Toward Comprehensive Cervical Cancer Prevention and Control

Region of the Americas

May 12–13, 2008 • Mexico City, Mexico
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Executive Summary

Public Health officials from throughout the Americas gathered with immunization and disease experts May 12–13, 2008 in Mexico City to discuss new approaches to fighting cervical cancer in the region. “Toward Comprehensive Cervical Cancer Prevention and Control in the Region of the Americas” was hosted by the World Health Organization (WHO), Pan American Health Organization (PAHO), Sabin Vaccine Institute and the US Centers for Disease Control and Prevention (CDC).

The meeting came as the emergence of cervical cancer vaccines has sparked intense interest in the potential of immunizations combined with improved screening to significantly reduce the considerable burden of the disease in Latin America and elsewhere in the developing world.

While cervical cancer incidence and deaths have dropped dramatically in the US and Canada, elsewhere in the Americas cervical cancer remains a major killer. According to presentations at the conference, each year there are 39,000 deaths from the disease in the Americas, and 33,000 of those occur in Latin America and the Caribbean (LAC). The cervical cancer mortality rate for LAC is seven times greater than in North America. In some countries, more than 25 out of every 100,000 women die each year from cervical cancer, compared to 2.5 in the United States and Canada.

One expert showed research predicting that absent new prevention and control efforts, cervical cancer rates will increase by 75% in Central America, 45% in South America and 36% in the Caribbean.

A central purpose of the conference was to explore the challenges and opportunities for controlling the disease through a two key interventions:

- Immunizing pre-adolescent girls with one of the two vaccines currently available that prevent infection from high-risk types of the human papillomavirus (HPV), the sexually transmitted disease that is the cause of all cervical cancers

- Screening women for early signs of cervical cancer, which, when done properly and consistently, can be highly effective at halting disease progression and saving lives

There was general agreement that neither intervention in isolation would be sufficient to subdue the disease. Rather, the focus was on the need to engage both simultaneously.

Prevalence of HPV in LAC

Assessing the potential of vaccines to control cervical cancer requires insights into the prevalence of HPV in the region. Researchers at the conference estimated that of the 336 million women in the Americas, about 52 million are infected with HPV and 5 million have pre-cancerous lesions.

A new study presented at the conference examined 15 years of data on HPV and cervical cancer in LAC. It found that the prevalence of HPV in 15–24 years old is “high” at around 20 to 30 percent. The study also indicated that HPV infections generally decrease through age 50, bottoming out at around 11% in women 45 to 54 years old before rising again and reaching about 20% in women over 65.

The study confirmed that HPV types 16 and 18, which are targeted by the two vaccines currently on the market, cause most of the cervical cancers in the region. That means that either of the vaccines now available—one is manufactured by Merck Vaccines, the other GlaxoSmithKline Biologicals—could prevent 60% to 70% of cervical cancers in LAC. However, several participants noted that the
vaccine is only effective at preventing HPV infections, which is why HPV immunization is seen as most effective if administered to girls before they become sexually active. The vaccines are not therapeutic.

In addition, there was discussion of the role of HPV in other cancers, including cancers in men. There was data presented showing that in LAC, HPV is responsible for 36% of cancers of the oral pharynx, 45% of penile cancers, and 90% of anal cancers. Overall, it appears HPV causes 11,400 non-cervical cancers annually in LAC. In particular, the role of HPV in cancers that affect men—coupled with the fact that it is men who infect women with HPV—prompted consideration of whether HPV immunization would be appropriate for boys as well as girls.

**Economic and Financial Considerations in Adopting HPV Immunization**

The relatively high cost of the HPV vaccines was viewed as a significant barrier to regional adoption of HPV immunizations. A new analysis of the economic and financial implications of adopting HPV immunizations was presented at the conference. It compared the cost of introducing HPV vaccines at various price points in six countries—Brazil, Colombia, Mexico, Peru, Argentina, and Chile—to costs associated with screening and treatment.

The study found that from an economist’s point of view, the vaccines would be a “cost-effective” intervention in all the countries studies at up to US$ 100 per vaccinated girl, but not at the current retail cost, which is about $360. The authors of the study acknowledged that cost-effectiveness does not address whether or not a vaccine is affordable within a country’s given budgetary constraints. Their data showed that at $25 per vaccinated girl, the combined costs for the 6 countries studied to vaccinate five consecutive groups or “birth cohorts” of 12-year olds would be US $290 million. At $360 per vaccinated girl, it would cost US $4.7 billion.

However, the study found the vaccines would be highly effective at saving lives. The researchers reported that vaccinating 70% of 12-year-old girls against HPV 16 and 18 in the countries studied would reduce the risk of contracting cervical cancer by anywhere from 39% (Chile) to 54% (Argentina). Overall, the researchers predicted that if for 10 consecutive years the targeted countries successfully immunized their 12-year-old girls, they would prevent half a million deaths from cervical cancer.

Officials from the Pan American Health Organization (PAHO) noted that PAHO’s Revolving Fund for Vaccine Procurement will be instrumental as a vehicle for negotiating an affordable price for HPV vaccines. They also stressed the need to avoid a “zero sum game” in which countries believe the only way they can adopt an HPV vaccine is by cutting funds for other health programs. In particular, PAHO officials said it will be important to incorporate HPV vaccines in a way that allows countries to preserve existing public health gains achieved via immunizations and, furthermore, maintain their ability to adopt additional new vaccines in the future.

HPV vaccinations are not currently in widespread use in the Americas outside of the US and Canada. However, there were discussions of a pilot project to test the use of HPV immunizations in Peru and another effort that may soon be undertaken to immunize low-income girls in Mexico.

**Opportunities to Improve Cervical Cancer Screening**

Several presenters considered highly important how countries in the region could improve efforts to screen women for early signs of cervical cancer, when treatment can be highly effective. They noted that one reason tens of thousands of women in LAC die each year from cervical cancer is
that screening programs are either not reaching or not properly testing women most at risk. In particular, there were many comments regarding the limitations of the most common screening tool for cervical cancer, the Pap smear.

Several participants pointed out that test involves a level of technology, expertise and health services unavailable in many areas of LAC and, furthermore, that it is prone to producing false negatives due to its low sensitivity.

Presenters explored two alternatives to the Pap smear for conducting cervical cancer screening. One, known as visual inspection, involves swabbing the cervix with vinegar, which contains an acid that, on contact, reveal suspicious cervical lesions. Data presented from a study conducted in Peru found that, in addition to being cheaper and easier, visual inspection was more sensitive than the Pap smear at detecting pre-cancerous lesions. Also, since the test results are available almost immediately, presenters noted that visual inspection could allow health professionals to screen and treat women in one visit.

The other test discussed at the conference involves screening for presence of the HPV virus in DNA. Early versions of the method were viewed as too complex and expensive for developing countries. However, a representative from the PATH philanthropy discussed a new project that has developed a simple, “rapid HPV test.” He said trials with the new test have been promising. In addition to the fact that it is highly effective at detecting HPV, the test can be quickly performed in even remote clinics, he said, and could soon be on the market at a cost of about US $5 per test.

Other discussions at the conference included consideration of:

- Clinical data indicating a high degree of effectiveness of both Merck and GSK’s HPV vaccines against HPV Types 16 and 18
- Lessons learned in the largely successful efforts in the US and Canada to introduce HPV vaccines
- The need for more advocacy to ensure cervical cancer prevention and control becomes a higher political priority
- The importance of looking for new financing strategies to facilitate adoption of HPV immunizations

There was agreement that while countries in LAC are not ready for the immediate introduction of the HPV vaccine, the conference essentially launched the discussion of how to make HPV immunizations a reality in the Americas as part of a broad and aggressive cervical cancer prevention and control initiative.

The meeting concluded with a declaration signed by officials from the participating countries. It stated, among other things, the need for an integrated approach to fighting cervical cancer; that the introduction of HPV vaccines provides an opportunity to strengthen cervical cancer diagnostic and treatment programs; and that the “primary limitation” for the use of HPV immunizations “is the high cost.”
Introduction

On May 12–13, 2008 health officials and researchers from the Americas gathered in Mexico City, Mexico to focus on the range of actions that must be undertaken to reduce the considerable burden of cervical cancer in Latin America and the Caribbean where, according to Ciro de Quadros of the Sabin Vaccine Institute, one woman is dying every 15 minutes from the disease.

