and molecular HPV tests designed especially for developing world conditions (page 7).
- **Improved precancer treatment using cryotherapy**—development and introduction of more reliable equipment for low-resource settings (page 9).
- **Advocacy for comprehensive cervical cancer prevention**—global partnerships and dissemination of science-based information for policymakers, program planners, clinicians, and the public (page 10).

Vaccinating young adolescent girls against HPV—while simultaneously improving cancer screening for older women—could reduce developing country cancer deaths to the very low levels currently observed in many developed countries. Yet there are many challenges to ensuring that vaccines, screening, and treatment become available to those who need them most. Cervical cancer, while a serious problem, is not well-known or understood in many communities, making education and advocacy another top priority.

Following are descriptions of PATH's contributions to the field, with a focus on activities in recent years. For additional information about HPV and cervical cancer, consult the resource guide at the end of this report.

PATH's *HPV Vaccines: Evidence for Impact* project

In 2006, shortly after new vaccines against HPV became available, PATH launched the *HPV Vaccines: Evidence for Impact* project. As mentioned previously, most cervical cancer deaths occur in developing countries. And while most of those countries have achieved good vaccine coverage for infants and very young children, HPV vaccine is intended for an older population—girls aged 9 and above. It is rare for developing world immunization programs

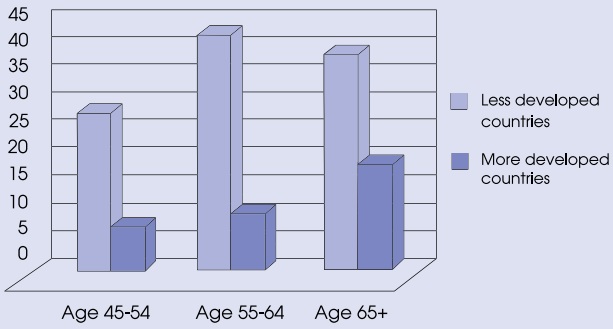
to have robust systems for reaching young adolescents, so the question becomes "how and where can we best reach young adolescent girls with HPV vaccine?" Furthermore, the fact that the vaccine generally is offered only to girls, and that HPV usually is transmitted through sexual contact, raises potential social and cultural concerns which must be addressed through carefully designed communication programs. Understanding existing health systems and opportunities and developing educational messages that resonate with girls, their parents, and others are keys to success.

The PATH project seeks to address these challenges by:

- Generating an evidence base for decision-making about public sector introduction of HPV vaccines, with an emphasis on researching vaccine introduction in four developing countries—India, Peru, Uganda, and Vietnam.
- Leveraging vaccine introduction activities to inform and support global advocacy efforts, regional HPV vaccine strategies, and introduction in other countries.
- Developing and disseminating strategic forecasts, investment cases, and decision-making tools to inform and influence industry production capacity and pricing decisions, international agency financing initiatives, and country government introduction plans.

The project is not a clinical trial of a new vaccine—the vaccines used in the project are already licensed in over 100 countries. Instead, the project aims to assess and document the best possible approaches to HPV vaccine delivery, and to address global issues of HPV vaccine availability. The project will be completed in 2011.

Age-specific cervical cancer mortality rates per 100,000 women



Source: Globocan 2002

Many more women die of cervical cancer in the developing world than in wealthier countries. In the industrialized world, effective screening programs help to identify precancerous lesions at a stage when they can easily be treated. But lack of screening programs in poorer countries means that the disease is not identified until it is too late, resulting in higher mortality.

Shaping strategies for HPV vaccine introduction

PATH is collaborating with many partners, including ministries of health and other government agencies, industry, and communities, to explore the most acceptable strategies for vaccinating young adolescent girls against HPV in India, Peru, Uganda, and Vietnam. The work is being implemented in three phases:

- Formative research to explore the knowledge, attitudes, and beliefs of diverse audiences, and to better understand health system and policy factors.
- Operations research (demonstration projects), informed by formative research data, to evaluate various strategies for reaching girls with HPV vaccine.
- Rapid dissemination of lessons learned to serve as an evidence base for governments that wish to develop or scale up cervical cancer prevention programs.

Formative research

During the first two years of the project, PATH and our partners conducted formative research in each country to better understand the medical, policy, fiscal, and sociocultural environments in which the demonstration projects would be implemented and to guide their design. PATH staff collaborated closely with local researchers, using a variety of qualitative and quantitative research methods. The teams met with national and regional stakeholders, policymakers, health care providers, parents, young adolescents, and other community members to understand which factors are most likely to result in a child receiving the HPV vaccine and which factors are most likely to foster institutional decisions that result in successful vaccine delivery. In addition to exploring target audience knowledge and attitudes about cervical cancer, the research teams also investigated clinic and school health programs, assessed equipment and training needs, and mapped the policy environment related to new vaccine introduction.

