**ADAPTING HPV TESTS FOR CERVICAL CANCER SCREENING IN DEVELOPING COUNTRIES**

**Why do we need to develop a new screening test for cervical cancer?**

Cervical cancer is the second most common cancer in women worldwide, with about 500,000 new cases and 274,000 deaths every year—over 85% of which occur in the developing world. Almost all of these cancers are caused by carcinogenic types of HPV and are completely preventable. Vaccination against HPV shows promise for future generations and is currently being implemented in many developed countries. However, the current vaccine has some significant limitations because it is most effective against two HPV types (-16 and -18) that account for about 70% of cervical cancer cases. Additionally, the vaccine is less effective in women who have been exposed to the virus—and that includes a variable fraction of women over the age of 20 years. Thus, screening remains the main hope for the current generation of women aged 20 years and older and screening will need to be continued for at least the next 30 years.

**What are the limitations of cytology-based screening in developing countries?**

It is broadly accepted that well-organized cervical cancer prevention programs based on primary screening with cervical cytology lead to impressive reductions in cervical cancer rates in developed countries. However, it has not been possible to translate this expertise to the developing world, where the infrastructure of cytology (continues on page 3)
THE SEX OF CERVICAL CANCER

HPV is a significant human carcinogen for both men and women. However, organ-to-organ susceptibility is strikingly diverse and the number of HPV-related cancers is strongly skewed, with women carrying the heaviest burden. The central public health impact of HPV-related cancers is thus first and foremost a woman’s issue. As a consequence, the priority in adopting HPV-related preventive actions reflects the social perception of the role of women in society and particularly of women in the middle age range. It also reflects the power and influence of women in the decision-making processes. The arrival of HPV vaccines and HPV-based screening tests has introduced a new angle in discussing cancer prevention that is closely related to sociology and cultural diversity.

Issues of cost and price aside, it is likely that the rapid and consistent decisions taken by virtually all developed countries to regulate and introduce HPV vaccines reflect the growing presence of women’s health issues amongst the criteria for priority in decision making. In contrast, in other parts of the world, several social issues have emerged as critically relevant and might require specific communication and educational efforts. The theme is that a “female-only cancer” might be perceived as a secondary health issue, particularly in the presence of other overwhelming health problems such as acquired immune deficiency syndrome (AIDS), malaria or water sanitation. Minimization or denial of the burden of cervical cancer usually happens in places with lack of formal cancer registries and uneven access to the population to medical services, largely depriving the lower socioeconomic groups of access to diagnosis, registration and treatment. In some of these populations, there is limited sexual behavior education, dramatic social stigma associated with HPV—a positive sex is related to sociocultural diversity prior to and outside marriage. A common feature in most of these countries is the limited presence or complete absence of women in the decision circles where health priorities are discussed and decided.

The qualitative difference between cervical cancer prevention and other pressing health priorities is that cervical cancer can now be prevented with novel, feasible options, both in the primary mode, by introducing HPV vaccines, and the secondary mode by adopting novel screening strategies. Significant advances are being made to make HPV screening also sustainable for developing countries, and this issue of HPV Today presents data from a critical recent trial in China. In the work that lies ahead, the leadership of women and the understanding that cancer prevention is also a culturally dependent women’s issue will be of importance.

F Xavier Bosch
HPV TODAY editor
screening either does not exist or has been problematic. Therefore, women in developing countries still suffer a disproportionately high burden of illness from cervical cancer. Cervical cancer remains the second leading cause of cancer incidence among women.

**What is the *careHPV*™ test?**

The *careHPV*™ test (QIAGEN, Gaithersburg, MD, USA) is specifically designed for screening of women in low-resource regions of the world in order to identify individuals at high risk of developing cervical cancer. The test works by detecting the presence of 14 high-risk, or potentially cancer-causing, HPV types. The test also meets the requirements necessary to be useful in low-resource regions of the world, such as parts of China, India, Africa, and Latin America. The test is able to rapidly (within 3 hours) produce accurate results, thus eliminating the need for additional patient trips to health clinics for further evaluation and treatment. If a woman is found to be HPV positive, she can undergo further confirmatory diagnostic testing immediately; if desired, or, in certain cases, get immediate treatment.

The *careHPV*™ test equipment requires only a small area (approximately 25 cm by 30 cm) of clean bench-top workspace, it does not require mains electricity or running water, and can be performed rapidly by non-technical support staff.

**How much training is needed to perform the test?**

The *careHPV*™ test is simple to perform, with minimal training required and with minimal infrastructure. During the performance trial and clinical-endpoint evaluation trial in Shanxi (China) in 2007, the tests were successfully conducted by village nurses with basic training.

**What is the sample requirement?**

The *careHPV*™ test requires samples of exfoliated cervical cells which can be collected either by a healthcare worker or self-collected (by the women) when cultural barriers discourage gynecologic examinations.

**Can developing countries afford this test?**

Yes. The development of this test was funded by the Bill & Melinda Gates Foundation, and the manufacturer (QIAGEN) is committed to making the *careHPV*™ test accessible at an affordable price to all governments and non-governmental organizations (NGOs) in need. My understanding is that there will not be a single set price since conditions and requirements vary from region to region. The *careHPV*™ test will be made available at a negotiated price that is affordable for every qualifying government or NGO that applies.

**What are the main conclusions of the study in China?**

The first clinical-endpoint trial of the *careHPV*™ test was completed in Shanxi province (China) and involved about 2500 patients. Results have shown the test to be 90% accurate in detecting precancerous cervical diseases, and 84.2% of the women without precancerous diseases were identified as negative by the test. For this reason, I feel that the test could provide an effective primary screening method for cervical cancer prevention in rural and low-resource settings.