The conference, “Towards Comprehensive Cervical Cancer Prevention and Control in the Region of the Americas,” was hosted by the World Health Organization (WHO), Pan American Health Organization (PAHO), Sabin Vaccine Institute and the U.S. Centers for Disease Control and Prevention (CDC). It explored all aspects of the problem and considered a host of solutions that have the potential to finally tame a disease that is a major health threat to women and the families and communities who depend upon them, particularly in the developing world.

The conference included:

- New research that confirmed and clarified the high rate of cervical cancer incidence and deaths in the region and provided new estimates for the prevalence of human papillomavirus (HPV) in LAC, the vaccine-preventable disease that causes cervical cancer

- Updated technical information on HPV vaccines and a review of the current challenges and opportunities involved with integrating them into existing immunization programs, which included a consideration of costs

- Discussion of new approaches to cervical cancer screening that have the potential to greatly improve detection and treatment in the region, particularly in low-resource settings, and an exploration of a supplementary intervention to secondary prevention in the future in which HPV immunizations could become routine care
Why Knocking Out Cervical Cancer Requires a One-Two Punch

The wide range of data presented and the discussions that ensued all pointed to the need for a comprehensive approach to cervical cancer control, one in which countries would consider adoption of HPV vaccines within the framework of a broader effort that includes enhanced screening and treatment. Health experts believe the combination of HPV immunizations with improved screening and treatment has the potential to save hundreds of millions of lives in the region.

Today, there are two vaccines available that are considered highly effective at preventing the two types of HPV responsible for the majority of cervical cancer cases. However, the vaccines are only useful for preventing HPV. They are of no benefit to a woman already infected with HPV types in the vaccines. Dealing with cervical cancer in the population already exposed to HPV requires effectively screening for signs of the disease and moving quickly to treat.

Mexico’s Secretary of Health, José Angel Cordoba, said it “has to be clear” that adoption of a vaccine does not mean “other interventions” to prevent and treat cervical cancer should be “put aside.”

“We all know that an isolated intervention does not make the difference,” he said. “The important thing is to develop comprehensive strategies for prevention and control of cervical cancer.”

Dr. de Quadros believes the combination of HPV vaccines with “other prevention measures” has the potential to be “something extraordinary” for improving the health of women in the region, noting that “ten years ago we did not think we would be discussing a vaccine for preventing cervical cancer.”

He said the meeting could one day be seen as the beginning of the most aggressive and effective cervical cancer prevention effort ever undertaken in the developing world.

“We all know that an isolated intervention does not make the difference.”

José Angel Cordoba
Secretary of Health, Mexico
The Burden of Cervical Cancer in the Region

Cervical cancer is a “significant public health problem in the Americas” where in many countries it is the leading cause of cancer deaths among women said Silvana Luciani, Project Manager for the Unit of Non-Communicable Diseases at the Pan American Health Organization (PAHO). She said that each year in the Americas there are an estimated 87,000 new cases and 39,000 deaths, most involving poor women in LAC.

She said the main priorities today are to improve the coverage and quality of cervical cancer screening programs, while preparing for the introduction of HPV vaccines for adolescents, which can stop cervical cancer from ever occurring. But the challenge is considerable. Luciani estimated that of the 336 million women in the Americas, about 52 million women are infected with HPV and 5 million have pre-cancerous lesions.

“So when we are talking about making HPV vaccines available and about screening women and targeting women, we’re talking about a large and significant number of women in this region that need to be captured in programs,” Luciani said.

Luciani said the overall cervical cancer mortality rate for LAC is seven times greater than in North America and even higher for poor countries. For example, in Nicaragua, Bolivia, Haiti and Guyana, mortality rates exceed 25 per 100,000, compared to 2.5 in the United States and Canada. Also, even in areas that have made progress in reducing deaths, there are “pockets of populations” of poor women where the death rate has been consistently high, she said.

FIGURE 1

Estimated Number of Women with HPV, Pre-cancer and Cancer in the Americas

From Silvana Luciani, Pan American Health Organization
FIGURE 2

Cervical Cancer in the Americas

87,000 new cases per year
39,000 deaths per year

Mortality per 100,000

- <4.9
- 5.0 – 9.9
- 10.0 – 19.9
- 20.0 – 29.9
- 30.0 – 39.9
- >40

From Silvana Luciani, Pan American Health Organization
Source: IARC, GLOBOCAN 2002
New Insights into the Prevalence of HPV in the Region

A centerpiece of the Mexico City conference was a new, comprehensive analysis of 15 years of research in the region that provides the best evidence to date of the prevalence and impact of HPV in Latin America and the Caribbean. The study was conducted by the Sabin Vaccine Institute in collaboration with PAHO, the CDC, the Harvard School of Public Health, and Barcelona's Catalan Institute of Oncology.

It reviewed 15 years of studies from Argentina, Barbados, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Surinam and Venezuela. By examining research that used DNA tests to detect HPV, the study concluded that HPV infections are relatively common regardless of whether a woman has a “normal cytology.”

According to one of the lead authors of the study, Maria Teresa Valenzuela of the University of the Andes, Santiago, Chile, the analysis concluded that for Latin American women in the general population with normal cytology, the prevalence of HPV in 15–24 years old is “high” at around 20 percent. She said infection decreases through age 50, bottoming out at around 11% in women 45 to 54 years old before rising again and reaching about 20% in women over 65. Infection rates are generally higher for women seen in health clinics, she said, and for women low and high-grade cervical lesions.

FIGURE 3

Age-Specific HPV Prevalence Among Women with Normal Cytology

From Maria Teresa Valenzuela, University of the Andes, Chile
For example, HPV prevalence was 56% in women found to have what are known as “atypical squamous cells of undetermined significance” or ASCUS, 79% in women with low grade cervical lesions (LSIL) and 94% in women with high-grade lesions (HSIL). Valenzuela said among women with cervical cancer the proportion with detectable HPV approaches 100%, as would be expected.

The analysis confirmed the importance of HPV types 16 and 18 as the lead causes cervical cancer. It revealed that while type 16 had only a 2.6% prevalence in the general population, it was found in 50% of cervical cancers. Type 18 had only a 1% prevalence in the general population, but “a 10% prevalence in the population with invasive cancer,” Valenzuela said.

She said there was not significant variation in HPV genotypes around the region, which means the existing vaccines, which protect against infection from types 16 and 18, should be uniformly effective from country to country.

“The vaccines that prevent high-risk viruses reach around 70%” of cervical cancers that occur in the region, Valenzuela said. “So we shouldn’t be limited by this problem of how much a vaccine with two genotypes covers.”

In addition, the study highlights the role of HPV in other cancers, including cancers in men. Valenzuela said HPV was responsible for 36% of cancers of the oral pharynx, 45% of penile cancers of the oral pharynx, 45% of penile

![FIGURE 4](image_url)

**FIGURE 4**

**Age-Specific Prevalence of High and Low Risk HPV Among Women with Normal Cytology**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>High Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
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<td>13.1</td>
<td>4.5</td>
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<td>25–34</td>
<td>8.3</td>
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<tr>
<td>35–44</td>
<td>6.9</td>
<td>2.1</td>
</tr>
<tr>
<td>45–54</td>
<td>5.6</td>
<td>3.9</td>
</tr>
<tr>
<td>55–64</td>
<td>6.3</td>
<td>3.7</td>
</tr>
<tr>
<td>65+</td>
<td>15.6</td>
<td>8.2</td>
</tr>
</tbody>
</table>

From Maria Teresa Valenzuela, University of the Andes, Chile
cancers, and 90% of anal cancers. Valenzuela said that, overall, it appears HPV causes 11,400 non-cervical cancers annually.

Valenzuela said the study also shows “that it is important to talk about the role of men in the transmission of this disease” because there are indications that there is an (HPV) “infection rate of 50% in men.”

One interesting observation from the study was the return of high HPV rates as women age. Doctor Nubia Muñoz, Consultant with the Catalan Institute of Oncology, said one reason for the spike in later life could be due to new infections that stem from renewed sexual activity following divorce or the death of a husband. “Some people talk about the Viagra effect,” she said.

Muñoz said there has been some discussion of the possibility of latent HPV infections can get “reactivated.” But she said there is not firm evidence that HPV can be latent in the cervix. Another possibility, she said, is that the studies are simply picking up large cohort of older women who were exposed to HPV ten, 20 or 30 years ago but had not been screened.

While the study offers the best portrait to date on the impact of HPV in Latin America and the Caribbean, Valenzuela said there are “still considerable holes in what we know for some specific countries in the region, especially epidemiological data.”

“The vaccines that prevent high-risk viruses reach around 60% to 70%” of cervical cancers that occur in the region. So we shouldn’t be limited by this problem of how much a vaccine with two genotypes covers.”