Summary of results: Overall, the research demonstrated low levels of knowledge and awareness regarding cervical cancer, HPV, and the HPV vaccine in all four countries. When given more information, however, most people responded positively about the HPV vaccine. Specific concerns about the vaccine and important health systems or policy obstacles were also identified in each country, and locally appropriate strategies were developed to address them (see box on page 3 and communication materials on page 6).

Demonstration projects

Drawing on the results of the formative research, PATH is working with national health officials and other local partners to design effective vaccine delivery strategies, appropriate communication approaches, and targeted advocacy efforts. The delivery strategies will be evaluated through demonstration projects in terms of vaccine coverage achieved and program feasibility, acceptability, and cost.

For example, formative research participants in all four countries supported school-based delivery of the HPV vaccine, along with additional efforts to reach girls who do not attend school. Some respondents in Uganda and Vietnam expressed strong support for also assessing HPV vaccine delivery in the community or at health clinics. In these two countries, a school-based vaccine delivery strategy will be compared with a strategy using existing, non-school outreach systems. In Uganda, a semi-annual event called Child Days Plus delivers an integrated package of preventative services (e.g., catch-up immunizations, vitamin A supplementation, and deworming medicine) to older children through health centers, churches, community centers, and schools. The Uganda project therefore will measure the effectiveness of school-based delivery compared with delivery through Child Days Plus. And in Vietnam, where there is a strong facility-based vaccination system already in place, the demonstration project will compare delivery of the HPV vaccine through schools with delivery through commune health centers.

Demonstration project timelines are a bit different in all four countries, in part due to the need to wait for the relevant vaccine to be licensed. The Peru demonstration project began first (June 2007), followed by Uganda (June 2008). At time of writing, India and Vietnam had not yet begun their demonstration projects, though it is anticipated that the vaccines will be licensed by national authorities by the end of 2008 or early 2009.

The Peruvian demonstration project differs slightly from the other countries because it is being implemented in two phases: a small study comparing two approaches to vaccination, followed by a scaled-up study that applies lessons learned from the first phase (see box on page 5).

Project update: On May 9, 2008, the second phase of Peru's demonstration project began with Minister of Health Hernán Garrido-Lecca in attendance. In the following months, more than 8,900 girls were vaccinated in over 700 schools. At the time of this writing, early demonstration project results in both Peru and Uganda show reasonably high levels of acceptance of the vaccine and very high continuation rates once a girl and her family consented to the first dose.

Cervical cancer, HPV, and vaccination: knowledge and perceptions from India, Peru, Uganda, and Vietnam

PATH/Robin Biellik

A girl receives HPV vaccine in Ibanda, Uganda.

PATH's formative research found that awareness of cervical cancer varies both within and among the four countries studied. For example, in Uganda, very few people recognized the term "cervical cancer," although many were able to accurately describe the condition's symptoms. In Vietnam, by contrast, 75 percent of parents in the study had heard of cervical cancer. Not many people had heard of HPV in any country, with the exception of some health workers in Uganda and Vietnam. In all four countries, once a general understanding was established, cervical cancer was perceived by most to be an important and very serious disease. As one teacher in India put it, "The mother is the heart of the family. If she got sick, the whole family would go into a depression."

Overall, participants in all four countries expressed that vaccination is important for preventing illness and has significant health benefits. One father in the Gulu district of Uganda reported that, "These days our children do not suffer from certain diseases like measles…I think it is because they started vaccinating children early in hospitals. That is the reason the disease is disappearing." In all four countries, when provided with objective information about the HPV vaccine by researchers, most participants responded positively. As one young adolescent girl in Peru stated, "We all have a right to receive that vaccine."

Participants in all countries did express concerns about side effects or possible long-term effects of the HPV vaccine. Concerns regarding fertility were expressed in Peru, Uganda, and Vietnam, due to the fact that the target group for this vaccine is young adolescent girls. However, it was widely noted in all countries that visible support from political and community leaders would go far in allaying people's doubts and fears. One participant in Vietnam explained, "The most important thing is to have support and leadership of people's committees and government agencies."

Vietnam alternative dosing schedule study

While the main focus of the *HPV Vaccines: Evidence for Impact* project is operations research, not clinical studies, one important clinical question will be addressed in Vietnam: do alternative dosing schedules for HPV vaccines—schedules that may mesh more effectively with country systems—offer the same levels of protection as the ideal dosing schedules suggested by the manufacturers?

Both HPV vaccines currently in the global market require three doses for full coverage. They also have similar vaccination schedules: the second dose is given either one or two months after the first dose, and the third dose is given six months after the first dose. However, it may be that more children could be reached more efficiently if the doses were offered quarterly, semi-annually, or annually. For example, the semi-annual Child Days Plus activities in Uganda create opportunities for providing the first and third vaccine doses only—special vaccination sessions will have to be organized to provide the second dose. But if the vaccine proves to be as effective when the doses are given six months apart—i.e., the second dose six months after the first and the third six months after that—it would be much easier for the girls and for the vaccinators, and may be less expensive for the government.