**What is the potential for global use of the *careHPV*™ test?**

The new test needs to be studied in many countries to confirm its suitability for cervical cancer screening on the global stage. Based on results in China, however, the *careHPV*™ test looks very promising as a test that will allow the rapid and accurate screening of women for cervical cancer. It is rapid, simple, affordable, and appropriate for use in low-resource settings.

If women 30 and older could be screened at least once in their lifetime with this test, and appropriate treatment administered during the same visit, deaths from cervical cancer would rapidly reduce by a third or a half.

More than four-fifths of the 493,000 annual new cervical cancer cases in the world occur in developing countries of Asia, Africa and Latin America. More than 70% of the women with this dreaded disease are diagnosed in very advanced clinical stages and, consequently, less than 40% of them survive for more than five years after diagnosis. Cervical cancer is preceded by precancerous changes in the cervical cells, collectively called high-grade cervical intraepithelial neoplasia of grade 2 and 3 (CIN 2 and 3), several years before the cancer symptoms occur.

The early detection of CIN by screening and effective treatment prevents the occurrence of cervical cancer. Lack of effective screening programs is responsible for this high-risk of cervical cancer in developing countries. The difficulties and challenges in introducing large-scale and frequently repeated rounds (every 3 or 5 years) of Pap smear screening in poor countries, encouraged a group of investigators from the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) (Lyon, France), Nargis Dutt Memorial Cancer Hospital, Barshi and the Tata Memorial Centre (Mumbai, India) to organize a large clinical trial to evaluate the acceptability and effectiveness of a single round of screening with either Pap smear, testing for HPV types that cause cervical cancer or visual testing with acetic acid (white vinegar) (VIA) in detecting cervical precancerous changes and in preventing cervical cancer deaths.

Some 131,746 healthy women aged 30-59 years living in 497 villages in Osmanabad district, a socioeconomically backward area in Western India, were grouped into arms to receive HPV testing using Hybrid Capture® 2 (HC2) (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.)) (34,126 women), Pap smear (32,058 women) or VIA (34,074 women) or the existing routine care (control group), i.e., no screening but education on how to prevent and detect cervical cancer early. The four groups had similar characteristics in terms of age, socio-economic status and education.

The results of participation of women in screening, the number with positive screening tests, those detected with high-grade precancerous changes, those diagnosed with cervical cancer, the proportion of cervical cancer cases in early clinical stages and the number of cervical cancer deaths during 2000-2007 in each of the four study groups are given in Table 1.

Table 1: Results of cervical cancer screening in Osmanabad district, India

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV Group (N = 34,126)</th>
<th>Pap smear group (N = 32,058)</th>
<th>VIA group (N = 34,074)</th>
<th>Control group (N = 31,488)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women screened</td>
<td>27,192</td>
<td>25,549</td>
<td>26,765</td>
<td>-</td>
</tr>
<tr>
<td>Test positive women</td>
<td>2812</td>
<td>1787</td>
<td>3733</td>
<td>-</td>
</tr>
<tr>
<td>Women with high-grade precancerous changes</td>
<td>245</td>
<td>262</td>
<td>195</td>
<td>-</td>
</tr>
<tr>
<td>Women diagnosed with cervical cancer during 2000-2007</td>
<td>127</td>
<td>152</td>
<td>157</td>
<td>118</td>
</tr>
<tr>
<td>Women with stage II or more advanced cancer</td>
<td>39</td>
<td>58</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>Women dying from cervical cancer during 2000-2007</td>
<td>34</td>
<td>54</td>
<td>56</td>
<td>64</td>
</tr>
</tbody>
</table>
Women attending health education session in Osmanabad District, India

changes in their cervix; these values were 10 and 7 respectively in Pap smear and VIA tested women. In the HPV group, 127 women were diagnosed with cervical cancer and 39 at an advanced stage; 34 women died of cervical cancer, compared with 118 cervical cancer cases, 82 advanced cancers and 64 deaths in the control group. There were 152 cervical cancer cases, 58 advanced cases and 54 cervical cancer deaths in the cytology group and 157 cervical cancer cases, 86 advanced cases and 56 cervical cancer deaths in the VIA group. These results indicate that HPV screening led to a significant 50% reduction in advanced cervical cancers and deaths as compared with those receiving routine care, whereas no significant decline in advanced cancers or cervical cancer deaths was observed in the groups of women allocated to Pap smear or VIA. During the eight-year follow-up period, eight of the 24,380 HPV-negative women developed cervical cancer as opposed to 22 of 23,762 Pap smear negative and 25 of 23,032 VIA-negative women, thus indicating that HPV testing more accurately identifies women at risk of developing cervical cancer. These results, published in detail in the New England Journal of Medicine recently,1 emphasize that HPV testing is more effective than Pap smear or VIA in preventing cervical cancer deaths in women over 30 years of age. Although HPV testing is currently expensive (20–40 US $), the parallel development of fast, accurate and affordable HPV tests makes HPV testing a feasible screening approach in low-resource settings.