Maria Teresa Valenzuela

University of the Andes, Chile
HPV and Cervical Cancer: Diseases that “Don’t Stop Surprising Us”

Xavier Bosch, a researcher at Barcelona’s Catalan Institute of Oncology, is one of the world’s leading experts on the link between HPV and cervical cancer. Bosch said even for researchers who have been studying the diseases for a long time, HPV and cervical cancers “don’t stop surprising us.” For example, he noted there is new data showing that many women assessed as “cytologically normal” via Pap smear are nonetheless carrying HPV and, frequently, a high-risk type such as 16 or 18, the key culprits in cervical cancer.

Bosch said the trends documented by researchers indicate that, absent successful interventions, cervical cancer is going get worse in the Americas. He presented a daunting analysis that considers a world in which “nothing changes” to interrupt the spread of HPV, such as widespread adoption of HPV vaccines, and cervical cancer prevention programs remain where they are today. It predicts that by 2020 there will be a 75% increase in cervical cancer in Central America, 55% in South America, 36% for the Caribbean and 23% for North America.

“In Latin America we are going to be in a much worse situation if we strictly maintain what we’re doing now,” he said.

Bosch also is interested in learning more about the particular subtypes of HPV that are causing cervical cancer.

He presented the results of an international study showing that of 8,000 cases analyzed, types 16 and 18—the two strains targeted by both HPV vaccines now on the market—are the first and second leading cancer-causing strains. Type 45 was number three. Looking specifically at Latin America, again 16 and 18 were the top to disease-causing types, responsible for 70% of cervical cancers in the region, followed by types 45, 31 and 33. There is some fluctuation. For example, Bosch reported that in Argentina, 16 and 18 are responsible for 75% of cervical cancers while in Colombia, they account for 60%.

Still, Bosch said all indications are that globally, the differences in HPV types that lead to cervical cancer are “small.” He said in Latin America, by targeting types 16 and 18, the existing HPV vaccines “have the potential to prevent some 70%” of cervical cancer in the region and half of all precancerous lesions.”

| FIGURE 5. Predicted Number of Cases of Cervical Cancer in 2020: the Americas by Area |
|-----------------|-----------------|-----------------|
|                 | 2002            | 2020* (% CHANGE) | 2020* (% BURDEN) |
| WORLD           | 493,243         | 702,746 (42%)   |                  |
| America         | 86,532          | 122,162 (41%)   | 100%             |
| Central         | 17,165          | 29,794 (74%)    | 24%              |
| South           | 48,328          | 74,785 (55%)    | 61%              |
| North           | 14,670          | 18,112 (23%)    | 15%              |
| Caribbean       | 6,369           | 8,685 (36%)     | 7%               |

*Projections assume constant rates in the interval at the 2002 estimates

From Xavier Bosch, Catalan Institute of Oncology, Spain
“This means we are set to move forward,” he said. “We are not in a situation where we need to conduct more studies in order to convince our Health Ministers” of the capacity of HPV vaccines to reduce cervical cancer incidence and deaths.

In addition to its impact on cervical cancer, Bosch said HPV immunization may prevent a “significant fraction of all other genital and oral cancers in women” which are also linked to the virus. Bosch suggested that there could be benefits to vaccinating men against HPV. Because HPV is a sexually transmitted disease, Bosch said male vaccination has the potential to interrupt transmissions and provide herd immunity for women.

“If we dare to enter into the vaccination of men, we could possibly see a double effect: a herd immunity effect,” he said. “That is, women, even those who are not vaccinated, are slightly protected by the fact that the circulation of the virus in the male community will be dramatically reduced.”

Bosch said male vaccination could be of further interest given the potential to achieve “significant reductions in penile, anal and oral cancers in men,” the majority of which are caused by HPV types 16 and 18.

Bosch also pointed out that one of the vaccines now on the market has the added benefit of protecting against HPV types 6 and 11, which causes troublesome non-cancerous lesions, namely genital warts. As Bosch noted, “genital warts aren’t going to kill the man or the woman, but they are probably going to kill the relationship.” And he said if the warts occur in a pregnant woman who delivers a child via a vaginal birth, there is a risk of the child developing a recurrent viral respiratory infection: respiratory papillomatosis.

“In Latin America we are going to be in a much worse situation if we strictly maintain what we’re doing now.”

Xavier Bosch

Catalan Institute of Oncology, Spain
Toward Comprehensive Cervical Cancer Prevention and Control in the Region of the Americas

Challenges to Reducing Cervical Cancer Deaths Through Screening

Cervical cancer can be prevented by screening women regularly for pre-cancerous cervical lesions—which today is usually accomplished with a Pap smear—and treating the lesions before they progress to cancer. One reason 33,000 women in Latin America and the Caribbean (LAC) die from cervical cancer each year is that, unlike in the United States, Europe or Canada, screening programs have had mixed success in reaching and properly testing women who are most at risk of developing cervical cancer and ensuring treatment for those with abnormal test results.

PAHO’s Luciani said that while intensified screening efforts have clearly lead to progress in the US and Canada—and produced a steady, though less dramatic, decline in deaths in Mexico, Chile and Costa Rica—other countries, such as Cuba and Colombia, have not “seen the same degree of impact” despite efforts to improve screening programs.

“This illustrates that there are challenges with cervical cancer screening in limited resources settings,” she said.

For example, she said health care services in Latin America are good at reaching younger women because the tests are offered when they seek out “reproductive services” or bring their children in for immunizations. But she said women who are most at risk of cervical cancer—women over 30 years old—are the least likely to get screened.

Other issues, she said, that that have complicated the use of screening to control cervical cancer in the region include the fact that:

- The effectiveness of the technology involved in the most common test for cervical cancer, the Pap smear, depends on the quality of the smear, the availability of transportation to deliver samples to a laboratory in a timely fashion, and a high quality laboratory, including sufficient numbers of trained personnel capable of accurately reading the results

- The Pap test, even when done correctly, is prone to “false negatives,” which means its success in detecting cancer is tied to regular screening that is so hard to accomplish in many areas

- Health services may not be efficiently organized to ensure that women at high risk understand they need to be screened and that screening can routinely require a minimum of three visits: one for initial screening, one to get results, and, if there were any abnormalities, another visit to conduct further diagnostic testing, with the possibility of additional visits to treat pre-cancerous lesions

- Many women are ashamed and embarrassed when it comes to getting a pelvic exam, particularly from a male doctor, and will not seek out screening if they do not experience symptoms

There are also impediments to using the newest screening technology on the market, which is a test that can detect HPV in human DNA. For example, Luciani said the technical requirements for executing the test exceed the infrastructure available in many poor areas. However, Luciani said there is a new, “fast” HPV DNA test under development that “does not require a sophisticated laboratory.” Instead, it can be administered and read in a primary health
Luciani said there is also increasing interest in a relatively low-technology approach that involves swabbing the cervix with an acetic acid solution—known as visual inspection with acetic acid (VIA) test—and then visually inspecting for suspicious precancerous lesions. This test can be done by a trained primary care doctor, nurse or midwife, she said, and, like the rapid DNA test, produce quick results.

A key advantage of both approaches—the rapid HPV DNA test and the VIA test—is that they could allow women to be tested and then treated for any pre-cancerous lesions in a single visit, what clinicians call the “screen and treat approach,” Luciani said.

“The Pap test, even when done correctly, is prone to ‘false negatives,’ which means its success in detecting cancer is tied to regular screening that is so hard to accomplish in many areas.”

Silvana Luciani
Pan American Health Organization
HPV Vaccines as a Catalyst for Comprehensive Control

Interestingly, it is the advent of the HPV vaccine and its potential, if given to young girls, to prevent cervical cancer in future generations of women that has generated new interest in revitalizing screening services, Luciani said.

“Having the HPV vaccine has really helped provide an impetus for the whole continuum of cervical cancer prevention and control (it has helped raise awareness of the HPV-related cancers,” she said. “We are seeing a lot more information in the media among different audiences that have not traditionally been involved in cervical cancer screening, such as immunization and adolescent health programs.”

Luciani said the development of HPV vaccines in tandem with the emergence of new screening methods has prompted PAHO to propose a “regional strategy and plan of action” that seeks to attract more attention and resources to cervical cancer control.

She said in terms of screening, the emphasis will be on adopting approaches and tests that are most likely to provide the best coverage, quality and follow-up care for the targeted population.

For vaccine introduction, PAHO recognizes, she said, that countries will need evidence on such issues as burden of disease, delivery methods and how an HPV vaccine could be incorporated into existing adolescent health programs. Luciani said PAHO also understands that for vaccination program to be sustainable, HPV immunizations would need to be available at an “affordable” cost.