The PATH project in Vietnam will measure immune response generated by several alternative dosing schedules to determine whether there is any immunogenic disadvantage when using the vaccines in this way. The study began in October 2007 and will generate initial results in 2009.

Answering new questions about HPV vaccination: A small grants program

To supplement the data from the four HPV vaccine demonstration projects, PATH also has established a small grants program to answer targeted questions around HPV vaccination in other developing countries and non-project states in India. To date, the CSI Holdsworth Memorial Hospital in Karnakata, India, and the Instituto Nacional de Cancerologia in Bogota, Colombia, have been funded to conduct studies on knowledge and acceptability of the HPV vaccine among health workers and parents of adolescents. Pending approval by an ethical review board, Centro de Estudios de Estado y Sociedad (CEDES) in Argentina will receive support to evaluate the actual uptake of the vaccine among families who receive motivational messages about HPV immunization emphasizing a cancer prevention perspective, compared with those who receive an STI prevention perspective. In the coming months and years, PATH will continue to solicit applications for its small grants program. For more information, visit the RHO Cervical Cancer website at www.rho.org.

Making the case for investment in HPV vaccination

Identifying and mobilizing resources for vaccine purchase and delivery is one of the most significant challenges to making the HPV vaccine widely available in the developing world. Therefore, another important element of the *HPV Vaccines: Evidence for Impact* project is to accelerate key supply, demand, and financing decisions related to HPV vaccines. As part of our country-level formative research, for example, PATH conducted baseline immunization financing assessments in each of the four countries. Also, as part of the demonstration projects, we are exploring affordability through estimating the program costs associated with introducing the HPV vaccine through different delivery strategies in each setting.

PATH is also working to map the process of decision-making in order to identify potential obstacles and develop creative and proactive ways to address them—for example, having data ready for governments and global

PATH/Amynah Janmohamed

A vaccinator in Vietnam meets with school girls to explain HPV vaccine.

actors before they are needed. A 2008 International AIDS Vaccine Initiative and PATH report, *HPV Vaccine Adoption in Developing Countries: Cost and Financing Issues*, provides an overview of some of these issues and is available at www.rho.org.

The GAVI Alliance, an immunization coalition of the world's top global health agencies, governments, and private partners, offers subsidized vaccines to over 70 countries of the developing world. Many low-income countries will rely on support from the GAVI Alliance to procure subsidized HPV vaccine. Generally, GAVI makes decisions about whether to allocate funds to support introduction of certain vaccines based on an investment case that analyzes the value of the vaccine. In the first year of the project, PATH convened a meeting of representatives from the World Health Organization (WHO), GAVI, vaccine manufacturers, and the Bill & Melinda Gates Foundation, among others, to develop the components of an investment case demonstrating the value of introducing the HPV vaccine in GAVI-eligible countries.

Cervical cancer…affects 500,000 women each year and leads to more than 250,000 deaths, the vast majority in poor countries…(GAVI's) strategy will attack some of the world's major killers and gives us a new challenge in our efforts to provide good health to the world's most vulnerable people.

Julian Lob-Levyt
Executive Secretary, GAVI Alliance

Two phases of Peru's demonstration project

The first phase of Peru's demonstration project, completed in January 2008, assessed the benefits and costs of "active follow-up" of school-based immunization, compared with simple provision of vaccine without active follow-up. Active follow-up included home visits for girls who missed first, second, or third doses of vaccine. The study team found that about 60 percent of girls accepted vaccination, regardless of whether they were actively followed-up or not.* Because follow-up did not really increase first-dose coverage, and had the potential to increase costs, follow-up after a missed first dose was was judged not to be a worthwhile approach.

An additional finding, however, was that drop-out rates were very low *between* doses of the vaccine. In other words, very few girls would require active follow-up after the second or third doses. Additionally, follow-up was considered important in terms of ensuring that those who initiated vaccination were fully protected (based on the current scientific evidence, which recommends three doses for full coverage). Therefore, in the second, scaled-up phase of the demonstration project, only those girls who received the first dose, but missed the second or third dose, are candidates for active follow-up. This is exactly the kind of evidence-based, programmatic decision-making that the project was meant to stimulate.

*Given that HPV vaccine is new and that study respondents were asked to sign consent forms for HPV vaccination (which does not happen for infant vaccines or other routine injections) the team considers 60 percent coverage in the first phase of Peru's demonstration project to be a success. The length and complexity of the consent forms seem to have increased parental concerns and to have been a significant barrier to vaccine acceptance. Preliminary data show that overall coverage in the second phase of Peru's project, when a simpler authorization form was used, reached about 85 percent.