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**SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR CIN 2+ OF THE CAREHPVTM TEST COMPARED TO OTHER SCREENING METHODS IN 2388 WOMEN AGED 30–54 YEARS IN RURAL CHINA**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>careHPVTM test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical specimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 RLU/cut-off ratio cut-point</td>
<td>90.0</td>
<td>84.2</td>
<td>14.7</td>
<td>99.6</td>
</tr>
<tr>
<td>1.0 RLU/cut-off ratio cut-point</td>
<td>84.3</td>
<td>87.5</td>
<td>16.9</td>
<td>99.5</td>
</tr>
<tr>
<td>Vaginal specimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 RLU/cut-off ratio cut-point</td>
<td>81.4</td>
<td>82.4</td>
<td>12.2</td>
<td>99.3</td>
</tr>
<tr>
<td>1.0 RLU/cut-off ratio cut-point</td>
<td>72.9</td>
<td>87.7</td>
<td>15.1</td>
<td>99.1</td>
</tr>
<tr>
<td><strong>HC2 test (cervical specimens)</strong></td>
<td>97.1</td>
<td>85.6</td>
<td>17.0</td>
<td>99.9</td>
</tr>
<tr>
<td><strong>Liquid-based cytology (ASC-H+)</strong></td>
<td>85.3</td>
<td>97.0</td>
<td>45.7</td>
<td>99.5</td>
</tr>
<tr>
<td><strong>VIA</strong></td>
<td>41.4</td>
<td>94.5</td>
<td>18.6</td>
<td>98.2</td>
</tr>
</tbody>
</table>


Pap has shown a similar sensitivity to VIA in many other studies. The performance of the careHPVTM test was also compelling when vaginal samples were self-obtained (81% sensitivity). This option should be further evaluated in future studies, as vaginal self-sampling would facilitate screening in areas where pelvic evaluation by male providers represents a barrier to access.
HPV TESTS AND TRIALS FOR CERVICAL CANCER PREVENTION IN DEVELOPING COUNTRIES

Jacqueline Sherris
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This issue of HPV Today contains an interview with Dr. Youlin Qiao from the Cancer Institute/Hospital, Chinese Academy of Medical Sciences, regarding the first published trial comparing the performance of the new careHPVTM test (Qiagen, Gaithersburg, MD, USA) with Hybrid Capture® 2 (HC2) (Qiagen Gaithersburg, Inc. MD, USA – previously Digene Corp.), visual inspection using acetic acid (VIA), and liquid-based cytology for detection of precancerous lesions of the uterine cervix (see “HPV in 100 slides”). As mentioned by Dr. Qiao, the careHPVTM test, used in developing-country, real-life conditions, showed high sensitivity (90%) for detecting cervical intraepithelial lesions of grade 2-3 (CIN2-CIN3), a rate comparable to the more expensive and lab-intensive HC2 (97%), and superior to VIA (41%) and liquid-based cytology (85%).

The idea of creating a lower-cost HPV DNA test suitable for use in developing countries arose after HC2 was approved by the U.S. Food and Drug Administration (FDA). Early on this idea was considered impossible, but the dream is becoming reality thanks to support from the Bill & Melinda Gates Foundation and the willingness of the manufacturer to pursue this social mission in collaboration with PATH and developing-country partners. Following several years of work, including collection of cervical samples from women with and without disease, results of a clinical study in China were published in 2008.

It is important to highlight some methodological details of the Chinese trial given the inherent complexities involved in evaluating cervical screening tests. First, to avoid any bias in confirmation of the final cervical disease status of study participants, final disease/no disease status was obtained only after referring all women with any positive test (careHPVTM, HC2, VIA or cytology) to colposcopic evaluation and biopsy. Small biopsies were obtained even when the colposcopist found no visual abnormalities, and a percentage of women with negative screening results were also evaluated with colposcopy. As a result of this strategy, almost 20% of CIN2+ diagnoses were detected in histological samples obtained from areas considered as non-significant by the colposcopists. These cases would have been missed if the decision to take biopsies had been based on colposcopic evaluation only. Missing 20% of cases with CIN2+ would have negatively affected the performance of some screening tests while it would have artificially inflated the performance of others.

A second important characteristic of the study is that only health workers with limited laboratory experience were selected to process the careHPVTM test, to approximate future field situations. The results from China confirmed that the careHPVTM test can be effectively performed by staff with only basic training. Availability of an affordable, easy-to-use and highly sensitive HPV DNA test, along with safe and effective HPV vaccines, expands the menu of possibilities for cervical cancer prevention in developing countries.

Now it is time to work with countries to plan for future, comprehensive prevention programs that include both screening for women over 30 years of age, the group at the highest risk of cervical cancer, and HPV vaccination of young adolescents before they start their sexual life.

WHO/ICO INFORMATION CENTRE ON HPV AND CERVICAL CANCER

Find the best available data/estimates on:

- Socio-demographics.
- Sexual behaviour and reproductive indicators.
- Burden and HPV type distribution in cancer: cervix, anus, vulva, vagina, penis, oral cavity, oro-pharynx, pharynx and larynx.
- HPV prevalence and type distribution in women with normal cytology and precancerous lesions.
- Statistics on cofactors for cervical cancer.
- Data on immunization coverage and screening practices.
- HPV in men, male circumcision and condom use.

www.who.int/hpvcentre
Beginning in 2007, meetings were held in all regions of the World Health Organization (WHO) to consider cervical cancer control in the context of the newly available HPV vaccines. Common themes emerged from all regions: decreasing the burden of cervical cancer through improved screening efforts, improved treatment and surveillance, and introduction of the HPV vaccine where possible.