She said overall, the knowledge and technology is available to achieve a substantial reduction in cervical cancer incidence and deaths in LAC. The challenge, she said, is “how do you put it all into practice?”

For example, Irma Ramos, head of the PATH Peru HPV Vaccine Project, observed that there are oncologists and scientists who are “very attached to Pap smears” and they may resist adopting new forms of screening, particularly if they are not convinced by evidence of their effectiveness. Luciani agreed that it can be difficult to get professionals to consider new approaches.

“Changing behaviors is always a long and difficult undertaking,” she said.

Gilda Codina with the Honduran Cancer Program said Honduras is familiar with the challenges to conducting screening in low resource settings that Luciani cited in her presentation. In particular, she said the relatively high costs of Pap smears have produced situations in which women provide samples but there’s no funding to pay the lab for testing, which ends up discouraging women from participating in screening programs.

Vance Dietz with the United States CDC said a successful comprehensive cancer control program that consists of both vaccines and screening will require better coordination within government health ministries between two programs that may have rarely collaborated: cancer prevention and vaccination programs.

“They are very different and are two different parts of the Ministry,” he said.
Seeking Alternatives for Screening in Low Resource Settings

As was previously noted, there is widespread consensus that the most effective approach to comprehensive cervical cancer control is one that involves adoption of HPV vaccine in conjunction with the implementation of more effective screening programs and technologies. José Jerónimo of PATH, which is supporting a range of efforts to combat cervical cancer in low resource settings, is particularly interested in the second part of that equation: developing approaches to screening and testing that are better suited to areas with minimal health services.

Jerónimo echoed previously expressed sentiments regarding the inadequacy of the Pap smear. For example, he said “sensitivity of the test” to finding suspicious lesions “isn’t optimal,” a shortcoming that is addressed in wealthy countries by simply increasing the frequency of testing. “If the first test does not detect the disease, the following tests” probably will, Jerónimo said. But cost and logistics of repetitive Pap smears are yet another factor that have rendered the test of limited value for improving cervical cancer screening in most developing countries, he said.

Jerónimo said the visual inspection method describe earlier—swabbing the cervix with an acetic acid solution (such as vinegar) and then visually inspecting for lesions is at least “as good” of a screening approach as the Pap smear in detecting lesions, while far simpler and cheaper.

But Jerónimo noted that more consistent and reliable screening can be accomplished by testing for HPV DNA. He said an early version of the DNA test, known as Hybrid Capture, was too expensive and technologically complex for widespread use in the developing world. The need for an inexpensive and practical HPV test prompted PATH to collaborate with the developer of the Hybrid Capture technique, Qiagen to create what is now called the Care HPV test.

**FIGURE 7. QIAGEN’s New HPV-DNA Test: Schematic**
Care HPV, which is expected to be available in the next year, was developed for use in limited resource settings. Jerónimo said Care HPV tests appear to be a very promising alternative for detecting HPV. For example:

- the results from the test can be available in about two and a half hours or less
- samples don’t require refrigeration
- the technology for conducting the test consumes only about two meters of space

“It can be installed in a laboratory or health center that has relatively simple conditions,” he said. Equally important, an individual Care HPV test costs less than US $5, he said.

Also, unlike the Pap smear or visual inspection, which requires some level of interpretation, the Care HPV test is either “positive or negative,” Jerónimo said, so “there’s not a lot to think about.”

“The problem we see with cytology (Pap smears) is that one cytologist reads it completely different from another cytologist,” he said.

Another short-coming of Pap smears is likely to be amplified by vaccination, Jerónimo said. The issue is that while the vaccine is considered highly effective at protecting women from the two types of HPV that cause the most cervical cancers, 16 and 18, vaccinated women would still require at least occasional screening. That’s because they can still acquire non-vaccine types that could put them at risk for cancer.

But Jerónimo said Pap smears have proven to be less likely to pick up abnormalities in the cervix when HPV types other than 16 or 18 are involved.

“In the future, when we don’t have HPV 16 and 18 anymore, the lesions that the cytologist reviews are going to be more confusing and some cases will go unnoticed,” he said. Further complicating screening via Pap smear, he said, is the fact that with a vaccine reducing the number of positive cases, cytologists will have a harder time maintaining their ability to spot abnormalities.

“Maybe in the future we will have to depend on an HPV test to identify at-risk women,” he said.

Jerónimo said a cheap and effective HPV test also could be valuable in monitoring the impact of HPV immunization programs. For example, he said the test could be used to sample different populations who have received the vaccine and for those who test positive for HPV, further investigations could probe what types of HPV are involved.

Such studies, he said, could reveal the extent to which the vaccine is providing partial protection against non-vaccine HPV strains or whether “other types of HPV that aren’t included in the vaccine could start to fill the niche left by” the demise of 16 and 18.

Jerónimo presented the results of a field study from China which showed the Care HPV test had 90% sensitivity to HPV, compared to 50% for Pap smears. In other words, Jerónimo said while the Care HPV test might produce a false negative in 1 out of 10 patients, “the Pap smear misses almost one out of every two” positive cases.

Finally, because the technique for obtaining a cervical sample required for the test is relatively simple, there is now a possibility of further reducing the complications of cervical cancer screening by having women obtain the samples themselves.

At the time of the conference, there were demonstration projects being developed in India, Uganda and Nicaragua to evaluate the test in different regions with high rates of cervical cancer.
He said one goal of the project is to understand how an effective screening program could make use of more than one form of screening.

For example, he said the HPV test could help define the subset of women who should be followed more closely and screened for suspicious lesions in subsequent visits either by visual inspections or other techniques. If they test positive for HPV, Jerónimo said, then “we already know they have the virus and they are at a higher risk than any other women.”

“When we don’t have HPV 16 and 18 anymore, the lesions that the cytologist reviews are going to be more confusing and some cases will go unnoticed. Maybe in the future we will have to depend on an HPV test to identify at-risk women.”

José Jerónimo
PATH, US
Vaccine Victories: Past Successes in LAC Show Potential Role for HPV Immunization

One reason there is so much excitement about the potential of an HPV vaccination to significantly reduce the burden of cervical cancer in LAC is that over the last few decades, immunizations have “played a very important role” in improving health in the region, said Cuauhtémoc Ruiz Matus, Chief of PAHO’s Immunization Unit.

“Immunization programs have always represented the edge of the sword that has allowed us, with other additional programs, to get to the most remote areas, to the most vulnerable populations, and moreover, achieve social and political awareness about healthcare,” he said.

Ruiz said past experiences have shown that the LAC region has been able to overcome considerable challenges to controlling disease via vaccines. For example, he noted that convincing warring factions in El Salvador to temporarily suspend fighting in order to permit immunizations was crucial to the region’s successful push to eradicate polio. He also observed that the last ten years has seen a steady expansion of immunizations, including the accelerated adoption of the measles, mumps and rubella (MMR) vaccine and, more recently, rotavirus vaccinations.

Ruiz said that immunization coverage in the region is exceptional. For example, between 2001 and 2006, coverage for the diphtheria, pertussis and tetanus (DPT), MMR, and polio vaccines was 95%.

“I can clearly say that there is no other region in the world that has these levels of vaccination coverage,” he said.

**FIGURE 8. Reduction in Infant Mortality in Latin America and the Caribbean, 2002**
Ruiz also pointed out that LAC is the only region in the world that has embraced the goal of eliminating rubella and congenital rubella syndrome. And he said the region moved especially rapidly in recent years to adopt the new vaccine for haemophilus influenzae B (Hib).

He said PAHO is looking to the future guided by what it calls its Regional Immunization Vision and Strategy for the Americas or RIVS. RIVS has three main focal points he said: protecting hard earned gains, completing unfinished business (such as the elimination of rubella and measles), and facing future challenges, which includes initiating or expanding the adoption new vaccines such as the new vaccines against rotavirus, pneumococcal disease and HPV.

Ruiz said the interest in the HPV vaccine highlights the needs to embrace a more expansive view of immunizations: as health interventions that have a role to play in all age groups, not just young children. He said immunizations are no longer childhood vaccinations but “family vaccinations” and that the region can draw on its past work to make this transition.

For example, he said recent success vaccinating 145 million adolescents and young adults against rubella shows that it is possible to reach this age group with vaccines, which is often cited as one of central challenges of introducing an HPV vaccine.