PATH/Amynah Janmohamed

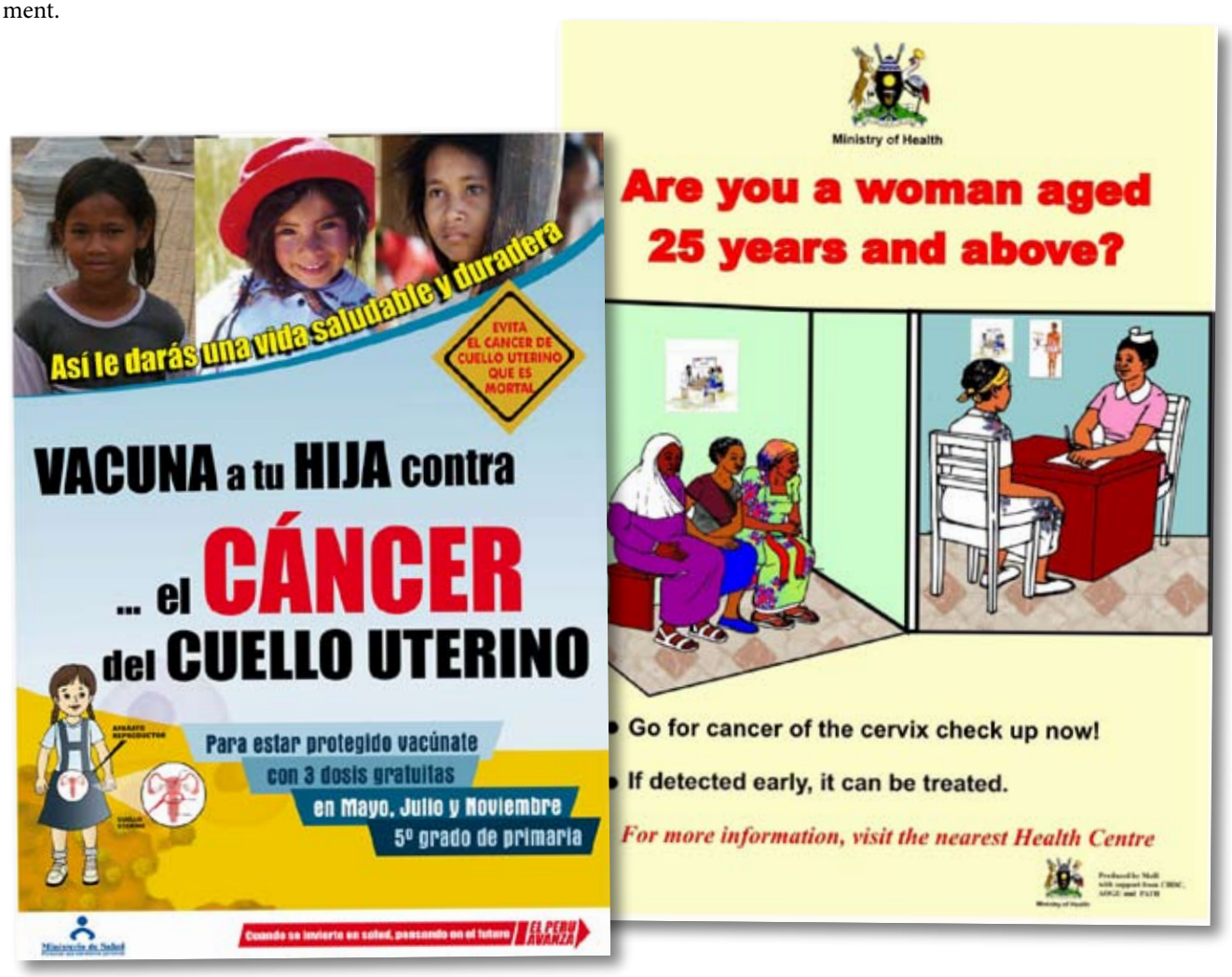
Girls in Piura, Peru display their vaccination cards after receiving HPV vaccine.

In order to build an HPV vaccine investment case for GAVI and other stakeholders, PATH has gathered and synthesized information on several components related to:

- The problem of cervical cancer, including the disease burden and challenges in preventing and managing the disease.
- The relevance of HPV vaccine and cervical cancer prevention to GAVI objectives and other international health priorities (e.g., the Millennium Development Goals and the WHO/UNICEF Global Immunization Vision and Strategy, or GIVS).
- The constraints on HPV vaccine delivery, and strategies for overcoming them.
- Cost-effectiveness in comparison or combination with other interventions.
- Supply and demand factors that will affect availability and access to the vaccine.
- Expected impact of vaccination at various levels of investment.

In June 2008, GAVI announced that it will include HPV vaccine among those it considers for future support.

Accurate vaccine demand estimates are also needed nationally, regionally, and globally to ensure a sufficient supply of vaccines and to support price negotiations. Working with the Boston Consulting Group, PATH developed a model for long-term demand, supply, and financing forecasting. As we move forward, data from the demonstration projects will be incorporated and used to refine global and country-level demand forecasts. PATH also worked with Applied Strategies Consulting to analyze the likelihood of additional HPV vaccine products entering the market, critical factors affecting HPV vaccine production costs, and the medium- and long-term evolution of the HPV vaccine supply landscape.