Results from these regional meetings, combined with a comprehensive HPV Vaccine Background Paper, were presented to the Strategic Advisory Group of Experts (SAGE) in November of 2008 to consider a global recommendation on HPV vaccination.1

On the basis of SAGE recommendations, WHO developed its position paper on HPV vaccination, which was published in April 2009.2

These recommendations recognize the importance of HPV disease burden worldwide and recommend that HPV vaccination should be included in national immunization programs if the prevention of cervical cancer and/or other HPV-related diseases are a public health priority, introduction of the vaccine is feasible and financing can be secured and is sustainable. The cost-effectiveness of vaccination strategies in the country or region should be considered.

WHO recommended that the primary vaccine target population be girls prior to initiation of sexual activity. Specific age ranges could be based on local data regarding age of sexual debut, but debut occurs most commonly between 9 or 10 to 13 years of age. WHO also recommended that the secondary target populations of older adolescent girls be considered if this is feasible and affordable, but only if it does not distract from the success of vaccinating the primary target. Vaccination of males to prevent cervical cancer in females was not recommended, as modelling data suggests that male vaccination is not cost-effective for cervical cancer prevention if high coverage is achieved in the target population. If possible, vaccine introduction should be in concert with a national cancer prevention program that includes education, screening, and diagnosis and treatment of precancerous lesions.

One of the major challenges remains vaccine financing. For low- to middle-income countries that are not GAVI eligible, the price of the vaccine is a major impediment to implementation in a national immunization program. Individual countries have negotiated prices with the vaccine manufacturers, whereas others have decided that, even at a lower price, screening remains more sustainable and implementation of the HPV vaccine is not feasible. It is hoped that the price of the vaccine will fall. Additionally, cost-effective tools are being developed by WHO and by other experts to allow each country to input their own variables and facilitate country-based decisions on cost-effectiveness.

Another challenge is implementation. Immunization programs, especially those in developing countries, have traditionally targeted young children. The primary target group of this vaccination, 10-13-year-old girls, is a population with whom we have little immunization experience. Initial results from demonstration projects are, however, encouraging and show that school-based programs are feasible and that high coverage can be achieved. Outreach programs are also being assessed, and are crucial for areas with a high proportion of girls in the peer group not attending school. Research is ongoing regarding how to best present the message about the HPV vaccine, and education concerning HPV as an etiology of cervical cancer.

Surveillance systems also need development, and research is ongoing to develop simple and reliable laboratory tools that will allow standardization of HPV testing and facilitate surveillance efforts. As of February 2009, the quadrivalent vaccine had been licensed in 109 countries and the bivalent vaccine in 92 countries. However, whereas many countries, including some low- and middle-income countries have already introduced the vaccine, it is clear that, despite continued efforts in areas such as financing, implementation strategies, cost-effectiveness, surveillance and laboratory testing, concerned creative effort and dedication are still required before the vaccine becomes part of immunization programs worldwide.

In 2009, routine HPV vaccination of girls and widespread cervical screening of women still seems out of reach in low-resource settings, although the situation is changing. The GAVI Alliance is interested in subsidizing HPV vaccine for the world’s 72 poorest countries,1 and lower vaccine prices are being negotiated for middle-income countries. Emerging data from demonstration projects suggest that adolescent vaccination may be broadly acceptable and programmatically feasible in Africa, Asia, and Latin America.2 All of this leads us to hope that vaccine may be introduced in some of those countries within the next few years. Additionally, recent success using visual inspection methods for both primary cervical screening and treatment triage, along with promising results from a new, low-cost and portable HPV DNA test (discussed in another article in this issue), has convinced us that, in the words of the International Alliance for Cervical Cancer Prevention (ACCP):

“...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 visual inspection of the cervix after swabbing it with acetic acid, or vinegar (VIA), then treat precancerous lesions using cryotherapy (freezing) or as indicated. This is optimally achieved in a single visit (currently possible with VIA plus cryotherapy) and can be carried out by competent physicians and non-physicians, including nurses and midwives.”3

Following decades of inequity, with 85% of cervical cancer deaths occurring in the developing world, one finally can imagine how use of these new tools and approaches could be coordinated to effect a significant global reduction in cervical cancer mortality within 10 to 15 years. There are many benefits to investing in both vaccination and screening, not the least being that screening now will save lives many years earlier than vaccination alone, and because the vaccine does not protect against all oncogenic types of HPV- even women who have been vaccinated require future screening. Vaccinating now includes an additional benefit of reducing the burden on future screening programs, with many fewer women testing positive and needing treatment. Efforts to raise awareness about cervical cancer in the community will benefit both screening and vaccination in an efficient and synergistic way. There are also political reasons to think broadly about cancer prevention. For example, when both screening and vaccination are discussed, PATH’s experience is that many and diverse partners become intrigued and look for ways to work together. This is certainly the case with the Cervical Cancer Action coalition,4 which, like the ACCP, strongly endorses comprehensive programming. However, before comprehensive cervical cancer prevention planning can become commonplace, there are significant obstacles to overcome, beyond price and availability of the technologies. Some of the barriers are attitudinal—the need to overcome prejudice against lower-tech screening methods, for example—whereas others are programmatic—clinics must procure equipment for VIA and cryotherapy and scores of local providers will have to be trained. Other challenges relate to ministry of health structures. For example, immunization services usually are centralized and therefore easier to regulate from the center. However, management of reproductive health and other clinical services have been decentralized to provincial or district levels in many countries, so different teams may be in charge of planning and budgeting these two types of services, which results in complex decision-making processes. Finally, local data may not be available to answer some of a health minister’s most fundamental questions, such as “what is the burden of cervical cancer in our country?” making it difficult to develop an evidence-based program proposal. Fortunately, tools and information resources to assist planners are available from technical agencies and online, and these can help answer some of the key questions program planners ask. Many of the documents can be found in the RHO Cervical Cancer library (www.rho.org). We are also pleased to note that many organizations that focus on cancer, reproductive health, adolescent health, immunization and gender equity are anxious to work together to tackle the problem of cervical cancer in a meaningful way. Perhaps in the end, the call for a comprehensive approach must come from the highest levels of the ministry of health, those who set the priorities of disparate teams responsible for either immunization or screening and treatment. Raising awareness of the great need, and of the exciting promise of soon-to-be-available technologies, is of paramount importance now, so that leaders and managers will be prepared to take best advantage of new opportunities when they present themselves in the near future.
Planning for both screening and vaccination is a complex process, and countries will need help weighing the benefits of alternative prevention strategies and determining optimal resource allocations for those services. Below are some of the questions country planners may want to answer for themselves. Fortunately, there are many information resources on the web to help them, such as those found at www.rho.org.