“We vaccinated them at their schools, at home, in discotheques, in the subway, wherever we could find them,” Ruiz said. “We didn’t have any problems. So we have ample experience in the Americans working with adolescent vaccinations.”

Another past success that will be instrumental to future immunization achievements, he said, is PAHO’s Revolving Fund for Vaccine Procurement. Created in 1967 to allow all countries in the Americas to purchase vaccines at the same low wholesale price, the fund is now purchasing $330 million worth of vaccines. Ruiz said the revolving fund is expected to play a key role in the effort to make new and under-used vaccines, including HPV immunizations, affordable to all.

But Ruiz said that while PAHO can provide considerable assistance, when it comes to adopting new vaccines like HPV immunizations, the key decisions will have to be made at the national level. He said these decisions must be “based on scientific evidence” of effectiveness and impact on burden of disease and with a clear understanding of the “financial sustainability for the program.” He also said new vaccines have to be seen as an expansion of immunization programs, not as supplanting existing vaccines.

“We need to protect our past achievements,” he said. “We cannot take even one step backwards or sideways.”

Ruiz said public health officials are now keenly aware that successfully incorporating a new vaccine into a national immunization program requires careful attention to such issues as having proper storage or “cold chain” capacity, establishing epidemiological surveillance programs to monitor the impact of the vaccine, ensuring staffing is sufficient at all points in the process, and understanding the relationship between the disease serotypes targeted by the vaccine and those that are circulating in the population.

He also pointed out that HPV vaccines have arrived on the market at time when countries in the region are considering an ambitious expansion of immunization activities that will significantly escalate costs for national programs.

“The current scheme for regular vaccination immunizations at rotating fund prices...is about US $19,” he said. “If we add the cost of seasonal influenza, the price goes up to US $24. If we add the cost of rotavirus vaccines to that, we’re at about $40. If we add three doses of the conjugated
pneumococcal vaccine our total is $150. And if we add three dose of (HPV vaccine) at around $360, that costs around $500.”

Ruiz said it is possible to introduce an HPV vaccine within “the schematic” of national immunization programs, “but not now, not today.”

“This is an extraordinary successful vaccine and it’s a vaccine with ample potential,” he said.

“That’s why we also have to be extremely careful in the introductory process. To do it right, we have to be prepared, because it will require a huge investment by the countries, and we want to act responsibly and in agreement with the Ministries of Health.”

“This is an extraordinary successful vaccine and it’s a vaccine with ample potential. That’s why we also have to be extremely careful in the introductory process. To do it right, we have to be prepared, because it will require a huge investment by the countries, and we want to act responsibly and in agreement with the Ministries of Health.”

Cuauhtémoc Ruiz Matus
Pan American Health Organization
The New Vaccines Against HPV

There are currently two vaccines available that protect against cancer-causing types of HPV. The first one to come on the market was Gardasil, which is manufactured by Merck Vaccines and is now widely used in the US and Canada. The other, Cervarix, developed by GlaxoSmithKline Biologicals (GSK), is a relative new-comer but is rapidly gaining regulatory approval in many countries in the Americas.

**Merck’s Gardasil Vaccine**

Randall Hyer, Senior Director, Medical Affairs and Policy at Merck Vaccines and Infectious Diseases, discussed the results so far with Gardasil. He noted that it is formulated to fight four HPV Types: 16 and 18—which cause the majority of cervical cancers worldwide—and 6 and 11, which can cause genital warts, low-grade dysplasias, and recurrent respiratory papillomatosis. He described the basic composition of the vaccine, how it employs synthesized, non-infectious HPV viral proteins to stimulate a natural immune response as if the body were being challenged by an actual infection.

Hyer said the vaccine is manufactured in yeast employing a safe, “tried and true” production technique that has been “used for hundreds of millions of doses of vaccine.” He noted that it is currently recommended that the vaccine be administered in three doses over a six month period.

Hyer cited peer-reviewed data indicating the vaccine is highly effective at preventing the targeted HPV types and that it appears to offer a degree of “cross protection” against certain non-vaccine disease types in what are known as A9 and A7 families.

He said recent studies show it is 100% effective in the prevention of disease caused by HPV 16 and 18 and 99% effective in with the prevention of disease caused by HPV types 6 and 11, which cause the majority of cases of genital warts and low-grade dysplasia and recurrent respiratory papillomatosis. But Hyer reminded the audience that Gardasil is a preventive, not a “therapeutic vaccine.” He said it can prevent disease from HPV types known to cause cervical cancer (and other forms of cancer) or genital warts, but it cannot cure an existing HPV infection nor be used to treat cancer or warts. (The same is true of Cervarix.)

Hyer was questioned about the fact that the high efficacy he cited is “greatly reduced” when one conducts an “intention-to-treat” analysis. In other words, if all subjects enrolled in the trials testing the vaccine are analyzed, not just those without previous exposure to HPV, then the efficacy of the vaccine is lower. Hyer acknowledged that when examined on an intention to treat basis, the efficacy results were lower. But he noted that it is widely understood that the vaccine is not effective against existing infections.

“You need to remember that this is a preventive, prophylactic vaccine,” he said.

Hyer asserted that the US Food and Drug Administration has found Gardasil “safe and effective” and that the WHO Global Advisory Committee on Vaccine Safety “concluded the current evidence on safety is reassuring and that no concerns with the safety profile were identified.” He also said that studies thus far show “a long duration of protection.”

In general, the vaccine is recommended for girls before they become sexually active to maximize the opportunity to immunize before exposure to HPV. However, Merck has also observed that most sexually active women are not infected with all 4 vaccine HPV types, and thus, could derive some benefit from vaccination. In fact, while the vaccine is currently approved for females ages 9 to 26 years old, Merck has produced efficacy data in older women and has applied
to the US Food and Drug Administration for approval in use in females up to age 45.

He said that Gardasil had been approved in more than 100 countries, including 17 countries in the Caribbean and Central America and eight in South America. Hyer said over 26 million doses have been distributed and eight million girls are thought to have received their first dose.

**GSK’s Cervarix Vaccine**

Eduardo Ortega, GSK Biologicals Vice President and Head of Clinical Research and Development for LAC, discussed his company’s Cervarix vaccine. He said the vaccine has been tested in over 40,000 women in studies conducted in 45 countries and has been approved by 50 countries, including the nations of the European Union.

He said the studies show the vaccine to be safe and effective against the two HPV types it targets, 16 and 18. GSK’s goal in developing vaccine, he said, was to “provide the best primary prevention possible against cervical cancer” by concentrating on the two most common cancer-causing types of HPV.

Ortega cited data from phase two study that, examining subjects about 6 years post-immunization, found the vaccine to be “100% effective” against “persistent infection” from types 16 and 18. He said other studies have provided evidence that the vaccine appears to provide some level of “cross protection” against viral types other than 16 and 18.

Ortega said there is also evidence that the vaccine will produce a long-lasting immune response in the great majority of those immunized. He said a study of immune response 6 years after immunization found that, for women 15–25 years old vaccinated with three doses of Cervarix, antibody titers against HPV peak after one month, then decrease until, at about 18 month post-immunization, they “plane out” but remain consistently elevated. He said when the antibody response observed thus far is fed into a mathematical model, the prediction is that “for both HPV 16 and HPV 18, the antibody titers are going to remain elevated for almost 50 years.”

Furthermore, he presented data showing that while antibody response is high for all women vaccinated, it is particularly strong in girls vaccinated between 10 and 14 years of age compared to those vaccinated between 15 and 25 years old.

“This is a guarantee that if we vaccine 10 to 14-year-old girls, the antibodies will probably last longer,” Ortega said.
HPV Vaccine Introduction: Perspectives from the Region of the Americas

The HPV immunizations now available are part of a new wave of innovative vaccines that present new opportunities for reducing sickness and death in the Americas. But a key feature of these new vaccines is their relatively high price, which means, “We need to collect and analyze even more data and evidence, in comparison to the history of immunizations,” said Jon Andrus, Lead Technical Adviser for PAHO’s Immunization Unit.

Andrus said decision makers need evidence on, among other things:

- burden of disease
- adverse events linked to the vaccine
- long-term stability of vaccine supply
- logistical and operational details, such as cold-chain capacity
- financing strategies to sustain introduction
- political commitment to the intervention
- community perception of risk

He said PAHO has been developing a five-year plan that would help accelerate vaccine adoption by supporting country efforts to address these issues. For example, as part of PAHO’s ProVac program, new tools are being developed to conduct economic studies, including one developed by Harvard’s Sue Goldie to analyze the economics of HPV prevention.