Community education and mobilization is crucial to successful cervical cancer prevention.

Innovative approaches to screening in low-resource settings

Working together to find alternatives

As mentioned earlier, HPV vaccination and cervical cancer screening programs are both needed to reduce related mortality, yet most developing countries lack the infrastructure and trained personnel needed to replicate the cytology-based, multi-visit approach used in wealthier countries to detect pre-cancer (Pap smears followed by colposcopy and biopsy). In an effort to find alternative strategies suitable to low-resource settings, PATH joined four other international agencies in 1999 to form the Alliance for Cervical Cancer Prevention, or ACCP.* Over the following nine years ACCP partners conducted studies comparing a number of screening techniques, including cytology, visual inspection methods using acetic acid (VIA) or Lugol's iodine (VILI), and a state-of-the-art HPV-DNA test. The tests were evaluated in over 20 low-resource settings around the world.

VIA has proven to be of special interest. ACCP found that VIA compares well to cytology in terms of sensitivity for disease detection, yet presents advantages because it requires fewer specialized personnel and less infrastructure, training, and equipment. Cervical cancer screening using VIA can be offered in remote, less equipped clinics, thereby reaching more women. Another important advantage is that VIA provides immediate results, making it possible to screen and either treat or refer women during the same visit. Immediate treatment, where available, means that women do not have to make an extra visit to the health center, thus reducing the number of women who are lost to treatment because they cannot return for one reason or another. In the ACCP studies, VIA has successfully been paired with cryotherapy, a relatively simple, inexpensive, and safe method of freezing affected

*The ACCP partners are EngenderHealth, International Agency for Research on Cancer (IARC), Jhpiego, Pan American Health Organization (PAHO), and PATH. The ACCP website can be found at www.alliance-cxca.org.

Alliance for Cervical Cancer Prevention 10 Key Findings and Recommendations for Effective Cervical Cancer Screening and Treatment

In 2007, ACCP partners developed the following findings and recommendations for global policy and practice based on previous key studies in India, South Africa, Peru, and Thailand:

1. Every woman has the right to cervical screening at least once in her lifetime. In low-resource settings, the optimal age for screening to achieve the greatest public health impact is between 30 and 40 years old.
2. Although cytology-based screening programs using Pap smears have been shown to be effective in the United States and other developed countries, it is difficult to sustain high-quality cytology programs. Therefore, in situations where health care resources are scarce, resources should be directed toward cost-effective strategies that are more affordable and to which access can be assured.
3. Studies have shown that the most efficient and effective strategy for secondary prevention of cervical cancer in low-resource settings is to screen using either HPV-DNA testing or VIA (visual inspection of the cervix after swabbing it with acetic acid), and then treat precancerous lesions using cryotherapy (freezing). This is optimally achieved in a single visit (currently possible with VIA plus cryotherapy) and can be carried out by physicians and non-physicians, including nurses and midwives.
4. The use of HPV-DNA testing followed by cryotherapy results in greater reduction of cervical cancer precursors than the use of other screening and treatment approaches.
5. Cryotherapy, when conducted by competent providers, is safe and results in cure rates of 85 percent or greater.
6. Studies suggest that cryotherapy is protective against the future development of cervical disease among women with current HPV infection. Because of this, and due to the low morbidity of cryotherapy, the occasional treatment of screen-positive women without confirmed cervical disease is acceptable.
7. Unless there is a suspicion of invasive cervical cancer, the routine use of an intermediate diagnostic step (such as colposcopy) between screening and treatment is generally not efficient and may result in reduced programmatic success and increased cost.
8. Women, their partners, communities, and civic organizations must be engaged in planning and implementing services, in partnership with the health sector.
9. For maximum impact, programs require effective training, supervision, and continuous quality improvement mechanisms.
10. Additional work is needed to develop rapid, user-friendly, low-cost HPV tests and to improve cryotherapy equipment.

cervical tissue. Cryotherapy can be done in a single visit, or later at a convenient referral site. Studies have shown that cryotherapy can be effectively and safely performed by trained nurses or midwives, in addition to physicians and gynecologists—though, as with all screening approaches, attention to consistent quality standards is key.

As the body of evidence on the safety and impact of single-visit approaches has accumulated over the past ten years, many countries have expressed interest in such strategies, and requests for assistance have exceeded the ability of technical agencies to respond. Countries like Thailand and the Philippines have implemented successful, large-scale, VIA-based programs, but more education and training are necessary if such programs are to expand regionally. As more global health leaders and international organizations urge health care providers to examine the evidence on alternatives to cytology, and as more providers hear about these alternatives, PATH expects that the new paradigms will be adopted, and adapted, for local situations.