- What is the disease burden of cervical cancer in our country and what is the potential impact of each of the interventions?
- What is the potential impact of other services that could be offered along with vaccination or screening?
- What is the potential for partnership to increase impact of our programs?
- Are there policies in place that would either hamper or support these efforts? Do we need new or updated policies?
- What level of support for cervical cancer prevention exists among our politicians, donors, and international agencies?
- What is the status and strength of our national adolescent immunization program?
- What is the status and strength of our current programs to screen and treat women?
- What is the quality, efficacy, cost, and cost-effectiveness of the new tools?
- How much would our new programs cost and how sustainable will they be financially?
- Taking all this into consideration, where should we invest our limited funding? A mix of both interventions? Or only one or the other (for now)?

References:
Getting three doses of HPV vaccine to the group who will benefit the most from it –preadolescent or adolescent girls before their sexual debut– seems like a daunting challenge, especially in developing countries where girls of this age seldom come into contact with health services. However, there are several trends at play that make this goal look feasible and suggest that the introduction of HPV vaccine could leverage other important health services for these girls, as well as for boys of the same age.

One of the most important trends is the increasing number of children –especially girls– completing primary school. One of the eight Millennium Development Goals is to achieve universal primary education by the year 2015. Primary school enrollment is rising, so that at least 70% of children in Africa and 90% or more in other regions are enrolled. Although too many girls are still left out, more girls than ever are attending primary school up to the age of 10-13 (see Figure 1). This creates a promising opportunity for school-based delivery of HPV vaccine. With carefully designed community outreach –as is done with Child Health Days in many countries– it should also be possible to attract many out-of-school girls to come to the school and get immunized at the same time as their school-going peers.

Many countries are interested in reaching this age group with valuable interventions, including other vaccines, nutritional supplements, basic treatments for endemic diseases, and promotion of healthy behaviors. Developing effective mechanisms for reaching young adolescents with HPV and other vaccines could pave the way for rapid introduction of an eventual HIV vaccine. Girls and boys this age may also benefit from periodic vitamin A supplements and deworming medications, and mass treatments for malaria, schistosomiasis, guinea worm, trachoma, and iodine deficiency. Providing older children with essential information about tobacco and drugs, body changes during puberty, and personal hygiene, in addition to life-choice decision-making skills, can lead to lifelong improvements in their health. Assessments of sociocultural issues, health system factors, and policy environments conducted by PATH and research partners have identified potential delivery strategies that are now being evaluated in demonstration projects in India, Peru, Uganda, and Vietnam.

Many barriers still remain –low awareness of the burden of cervical cancer and the link with HPV, the high cost of the vaccine, sociocultural concerns about a vaccine for girls, and other competing health demands– but there are opportunities now as never before with the rapid growth in primary school attendance, the anticipated GAVI Alliance support for HPV vaccines, and a growing recognition that we must invest in older children’s health if we are going to reap benefits similar to those we have seen in recent decades from the push to reduce mortality among infants and children under five. Delivery of HPV vaccine can build on these opportunities and serve as a catalyst for further improvements in health care for young people at a critical time in their lives.


Figure 1.

Increasing girls’ enrollment in primary school as compared to male enrollment (1999 – 2005).


[10]
INTRODUCING HPV TESTING IN DEVELOPING COUNTRIES: THE START-UP PROGRAM AT PATH

After receiving the positive results from the clinical study in China, PATH began to plan for the implementation of a cervical cancer prevention program based on the careHPV™ test (QIAGEN, Gaithersburg, MD, USA). However, there are some questions to answer and challenges to address before a successful cervical cancer prevention program based on the careHPV™ test can be implemented into a developing-country setting.

PATH is currently developing four demonstration projects through the Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention –Utility and Program Planning (START-UP) project in three low-resource countries: India, Nicaragua, and Uganda. These demonstration projects include activities that will inform the global health community about new cervical cancer testing methods and provide the data needed for ministries of health to determine the best cervical cancer screening options to suit their needs and resources.

Because women are the most important component in any cervical cancer prevention program, it is crucial to find out what they understand about cervical cancer screening, existing barriers to accessing screening services, HPV infection, the careHPV™ test’s ability to detect the virus, and interpreting test results. It is also critical to understand how this health information is transmitted and shared within the community.

In order to answer these questions, and in preparation for the demonstration projects’ initiation in mid-2009, PATH conducted medical consensus workshops at all four START-UP project sites. The purpose of these workshops was to allow health care workers, government officials, community members, and other stakeholders a forum to discuss the potential challenges to the implementation of the demonstration projects and to explore possible solutions.