With regards to cost effectiveness, Andrus reiterated the fact that even if the price of the vaccine dropped considerably from its current cost of $120 per dose, HPV immunizations are still likely to have a huge impact on national budgets. For example, if the price of a vaccine

<table>
<thead>
<tr>
<th>Price per dose</th>
<th>Cost effectiveness</th>
<th>Budget*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ 5.00</td>
<td>&lt; $400 to avert DALY</td>
<td>$360 million</td>
</tr>
<tr>
<td>$12.25</td>
<td>&lt; $800</td>
<td>$811 million</td>
</tr>
<tr>
<td>$19.50</td>
<td>&lt; $1,400</td>
<td>$1.26 billion</td>
</tr>
</tbody>
</table>

*Financial cost to vaccinate 70% of 5 consecutive birth cohorts of South America

FIGURE 9. Cost Effectiveness and Affordability

From Jon Andrus, Pan American Health Organization
dropped all the way to $5 a dose, he said it would still cost South American countries about $360 million to vaccinate the majority of five successive groups or “birth cohorts” of girls in the targeted age range.

“We have to use this information to negotiate more affordable prices,” Andrus said.

For example, he said that Paraguay was considering an approach to adopting the HPV vaccine in which it would receive the vaccine free for three years, on the condition that after three years it would pay for immunizations at a price to be negotiated. However, Andrus said that “after some time, the country said ‘we have to stop discussions because the price is still prohibitive at $35 per dose’.” He said there was a similar effort to find a way to introduce HPV vaccines in Jamaica, “but again, Jamaica practically has the syringe in hand to use the vaccine, but the price is prohibitive.”

Andrus said the challenges involved in adopting an HPV vaccine raise a larger issue, which is how to ensure the sustainability of national immunization programs. For example, he said in dealing with affordability, countries need to look for new sources of financing, improve program efficiency, and consider opportunities to develop alliances with the private sector. Andrus also reiterated the importance of PAHO’s Revolving Fund in securing affordable vaccines.

“For us, negotiating affordable prices so that you can use the vaccine will be a great challenge,” he said.

PAHO is particularly keen, Andrus said, to avoid a “zero sum game” situation in which countries see the only way to adopt an HPV vaccine is to cut some other critical health program.

Sabin’s Ciro de Quadros said his definition of an affordable vaccine is one that is “affordable to the buyer and the seller.” Vaccine developers also need to view the prices as adequate, he said, “because you don’t want to kill the goose that laid the golden eggs.”

“It is important that vaccine manufacturers continue to produce vaccines because HPV isn’t the last vaccine we are going to want,” he said. “In the future we’ll want other vaccines.”

“For us, negotiating affordable prices so that you can use the vaccine will be a great challenge.”

Jon Andrus
Pan American Health Organization
The Cost Effectiveness of an HPV Vaccine in Selected Latin American Countries

Along with providing a better understanding of the burden of HPV related diseases in Latin America and the Caribbean, another goal of the conference was to focus on the economic aspects of HPV vaccination.

Prior to the conference, a group of researchers that included some of the world’s leading experts in the economics of immunization conducted a detailed analysis of introducing HPV immunization in six Latin America countries: Brazil, Colombia, Mexico, Peru, Argentina, and Chile. They estimated the costs of dealing with cervical cancer in these countries and compared them to the costs of introducing a vaccine at various price points ranging from $25 per vaccinated girl to $360 per vaccinated girl.

The results of the study show that, from an economic perspective, the vaccines’ cost-effectiveness ultimately will depend on combination of factors, which can vary depending on:

- how one estimates the current costs of dealing with cervical cancer;
- the existing burden of cervical cancer in a given country; and
- the cost of an HPV vaccine.

According to a presentation of the results from Dagna Constenla, a health economist who worked on the study, the scenarios range from situations in which a relatively low-cost vaccine would save money by preventing HPV infections to situations in which a more expensive product would not be cost-effective compared to screening and treatment.

To develop a comparison to cancer control via vaccine, Constenla said researchers “assumed that all women” with invasive cervical cancer would be treated. Two categories of treatment costs were developed, she said, a lower number or “lower bound” cancer costs that included only direct medical treatment, and a higher number or “upper bound” cancer cost—which was developed following a series of interviews with doctors who treat cervical cancer patients—that included the cost of providing palliative care to dying patients.

The study assumed that either of the two currently available vaccines would be 100% effective against HPV Types 16 and 18 and considered a scenario in which immunizations would cover 70% of 12-year-old girls. Constenla said disease burden was calculated by assessing deaths and incidence of cervical cancer in the targeted countries and also by adding up the loss of what health economists call “Disability Adjusted Life Years” or DALYS. A DALY measures years of life lost to either death or disability caused by a particular disease or condition.

While the cost of the vaccine for the region has yet to be determined, for the purposes of the study, Constenla said researchers looked at a number of hypothetical scenarios that assumed various “costs per vaccinated girl.” These costs included the price of the vaccine—which comprised the bulk of the expense—along with costs associated transportation, disposal, administration and other immunization services. The scenarios they examined ranged from situations in which the cost would be $25 per vaccinated girl to $360 per vaccinated girl for the complete three dose regimen.

One thing that appears clear from the study: the vaccine could have an enormous impact on disease. The researchers found that vaccinating 70% of 12-year-old girls against HPV 16 and 18 would reduce the risk of contracting cervical cancer by anywhere from 39% (Chile) to 54%
(Argentina). Overall, the researchers predicted that if for 10 consecutive years the targeted countries successfully immunized their 12-year-old girls, they would prevent half a million deaths from cervical cancer.

“If we consider that there is an underestimation of cervical cancer cases in the records of each country of around 30% to 50%, the prevention of deaths would increase proportionately,” she said.

But from an economic perspective, what are the costs of saving all those lives and how do they compare to the existing costs countries are essentially paying to treat cervical cancer?

At $25 per vaccinated girl (which is $5 a dose plus the various immunization expenses) the study found countries would actually save money by vaccinating if one assumes cervical cancer treatment costs at the higher level; that is, the category of costs that includes palliative care expenses. But Constenla said at the lower cost assumption for cervical cancer treatment, the $25 price tag would generate savings in only two countries.

However, Constenla said that from an economic perspective, a vaccine does not have to save money to still be cost-effective.

Today, health economists use a benchmark for establishing cost-effectiveness of immunizations that was developed by the World Health Organization. It is a method that classifies a vaccine as cost-effective if the investment required for each DALY saved by the vaccine is less than three times per capita GDP. (In other words, if each disability adjusted life-year saved by the vaccine ends up costing a country $75 and its per capita GDP multiplied times three is more than $75, then the vaccine would be considered cost-effective.)

Constenla said by this measure, an HPV vaccine was found to be cost-effective in all six countries even at $75 per vaccinated girl.

Predictably, as prices increased, cost-effectiveness decreased. For example, at $100 per vaccinated girl, the vaccine was no longer cost-effective in Peru, Colombia and Brazil. At its

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**FIGURE 10. Adolescent HPV 16,18 Vaccination: Health Outcomes**

<table>
<thead>
<tr>
<th>COUNTY</th>
<th>CANCER INCIDENCE</th>
<th>LIFETIME REDUCTION IN CANCER, %</th>
<th>CASES OF CANCER AVERTED</th>
<th>CANCER DEATHS AVERTED</th>
<th>% OF CASES/DEATHS AVERTED</th>
<th>YEARS OF SAVED (YLS)</th>
<th>TOTAL FOR 6 COUNTRIES</th>
<th>TOTAL FOR 33 COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>23.2</td>
<td>53.86</td>
<td>5,796</td>
<td>3,478</td>
<td>6%</td>
<td>86,921</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>23.4</td>
<td>48.17</td>
<td>35,363</td>
<td>21,218</td>
<td>35%</td>
<td>474,912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td>25.8</td>
<td>39.41</td>
<td>2,767</td>
<td>1,660</td>
<td>3%</td>
<td>48,461</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td>36.4</td>
<td>40.30</td>
<td>9,512</td>
<td>5,707</td>
<td>10%</td>
<td>140,264</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>29.5</td>
<td>39.60</td>
<td>15,213</td>
<td>9,128</td>
<td>16%</td>
<td>215,813</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peru</td>
<td>48.2</td>
<td>47.46</td>
<td>5,218</td>
<td>3,131</td>
<td>5%</td>
<td>69,046</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total for 6 countries</td>
<td></td>
<td>73,869</td>
<td>44,322</td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total for 33 countries</td>
<td></td>
<td>97,984</td>
<td>58,791</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Results shown are for a single birth cohort, 70% coverage by 12 years of age; e.g., for example, in Brazil, vaccinating 70% of the 12 year old girls next year would prevent 35,363 cervical cancer cases over the lifetime of that birth cohort.