Developing rapid screening tests

World health experts recommend use of HPV-DNA testing for primary cervical cancer screening, noting that it is at least as effective as cytology. Based in part on lessons learned by the ACCP, in 2003 PATH launched the Screening Technologies to Advance Rapid Testing (START) project. The project sought to develop two different HPV screening methods appropriate for use in the developing world. It was important that the tests be acceptable to women and their providers, relatively simple to use, accurate, affordable, and rapid, to allow for single-visit efficiencies.

By the time the project ended in 2008, START had developed a test based on the more complex Hybrid Capture II (HCII) test, produced by QIAGEN. The HCII test is not seen as suitable for low-resource settings because it requires laboratory equipment, refrigeration, and other resources often not available in the developing world. But the equipment used to analyze samples for the new test is portable and can be powered with rechargeable batteries, the reagents do not require refrigeration, and results are available in two to three hours. Test results are easy to read and, unlike cytology and VIA, are not vulnerable to misinterpretation.

Clinical performance of the new test was evaluated in China and India. In Shanxi, where 2,500 rural women were screened using vaginal and cervical samples, study results showed that the sensitivity of the test was much better than VIA and approached that of Hybrid Capture II. Results from India are still being analyzed. The test will be produced in China and commercialized in 2009.

The other test developed under the START project detects the E6 protein, levels of which may indicate the risk that HPV infection will progress to cervical cancer. The technology is still in development and current efforts are focused on improving the sample medium, simplifying sample preparation, and adding the ability to detect E6 proteins of the seven most prevalent high-risk types.

PATH recognizes that creation of new tests alone will not suffice. In developing countries, challenges exist to widespread adoption of new technologies. Before incorporating tests into national cervical cancer prevention strategies and plans, ministries of health need evidence that the tests are feasible and appropriate for their health system infrastructure and their geographic, cultural, and economic circumstances. In addition, private industry needs guidance navigating the complexities of product introduction in the public sector of developing countries, which are generally perceived as "high-risk and low-return" markets.

QIAGEN

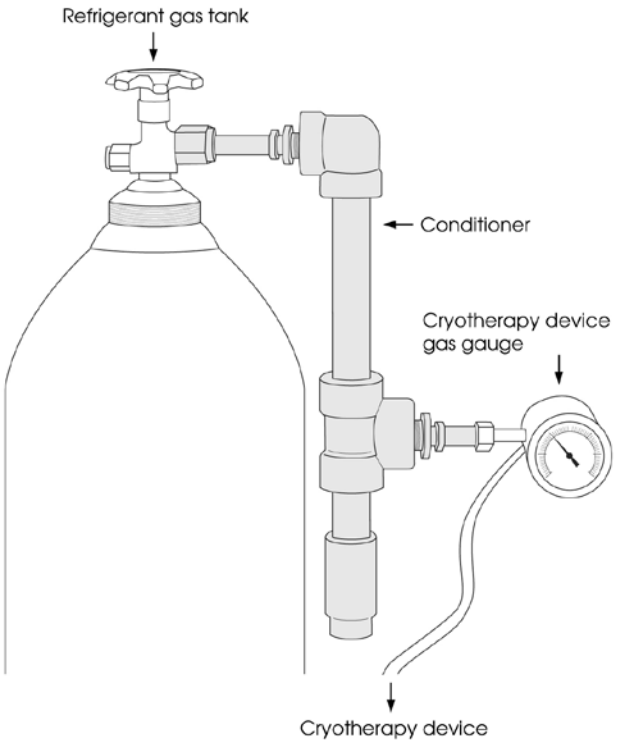
The careHPV™ test, an updated version of the Hybrid Capture II test, produced by QIAGEN.

To address these challenges of new technology introduction, in November 2007, PATH inaugurated a follow-up project to START, called START-UP. START-UP focuses on four sets of activities:

1. **Support and assist early-introduction projects to demonstrate the feasibility, effectiveness, and acceptability of the new, quicker HPV-DNA screening test within the context of developing-country public-sector health care systems.** Working collaboratively with ministries of health and other key stakeholders, START-UP will compare the new test against other screening strategies in India, Nicaragua, and Uganda. Concurrently, and as resources allow, PATH will assist other low- and medium-resource countries interested in the new screening tests to design projects and secure separate funding.
2. **Strengthen industry knowledge and understanding of developing-country public health care systems, policy and guideline decision-making, and supply and demand factors to be addressed in their public-sector commercialization plans for new rapid tests.** In order to accelerate access to the new test, PATH will assist our industry partner to map the regulatory approval process in the three project countries, map the health commodity procurement and distribution systems in the public sectors, and forecast potential demand for the test in the public and private sectors.
3. **Use lessons learned from the START-UP demonstration projects to inform other developing countries about the feasibility, effectiveness, and acceptability of the new test.** PATH will aggregate and analyze clinical and other data from the three demonstration projects, make presentations at regional and global conferences, and garner support for the new tests from WHO, International Federation of Gynecology and Obstetrics (FIGO), and other key agencies for use in advocating for and guiding developing-country cervical cancer prevention programs.
4. **Assess the clinical performance of E6 rapid-strip test prototypes in a low-resource setting.** START-UP also will assess the clinical utility of the E6 rapid-strip test, and E6 in general, as a means of detecting pre-cancerous lesions when used as a primary screening tool, and secondly as a means of predicting risk of progression from lesions to cancer. Evaluation results will guide future decisions about use of the technology.