The main findings from the consensus workshops included the following:
1. There was a lack of knowledge about HPV and its link to cervical cancer at all four sites. Even though this was expected, it emphasizes the critical role of health information dissemination and education within the community.
2. Presenting HPV as a sexually transmitted virus was problematic for some women because a positive screening result could potentially lead to anxiety and even physically aggressive conflict within their relationships with spouses. Some of the workshop participants suggested counseling as an appropriate response to relationship anxiety and conflict. Another suggestion was to make disease (cancer) prevention, rather than infection (HPV) control, the focal point of education efforts. Furthermore, information related to HPV infection modes of transmission should be delivered in a non-technical, simplified way, thus building on the existing awareness of illness and infection processes.
3. Husbands and male partners are often a very influential component in a woman’s decision to seek medical care. Hence, reaching out to male community and family members is of vital importance—in addition to educating female community members themselves. Men are usually accessed through venues where both genders can gather. If men are not educated about the demonstration project, they could pose a serious barrier to women completing necessary follow-up.
4. Self-collection of the careHPV™ test sample seemed generally acceptable among the workshop participants. Lack of skill and knowledge were suggested as the main reasons for women’s reluctance to self-collect a vaginal swab. In order to counter this reluctance, it was suggested that a nurse provide the woman with clear, culturally sensitive instructions (either printed or in video format).

Preparations for other activities of the START-UP project are underway. These activities include:
• Conducting a study to assess the clinical performance of E6 rapid-strip prototypes in a low-resource setting and evaluating the prognostic value of E6 detection for risk of disease progression.
• Working to establish sustainable service-delivery platforms that have the potential to incorporate new screening tests as they are developed and commercialized. These activities will include the development of a “Training Excellence Center” (TEC) in Peru, using this facility to train providers from two additional countries in the region, supporting the newly trained providers as they build experience for one year, and finally training them to develop local TECs and train additional providers in their respective countries.
• Strengthening regional and global champions for alternative screening and treatment technologies by working closely with a variety of international agencies, including professional organizations, to educate staff and members about screening and treatment, and to promote newly harmonized practice standards.

The main objectives of the START-UP project are:
1. Provide ministries of health with data comparing various screening approaches –Pap smear, visual inspection with acetic acid (VIA), and the careHPV™ test– to allow them to plan for long-term, wide-scale adoption of screening and treatment programs.
2. Provide the manufacturer with information needed to respond to public-sector investment risks, constraints, and opportunities in developing countries.
3. Share tools for progress with neighboring countries to strengthen and expand regional readiness for cervical cancer prevention programs.

Launching the HPV Vaccine Global Community of Practice

The Department of Reproductive Health and Research of the World Health Organization (WHO), in collaboration with Cincinnati Children’s Hospital Medical Center and the United Nations Population Fund (UNFPA), recently launched the HPV Vaccine Global Community of Practice (CoP) in an effort to facilitate global dialogue about cervical cancer prevention and the role of HPV vaccines (http://hpv-vaccines.net). The CoP is guided by a 33-member steering committee representing WHO and its regional offices, UNFPA, academic institutions, non-governmental organizations, public health institutions, and foundations. The CoP is supported by the Implementing Best Practices (IBP) Knowledge Gateway (www.ibpinitiative.org), an electronic communication platform that was developed in 2004 by WHO/Reproductive Health and Research (RHR) and IBP partners to support virtual communities of practice. It uses low-resolution, web-based technology and e-mail messaging to share and exchange information, knowledge, and experiences.

Community of Practice Activities

The CoP was launched in June 2008 by a global videoconference on cervical cancer prevention and HPV vaccines. The global videoconference linked nine sites across four regions, including Abuja (Nigeria), Cincinnati (U.S.), Copenhagen (Denmark), Geneva (Switzerland), Harare (Zimbabwe), Lima (Peru), New York City (U.S.), Rabat (Morocco), and Washington D.C. (U.S.). The videoconference recording was also available online for those who could not attend the live session, and was accessed by 147 viewers in 36 countries. The global videoconference included keynote addresses by leaders in the WHO and other organizations, and speakers from each of four WHO regional offices – the Americas, Africa, Eastern Mediterranean, and Europe.

The on-line discussion led by experts served as the transition between the launch of the CoP and its daily activities. Many ongoing discussions have occurred, initiated by either the facilitators or the members of the CoP. In addition to discussions, CoP members may post announcements at any time and can access all previous discussions and announcements via their private website. The website also has a library containing articles and resource information, and an events page with information about upcoming conferences and meetings around the world.
EFFICACY OF HPV-16/-18 AS04-ADJUVANTED VACCINE AGAINST CERVICAL INFECTION AND PRECANCER CAUSED BY ONCOGENIC HPV TYPES (PATRICIA): FINAL ANALYSIS OF A DOUBLE-BLIND, RANDOMISED STUDY IN YOUNG WOMEN


This trial assesses the efficacy of the HPV-16/-18 AS04-adjuvanted vaccine (Cervarix® - GlaxoSmithKline Biologicals, Rixensart, Belgium) in a final event-driven analysis. A total of 18,644 women aged 15-25 years were randomly assigned to receive Cervarix® or a control hepatitis A vaccine at 0, 1, and 6 months. Mean follow-up was 34.9 months after the third dose.

In the according-to-protocol (ATP) cohort, vaccine efficacy against cervical intraepithelial neoplasia of grade 2 or higher (CIN2+) associated with HPV-16/-18 was 92.9% in the primary analysis and 98.1% in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncocogenic types. Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30.4% in the total vaccinated cohort (TVC; all women receiving at least one vaccine dose regardless of their baseline HPV status; represents the general population including sexually active women), and 70.2% in the TVC-naïve cohort (women with no evidence of oncogenic HPV infection at baseline; represents women before sexual debut). Corresponding values against CIN3+ were 33.4% in the TVC group and 87.0% in the TVC-naïve group. Vaccine efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54%.