From Dagna Constenla, Health Economist, Belgium
“So the question Dr. Ruiz asked yesterday, ‘are we ready for a vaccination program for HPV?,’ we can clearly see that many factors should be considered, not just efficacy, but also the cost-effectiveness and financial stability of this investment for each country.”

Dagna Constenla
Health Economist, Belgium

SIDEBAR
The Need for Advocacy in the Fight Against Cervical Cancer

Scott Wittet, Director of Cervical Cancer Advocacy with PATH encouraged health officials in Latin America and the Caribbean to join a new global effort he chairs that is dedicated to fighting cervical cancer. Known as Cervical Cancer Action, Wittet said the group is responding to the need for advocacy to “encourage political commitment and prioritization of cervical cancer prevention at all levels.”

For example, Wittet said that for poor countries, the hope at the moment is that the GAVI Alliance will “pick up the HPV vaccine” and offer it at a “considerably subsidized price.” But he said for middle income countries, which includes most of the nations of LAC, advocacy is needed to get leaders focused on finding new sources of financing that can enable the adoption of both the vaccine and new screening technologies.

“We need to mobilize individuals and communities to demand access to these life-saving tools from their own governments and for governments to be demanding access on a global scale,” he said.

Cervical Cancer Action, he said, was founded by eight global health organizations, including PAHO and PATH, and now has 1500 member organizations. The goal of the group is not focused on a single intervention, Wittet said, but on integrating all tools into a targeted campaign against cervical cancer and expediting access and affordability.

The organization’s activities thus far range from seeking signatories to an online petition for a global push to stop cervical cancer; a newsletter that focuses on such timely topics as vaccine pricing and new data on screening techniques; policy briefs on issues relevant to cervical cancer prevention and treatment; and media outreach. Wittet said the group also had recruited high-level officials, including the former President of Ireland, Mary Robinson, to assist with the effort.

At the conference, Wittet and PAHO’s Jon Andrus asked representatives from national health ministries to send formal letters to the CCA noting the importance of addressing cervical cancer as a public health priority and calling for a high-level of commitment to increasing control and prevention activities. Andrus said CCA can use these communiqués to build a case at the global level for devoting more resources to fighting cervical cancer.

Wittet added that anyone can also go to the CCA web site, cervicalcanceraction.org and sign-on to the CCA “call to action.’
FIGURE 11. Affordability and Budget Implications of HPV 16,18 Vaccination

<table>
<thead>
<tr>
<th>Country</th>
<th>$25</th>
<th>$50</th>
<th>$360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>$22,708,877</td>
<td>$50,145,266</td>
<td>$389,255,369</td>
</tr>
<tr>
<td>Brazil</td>
<td>$124,247,788</td>
<td>$266,520,877</td>
<td>$2,026,508,740</td>
</tr>
<tr>
<td>Chile</td>
<td>$9,321,447</td>
<td>$19,749,461</td>
<td>$148,799,093</td>
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<tr>
<td>Colombia</td>
<td>$31,854,537</td>
<td>$69,912,684</td>
<td>$540,388,762</td>
</tr>
<tr>
<td>Mexico</td>
<td>$81,353,368</td>
<td>$169,684,024</td>
<td>$1,263,359,012</td>
</tr>
<tr>
<td>Peru</td>
<td>$20,817,860</td>
<td>$44,927,599</td>
<td>$343,121,615</td>
</tr>
<tr>
<td>All 6 countries</td>
<td>$290,303,902</td>
<td>$620,939,961</td>
<td>$4,711,432,951</td>
</tr>
</tbody>
</table>

Shown are financial costs in U.S. dollars to vaccinate 5 consecutive birth cohorts with 70% coverage (Present value, 3% annual discounting).

From Dagna Constenla, Health Economist, Belgium

SIDEBAR
Going Online to Gather More Data on Cervical Cancer

The process of designing the most efficient and effective approaches to detecting and preventing cervical cancer is heavily dependent on having a steady supply of statistics and analysis on all things related to cervical cancer and HPV.

The World Health Organization in collaboration with the Catalan Oncology Institute (ICO) has established an online “HPV Information Center” in order to provide the global, regional and country-specific data that can assist in making informed decisions and strategies for combating cervical cancer, said ICO’s Silvia de San Jose. (It is available at http://www.who.int/hpvcentre/en/)

The web site, she said, includes data on such issues as prevalence of HPV infection in women for whom testing showed no abnormalities and for women with different grades of abnormalities. It also compiles data from published studies to shed light on such issues as potential co-factors involved in cervical cancer and current immunization coverage rates in different countries.

The information is organized in a way that allows users to download technical reports that contain data relevant to a specific country, de San Jose said. The center is also working to produce a comprehensive publication on everything we know today about HPV and cervical cancer in addition to a regional report for Latin America and Asia Pacific countries.
“We need to mobilize individuals and communities to demand access to these life-saving tools from their own governments and for governments to be demanding access on a global scale.”

Scott Wittet
PATH, US

current retail price of $360, vaccination was not cost-effective in any of the countries studied, Constenla said.

Another wrinkle in the analysis, said Constenla, is that in countries that have the necessary infrastructure, the most cost-effective strategy in certain scenarios would be to combine vaccination with an enhanced screening program.

Finally, Constenla reiterated what other speakers had observed, namely that cost-effectiveness does not necessarily mean affordability. For example, she pointed out that even at $25 per vaccinated woman, the combined costs for the 6 countries studied to vaccine just five consecutive groups or “birth cohorts” of 12-year-olds would be US $290 million. At $360, it would be US $4.7 billion.

“In spite of the significant financial indicators, cervical cancer is currently costing the region around US $360 to $670 million annually,” she said. “So the question Dr. Ruiz asked yesterday, ‘are we ready for a vaccination program for HPV?’, we can clearly see that many factors should be considered, not just efficacy, but also the cost-effectiveness and financial stability of this investment for each country.”
Widespread Introduction of HPV Vaccine: Reports from the Frontlines

HPV vaccines have been successfully introduced in Canada and the United States, but the effort has not been free of friction or challenge.

**HPV Immunization: the US Experience**

Markowitz said that in March of 2007, the CDC’s Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccinations for 11 and 12 year old girls and a “catch-up” vaccination for females 13 to 26 years old.

She noted that the targeted age selected was based in part on national surveys showing 26% of US females report having vaginal sex by age 15. As of the March of 2008, Markowitz said over 15 million doses of Merck's quadrivalent HPV vaccine—the GSK bivalent vaccine was still undergoing regulatory review at time—had been distributed in the US, which accounted for over half of the Merck HPV vaccine distributed worldwide.

**FIGURE 12. Adolescent Vaccination in the US**

![Recommended Immunization Schedule for Persons Aged 7–18 Years — United States • 2008](image)
She said that prior to introducing the vaccine, a national survey of pediatricians revealed that most physicians supported the vaccine, but physicians might be less likely to recommend HPV immunization to the targeted group than they would to older adolescents. About 89% said they would be “likely to vaccinate a 16 to 18 year old versus only 46% a 10 to 12 year old,” Markowitz said.

“This survey also showed some issues around knowledge by pediatricians about HPV, about sexuality, and about transmissions of HPV, illustrating a need to educate not only the public but also providers about HPV epidemiology,” she said.

Markowitz noted that while ACIP is not involved with recommendations regarding cervical cancer screening, it did issue a statement about the need for continued screening, particularly since the vaccine does not cover the HPV types that cause 30% of cervical cancers.

While the US is considered a wealthy country, Markowitz said the price of the HPV vaccine has been a concern. She said the US is currently paying $96 a dose (compared to the retail price of $120) for the Gardasil vaccine it supplies through a federal program that provides immunizations for low-income children, which currently accounts for about 45% of all vaccine doses purchased in the US.

The CDC is starting to get some data on coverage from various “sentinel sites” around the country. For example, the percentage of females 11 to 18 years who received at least one dose of the vaccine in the first six months after implementation ranged from a low of 7% in these sentinel sites in the state of Montana to a high of 22% in Oregon.

Markowitz said those numbers may seem low however, they reflect data from areas that had just received HPV vaccine in the first half of 2007.

She said a survey of parents who had not gotten their daughters vaccinated found that 22% wanted more information, 17% had not yet visited a doctor to discuss it, 16% said their daughter was too young, 14% said they had never heard of HPV vaccination, and 12% said their daughter wasn’t having sex yet. But while in the US there have been some who have opposed HPV immunization due to fear that it would encourage sexual promiscuity, Markowitz said only 1% cited this concern as a reason their daughters had not been vaccinated.