Improved treatment using cryotherapy

PATH recognizes that it is important to develop programs offering comprehensive screening, diagnosis (where feasible), and treatment, not screening alone. In addition to identifying pre-cancerous lesions, visual inspection with acetic acid (VIA)—discussed in a previous section—also allows clinicians to assess treatment options for patients with HPV infection, determining which are candidates for cryotherapy in the local clinic and which must be referred to higher level care for more specialized treatment, such as the loop electrosurgical excision procedure (LEEP). When screening using HPV testing becomes more common, VIA for triage and cryotherapy for treatment will be needed to manage women with positive HPV test results. Current work to stimulate development of VIA and cryotherapy skills in developing countries can establish a service delivery platform prior to HPV test availability.



PATH's cryotherapy gas conditioner has been developed to prevent blockage of cryotherapy devices.

Developing better equipment for low-resource settings

As noted in the ACCP recommendations on page 7, cryotherapy (freezing cervical tissue that is likely to develop into cancer) is an appropriate treatment method for low-resource settings. It is effective, has limited side effects, does not require electricity, is inexpensive compared to other treatment options for precancerous lesions, is technically simpler than other methods, and can be performed by local health workers.

Cryotherapy units achieve freezing temperatures through use of compressed gas. Unfortunately, the cheapest and most commonly available compressed gas, carbon dioxide, leads to blockage of some cryotherapy devices as much as 50 percent of the time.* This blockage may prevent completion of the procedure or may result in warmer temperatures in the freeze

*Nitrous oxide, the most common gas used for cryotherapy in industrialized countries, is difficult to obtain in some areas of the developing world, and costs several times more than carbon dioxide.

probe. One method for preventing blockage is to intermittently "clear" the gas lines during the freezing process. This is known as the "cough" technique and is routinely taught during cryotherapy training—but PATH has identified limitations with this technique. The blockage problem, coupled with doubts about the cough technique as a solution, has raised questions about whether cryotherapy in its current form is an effective treatment for cervical precancer.

In response, PATH has developed an in-line "gas conditioner" which is placed between the gas tank and the low temperature cryotherapy probe. To date, product testing has shown promising results—the cryotherapy conditioner has eliminated the problem of tip blockage and did not negatively affect the temperature achieved by the device—a critical measure of treatment effectiveness. PATH currently is collaborating with WHO and other partners to determine next steps, which may include a market survey of existing equipment, bench testing of that equipment, creation of comprehensive repair manuals designed for developing world technicians, and improvement and field testing of the gas conditioner through a randomized clinical trial.

PATH's RHO Cervical Cancer website (www.rho.org) and PATH and Cervical Cancer Action's "Evidence of Developing Country Support for Improved Cervical Cancer Prevention" serve as key tools for communication and advocacy.

Advocacy for comprehensive cervical cancer prevention

As documented through PATH's formative research and other studies, accurate, in-depth knowledge about cervical cancer tends to be low worldwide. Education and advocacy initiatives implemented by PATH and our partners seek to raise awareness and help decision-makers, clinicians, and families make evidence-based decisions that could save lives.

Mobilizing communities globally

The issue of cervical cancer prevention has the potential to galvanize advocates from diverse fields, including cancer, reproductive health, gender equity, adolescent health, STIs, and immunization, to name a few. PATH knows from experience that the impact of many advocates could be far greater than that of one individual organization working independently. PATH was therefore instrumental in the creation of a new global advocacy coalition called Cervical Cancer Action (CCA) (www.cervicalcanceraction.org). Other key CCA partners include the Pan American Health Organization (PAHO), International Union Against Cancer (UICC), Cancer Research UK (CRUK), American Cancer Society (ACS), International Federation of Gynecology and Obstetrics (FIGO), the International AIDS Vaccine Initiative (IAVI), AIDS Vaccine Advocacy Coalition (AVAC), and the International Planned Parenthood Federation (IPPF).

Collaboration with CCA partners has generated many opportunities. For example, PATH and our CCA partners learned early on that WHO's Strategic Advisory Group of Experts (SAGE) had requested feedback from countries relevant to introduction of HPV vaccine, in time for their November 2008 meeting. In preparation for the meeting, PATH, in collaboration with CCA, produced one of the most innovative elements of its portfolio on cervical cancer prevention. "Evidence of Developing Country Support for Improved Cervical Cancer Prevention" is a dossier compiling personal letters of support from ministries of health, nongovernmental organizations, and individuals in Africa, Asia, and Latin America. The dossier also includes editorials, op-eds, resolutions, and declarations calling for improved cancer control, along with the names of the 1,200 people who endorsed CCA's online Global Call to STOP Cervical Cancer. In gathering and sharing these documents, PATH and CCA seek to raise awareness about the widespread support for better screening and vaccination programs. The dossier is a dynamic document, with new letters arriving each week. Look for the dossier on the RHO Cervical Cancer website (www.rho.org), where it has been posted for use by any interested advocacy group.