Individual cross-protection against CIN2+ associated with HPVs -31, -33, and -45 was seen in the TVC. Cervarix showed high efficacy against CIN2+ associated with HPV-16/-18 and non-vaccine oncogenic types and substantial overall effect in cohorts that are relevant to universal mass vaccination and catch-up programmes.

Membership in the HPV Vaccine Global CoP
Since its launch in June 2008, the HPV Vaccine Global CoP has grown rapidly and members represent a diverse group of stakeholders in cervical cancer prevention. The CoP currently has 707 members from 100 countries, representing all world regions. Professions represented include physician (30%), researcher/professor (27%), program manager (19%), epidemiologist (12%), and nurse/nurse practitioner (8%). The most common reasons for joining the community are access to resources such as guidelines and technical documents (72%), education about the role of HPV vaccines in cervical cancer prevention (60%), and sharing knowledge/experiences related to HPV vaccine delivery (56%).

Evaluation Process
Two months after the videoconference and the initial discussion forum, we assessed user satisfaction with the dialogue. Among respondents to the on-line satisfaction survey (N=44), 98 - 100% were satisfied with the content of the global forum and on-line discussions and 88% thought that they were able to add their voice and experiences to the discussion. In addition to supporting ongoing dialogue with members, the facilitators have launched a sub-community on research issues and a Spanish language sub-community, and are planning another global videoconference and on-line discussion series with a focus on the Asian-Pacific region. In summary, the HPV Vaccine Global CoP is a promising new mechanism for global discussion about cervical cancer prevention and HPV vaccines.
Cervical cancer, unlike most other cancers, is largely preventable because precancerous cervical lesions can be detected and treated, thus halting progression to invasive disease.

Screening tests can effectively detect precancerous cervical lesions in asymptomatic women, but a key component of any effective screening strategy is follow-up of women who screen positive to ensure appropriate treatment of the precancerous cervical lesions.

Indeed, identifying disease without providing treatment is a waste of both time and resources and is ethically unacceptable.

A review of clinical follow-up of screen-positive women in Latin America and the Caribbean found that rates of diagnosis and treatment in Peru (25%) and diagnosis in Bolivia (59%) contrast with much higher rates in Chile and Cuba (>90%). The authors note that these figures are consistent with the trend and rates of cervical cancer mortality in these countries and suggest that lack of follow-up of positive screening results may be one of the primary reasons for the lack of impact on the reduction of mortality rates.

Several options are available for treatment of precancerous cervical lesions, ranging from inpatient surgical methods such as cone biopsy and hysterectomy to simpler, less-invasive outpatient treatment methods such as loop electrosurgical excision procedure (LEEP) or cryotherapy. Since 80% of cervical cancer cases occur in developing countries, treatment options must be available and appropriate for low-resource settings.

Cryotherapy is currently the most practical, feasible, and effective approach to treating cervical lesions in low-resource settings if the lesions are of appropriate size and accessible to the cryotherapy probe.

In addition, cryotherapy treatment can be used in a single-visit screen-and-treat approach in primary care settings, an approach which has been demonstrated to increase follow-up rates.

Cervical cryotherapy uses a freeze probe on the cervix to destroy abnormal cells, which are then shed in a watery discharge. The cryotherapy probe is connected by flexible tubing to a gas tank with a refrigerant and non-toxic, non-explosive gas, generally nitrous oxide or carbon dioxide.

This procedure gained popularity in the industrialized world in the 1970s and 1980s because of its low cost and ease-of-use. Cryotherapy use decreased in many settings when newer technologies, such as LEEP and laser ablation, were introduced. Cryotherapy, however, has many advantages over these newer technologies, particularly in low-resource settings. Cryotherapy has limited side effects, does not require electricity, is inexpensive compared to other treatment options, and is technically simpler than other methods. Therefore, cryotherapy can be performed by non-specialized primary health care providers who receive appropriate training and supervision.

The effectiveness, acceptability, and safety of cryotherapy for cervical precancer treatment have been well described.

A systematic literature review, which examined 32 studies of cryotherapy effectiveness, found an overall cure rate of 89.5% for all grades of cervical intraepithelial neoplasia (CIN) after one cryotherapy treatment at 12 months post-treatment. More recent studies, included in a 2009 update to the systematic literature review, have found cure rates similar to those reported in the 2003 systematic literature review.

Likewise, cryotherapy offers a safe treatment option for outpatient settings. In the 2003 and the 2009 systematic literature reviews of cryotherapy, 46 articles reported on issues of cryotherapy safety. Only two cases of severe bleeding which required medical attention, and only six cases of pelvic inflammatory disease (PID), were reported in these articles. The reviews suggest that major complications, including severe bleeding and PID, are very unlikely events following cryotherapy and occur less often than after laser ablation treatment or LEEP.

It is common for women to experience side effects following cryotherapy treatment, particularly vaginal discharge for 2 to 4 weeks after the procedure; less often women will experience pain or cramping, feeling flushed or faint, or spotting or light bleeding. In the systematic literature reviews, seven articles included information on women’s satisfaction and acceptability with the cryotherapy procedure. Overall, 85% - 95% of women
reported satisfaction with cryotherapy treatment and 96% - 99% were satisfied enough to recommend the procedure. Recent research indicates that women in developing-country settings have tolerated the procedure well.4,9,7,10,11 As with any surgical procedure, effective counseling about side effects and warning signs for complications is recommended.