Disseminating the evidence base

Given the clear need for better access to scientifically accurate information on cervical cancer, one of the first communication and advocacy tools PATH developed under the HPV vaccine project was the RHO Cervical Cancer website (www.rho.org), a comprehensive library of cervical cancer infor-

mation. The website offers background papers, training materials, films, PowerPoint presentations, and a host of other documents and tools published by the world's leading HPV experts and organizations, including WHO, the US Centers for Disease Control and Prevention, US National Cancer Institute, UICC, PATH, and many others.

Sometimes news must be disseminated quickly, and waiting for users to visit a website is not adequate. PATH created HPVflash email updates to share timely, cervical cancer-related information around the globe. Recent alerts included news of the May 2008 declaration from the Americas supporting cervical cancer prevention and GAVI's June 2008 decision to consider prioritization of HPV vaccine. Users can subscribe to HPVFlash through RHO Cervical Cancer.

Additionally, since the beginning of the project, PATH staff have contributed to or published more than 30 articles or reports documenting evidence on cervical cancer prevention. One paper designed for broad distribution is the HPV issue of PATH's flagship reproductive health resource, *Outlook*. The 12-page document provides an easy-to-understand overview of the subject, and is available in English, Chinese, French, Spanish, Russian, and Vietnamese. PATH has also produced a "key points" document in collaboration with WHO and United Nations Population Fund (see list of resources on page 12).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Women participate in a mapping exercise during the PATH cervical cancer vaccine project formative research in Gujarat, India.

Conclusion

PATH is excited to have so many activities aimed at exploring the most effective strategies for improving cervical cancer prevention worldwide. We also are pleased to note that support for a comprehensive approach to cervical cancer prevention continues to grow at national, regional, and global levels:

- At a May 2008 meeting to discuss plans for **Latin America,** health officials and researchers from 21 countries formally declared their intention to "…strengthen prevention and comprehensive control [of cervical cancer] through improving coverage and quality of screening, diagnostics, and treatment services."
- From **India,** Member of Parliament Shabana Azmi recently wrote, "Although our country has been committed to end this disease for some time, we have not had the appropriate tools, until now. Today, vaccines for girls, and new and improved screening for all women, provide the opportunity to realize our commitment."
- And in a video message to a major cervical cancer meeting in the fall of 2007, President of **Liberia** Ellen Johnson-Sirleaf stated, "Today I would like to add my voice to those demanding that cervical cancer prevention gets the international political recognition it deserves…Let us now make this rhetoric into reality."

Political will is growing and the technical data are clear—it is possible to do something about cervical cancer in the developing world. We know how to train health workers to perform appropriate and effective procedures like VIA and to treat women using cryotherapy. And one day soon, when low-cost HPV-DNA tests become commonplace, the same trained staff can use the new tests as well. We know that a single-visit approach can be incorporated into primary-care services and that it brings the services closer to where women reside, reduces the number of clinic visits required, and reduces barriers to screening and follow-up care. These lifesaving interventions are available and proven.

Another new technology, the much-heralded HPV vaccine, also has an important role to play in a comprehensive cervical cancer control program. While screening is needed for women who may already have been infected with HPV, vaccines can protect young adolescent girls against infection in the first place. This two-pronged strategy—screening plus vaccination—has the potential to save millions of lives over the next decades.

PATH will continue working to ensure that every woman can realize her right to screening, and every girl her right to HPV vaccination.

Key cervical cancer resources

- **RHO Cervical Cancer—an online collection of reliable information from the world's leading institutions**
  www.rho.org

- ***Outlook*. Preventing Cervical Cancer: Unprecedented Opportunities for Improving Women's Health**
  www.path.org/publications/details.php?i=1508

- **Cervical cancer, human papillomavirus (HPV), and HPV vaccines: Key points for policy-makers and health professionals (WHO, PATH, UNFPA)**
  www.rho.org/files/WHO_PATH_UNFPA_cxca_key_points.pdf

- **Alliance for Cervical Cancer Prevention**
  www.alliance-cxca.org

- **Evidence of Developing Country Support for Improved Cervical Cancer Prevention**
  www.rho.org/CCAdossier

- **PATH Cervical Cancer Programs**
  www.path.org/cervicalcancer

- **World Health Organization cervical cancer resource page**
  www.who.int/reproductive-health/publications/cancers.html

- **Cervical Cancer Action**
  www.cervicalcanceraction.org

- **International Agency for Research on Cancer**
  www.iarc.fr

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PATH
A catalyst for global health

1455 NW Leary Way
Seattle, WA 98107 USA
Phone: 206.285.3500
Fax: 206.285.6619
www.path.org