Whereas cryotherapy can effectively treat precancerous cervical lesions, there are challenges with its wide-scale application in population-based screening programs in low-resource settings. Some commercial models, for example, have experienced clogging or failure due to the use of low-grade gas or certain freezing techniques. The World Health Organization (WHO), the United Nations Population Fund (UNFPA), and PATH are currently collaborating to identify mechanisms to address these technical issues and to build consensus on approaches to improving cryotherapy service delivery to prevent cervical cancer. WHO, UNFPA, and PATH are also developing technical specifications for cryotherapy units, accessories, and gases to facilitate and support country-procurement mechanisms. These groups and additional key partners and experts have also initiated a process to develop WHO clinical recommendations on the use of cryotherapy for cervical cancer prevention. Together, with improved cryotherapy equipment and clinical guidelines, it is our goal that more women will have greater access to cervical cancer prevention services, especially in developing countries.

The Alliance for Cervical Cancer Prevention (ACCP)12, is a group of international health organizations who have worked on a coordinated research agenda, including the assessment of a variety of approaches to cervical cancer screening and treatment, especially approaches that may be better suited to low-resource settings, included cryotherapy in four of their key findings and recommendations for effective cervical cancer screening and treatment programs:

- 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 visual inspection with acetic acid, then treat precancerous lesions using cryotherapy (freezing).

- 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.

- Cryotherapy, when conducted by competent providers, is safe and results in cure rates of 85% or higher.

- Studies suggest that cryotherapy is protective against the future development of cervical disease among women with current HPV infection. In light of this, and due to the low morbidity of cryotherapy, the occasional treatment of screen-positive women without confirmed cervical disease is acceptable.

These findings published by ACCP have been key in the ongoing work by WHO and partners to develop clinical recommendations for the use of cryotherapy for cervical cancer prevention, as well as to develop technical specifications for cryotherapy units, accessories, and gases.
**INTERNATIONAL AGENDA**

**Cernobbio, Como, Italy**
8th – 11th November 2009
3rd International Cancer Control Congress
Venue: Spazio Villa Erba
E-mail: m.blake@elsevier.com
Web: www.cancercontrol2009.com

**Dar Es Salaam, Tanzania**
11th – 14th November 2009
Organising Committee for the African Organisation for Research and Training in Cancer (AORTIC) 2009 Conference
Venue: Kuduch Beach Hotel and Resort
E-mail: aortic@telkomsa.net
Web: www.aortic2009.org

**Bangkok, Thailand**
12th – 15th November 2009
The 3rd Asia Pacific Congress on Controversies in Obstetrics, Gynecology Infertility (COGI)
Venue: Shangri-La’s Kerry Centre Hotel
E-mail: info@comtecmed.com
Web: www.comtecmed.com/cogi/beijing

**Kuala Lumpur, Malaysia**
17th – 19th November 2009
BioMalaysia 2009
Venue: Kuala Lumpur Convention Centre
E-mail: malinda@protempgroup.com
Web: www.biomalaysia.com.my

**Bangkok, Thailand**
17th – 20th November 2009
11th World Congress of Pediatric Dermatology
Venue: Queen Sirikit National Convention Centre
E-mail: wcpd@kenes.com
Web: www.kenes.com

**Beijing, China**
24th – 26th March 2010
2nd World Vaccine Congress (WCV) 2010
Venue: Beijing International Convention Centre
E-mail: sean@vaccinecon.com
Web: www.vaccinecon.com/2010/overview

**New Delhi, India**
26th – 28th March 2010
Asia Oceania Research Organisation on Genital Infections and Neoplasia (AOGIN)
Venue: Taj Palace Hotel
E-mail: secretariat@aoginindia.org
Web: www.aoginindia.org

**Istanbul, Turkey**
3rd – 7th April 2010
5th International Asian Pacific Organization for Cancer Prevention (APOCP) Conference
Venue: Istanbul Convention & Exhibition Centre
E-mail: info@apoap.org
Web: www.apoap2010.net/

**Washington, USA**
19th – 22nd April 2010
World Vaccine Congress 2010
E-mail: gina.geldenhuys@terrapinn.com
Web: www.terrapinn.com/2010/wvcdc

**San Francisco, California, USA**
25th – 28th April 2010
23rd International Conference on Antiviral Research (ICAR)
Venue: Hyatt Regency San Francisco
E-mail: ISAR@courtesyassoc.com
Web: isar.phrm.cf.ac.uk/node/17

**Edinburgh, Scotland**
16th – 20th May 2010
17th International Congress of Cytology
Venue: Edinburgh International Conference Centre
E-mail: cytology2010@meetingmakers.co.uk
Web: www.cytology2010.com

**Berlin, Germany**
27th – 29th May 2010
5th European Congress of the European Federation for Colposcopy and Cervical Pathology
Venue: Hotel InterContinental
E-mail: S.Hagenstedt@cpo-hanser.de
Web: www.esf2010.de

**Montreal, Canada**
3rd – 8th July 2010
26th International Papillomavirus Conference and Clinical Workshop
Venue: Palais Dès Congrès
E-mail: info@iseventssolutions.com
Web: www.hpv2010.org

**Berlin, Germany**
17th – 22nd September 2011
27th International Papillomavirus Conference and Clinical Workshop
E-mail: hpv2011@cpo-hanser.de
Web: www.hpv2011.org

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