In addition, she said neither cost, insurance coverage, nor safety registered as impediments to getting an HPV vaccination.

HPV vaccine has been the target of some controversy in the US, particularly around an early push for school entry immunization requirements in some states.

As for safety, Markowitz said US officials have established a system for reporting adverse events related to the vaccine and has required the manufacturer to conduct a large “post marketing study in managed care organizations.” Markowitz noted that there has been overall increase in reported incidents of syncopal (fainting) in the wake of the introduction of three new adolescent vaccines, which include, in addition to HPV, immunization against tetanus, diphtheria toxoids, and acellular pertussis (the Tdap vaccine) and immunization against meningococcal (MCV4).

“We don’t know if this is just because more vaccines are being given to adolescents...or whether or there’s an increased number of syncopal episodes after HPV,” she said. “Those issues are being investigated.”

Looking to the future, Markowitz said US officials were expecting GSK’s bivalent HPV vaccine to be approved and available in the US market by 2008 or 2009, raising the question of whether there will be different recommendations for each vaccine.
She wondered whether there would be “difference related to protection” against types 16 and 18, which both vaccines cover, and how to deal with the fact that the Merck vaccine covers two additional HPV types, which are linked to non-cancerous genital lesions. Thus far, she said the data show that both vaccines have “high efficacy” against 16 and 18 and may offer some cross protection against other types, “but how important that is, is not clear,” Markowitz added.

Unknown thus far she said is whether the duration of protection will be the same for both vaccines and how they will compare in terms of costs. If both vaccines are available in the US, there is also the possibility, she said, that a patient could get one vaccine for her initial dose and then “present to a provider who has a different vaccine for later doses.” There are no data on interchangeability of the two vaccines.

“These are all questions that are currently being addressed by the committee (ACIP),” she said.

**HPV Immunization: The Canadian Experience**

Mahnaz Farhang Mehr, Chief of Immunization Programs for the Public Health Agency of Canada, said that the National Advisory Committee on Immunization (NACI), a scientific group that advises the Public Health Agency of Canada has recommended the Merck quadrivalent HPV vaccine, the only authorized vaccine for use in Canada at the present time, for three groups of women:

- Females between 9 and 13 years of age, since this is before the onset of sexual debut for most females in Canada;

- Females between the ages of 14 and 26 years would benefit from HPV program, even if they are already sexually active, as they may not yet have HPV infection and are very unlikely to have been infected with all four types in the vaccine; and

- Females between the ages of 14 and 26 years who have had previous pap abnormalities, including cervical cancer, or genital warts. These women may not have had infection with the
HPV types included in the vaccine and are very unlikely to have been infected with all four HPV types contained in the vaccine.

Prior to implementation, Farhang Mehr said a joint working group of NACI, Canadian Immunization Committee and other stakeholders involved in HPV control and treatment was formed to provide a programmatic recommendation for the introduction of this vaccine using the “Analytical Framework” for introduction of a new vaccine. This framework addresses: diseases characteristics and burden; vaccine characteristics; alternative immunization strategies and programs; feasibility and acceptability of alternative program strategies; evaluation questions; research questions and other issues important for consideration before introduction of a vaccine. To fulfill the requirements of the framework and to have a better understanding of different options, economic analysis and modeling was done. In addition surveys were conducted to assess knowledge, attitude and belief and also feasibility and accessibility for the HPV vaccine. Based on scientific evidence available and studies carried out, the following recommendation for the introduction of HPV vaccine was made to the Provinces and Territories.

Immunize one cohort of school aged girls in grades 4, 5, 6, 7 or 8 with three doses of HPV vaccine. A catch up program, for one or two cohorts based on resources available should also be considered.

Farhang Mehr acknowledged that introduction of HPV vaccine received much media attention partly because of negative impact of an intensive promotional campaign launched by the vaccine manufacturer. She said a prominent women’s group was also negative about the vaccine that received much media attention. Farhang Mehr showed the front page of a Canadian national magazine that said “OUR GIRLS ARE NOT PIGS” to show an example of the negative coverage.

On the other hand, she said the medical and cancer care communities were very supportive of the vaccine introduction and coverage rates around the country range from 50% to 80% of the targeted groups at present time.
Cervical Cancer Control: Country and Sub-regional Perspectives

The Caribbean: Establishing a New Foundation for Prevention

Cervical cancer is a major cause of disease and death in the 21 countries of the Caribbean sub-region where it kills a estimated 16 of every 100,000 women annually, according to Beryl Irons, an epidemiologist with PAHO. She said that “key stakeholders” from the region met in Barbados in June of 2007 to discuss the challenges associated with preventing cervical cancer and adopting an HPV vaccine.

She said an analysis of studies conducted in the Caribbean between 1988 and 2005 revealed that HPV types 16 and 18 occur in a lower proportion of cervical cancers in the region than they do in North America. Nonetheless, she said there is agreement that an HPV vaccine should be incorporated in each country’s Expanded Program on Immunization (EPI), provided it is “pre-qualified” by the WHO. There is also need, Irons said, for studies on cost-effectiveness that “clearly support vaccine introduction” along with assurances that Pap smear screening would be “continued and strengthened as necessary.”

In addition, Irons said Caribbean health officials want to establish a network consisting of two laboratories, one that would focus on cervical cytology and another on HPV testing.

Since the meeting, Irons said three countries have “stated interest” in introducing an HPV vaccine in two years as part of broader effort to improve their cervical cancer prevention program.

Overall, she said Caribbean countries have embraced the potential of HPV vaccination to serve as a catalyst for a comprehensive and more effective cervical cancer prevention program. She said that while successfully introducing an HPV vaccine will require stronger partnerships, enhanced screening, and a clear definition of the targeted population, governments “will support” immunization.

“Our major challenge is the price of the vaccine,” Irons said, “so I hope industry is listening.”

Costa Rica: An Ambitious Goal to Eliminate Cervical Cancer Deaths

Deaths from cervical cancer decreased in Costa Rica between 1995 and 2005, though there was a slight increase in mortality in 2004, largely due to an influx of immigrant populations who do not use health care services, said Rafael Salazar, an OB/GYN who also works with the Costa Rican Ministry of Health.

He said in 2008, Costa Rican health officials signed an agreement committing the country to reducing deaths “due to cervical cancer to zero.” As part of that agreement, he said officials declared that all women regardless of income “have a right to a Pap smear when they need it and to receive treatment when it is necessary.”

Salazar said achieving these ambitious goals will be a challenge, particularly given the fact that “we have extreme poverty in Costa Rica, we have long stretches of marginalized populations in the capital city of San Jose, the cost of living has increased tremendously, and access to health services has become more difficult.”

Another challenge, Salazar said, is that screening programs have been deficient because they are usually performed by general physicians who do not know how to obtain adequate sample for testing.

Salazar said Costa Rica is working to improve screening and recently established a new system for monitoring the quality of cervical cancer detection, diagnosis and treatment services. In addition, health officials have been negotiating with GSK in an effort to purchase HPV vaccines at a discount. However, it temporarily suspended those discussions, he said, because the
government is seeking a situation in which it can provide the vaccine “to the entire Costa Rican population and not just a specific group.”

At the time of the conference, HPV vaccination was only available in Costa Rica in the private sector.

Brazil: High Variations in Disease and Screening, High Interest in Vaccines

The incidence of cervical cancer in Brazil varies considerably from region to region, with rates up to 30 per 100,000 women in the North and Central-West regions compared to 20 to 25 per 100,000 in the South and Southeast, said Claudio Noronha, of Brazil’s National Cancer Institute. He said overall, the disease kills about 5,000 women in Brazil each year and that number has remained constant for 25 years despite intensive efforts to improve screening programs.

He said experts believe 80% of Brazilian women over 25 undergo screening at least once in their lifetime, “but there is a large variation, especially in districts in the Northeast region.” Noronha said “follow-up” care is weak.

He said Brazil has approved both the quadrivalent (Merck) and bivalent (GSK) HPV vaccines and at the time of the conference was evaluating the possibility of incorporating them into the publicly funded immunization program.

While experts in Brazil believe a vaccine could be an “important instrument to control cervical cancer,” obstacles to adoption remain, including the relatively high price of the vaccines. Noronha said at the current cost a “three dose set for 9 to 11 year old girls will require three times as much as the entire cost of the yearly immunization program for Brazil.”

He said there are discussions in Brazil about making the HPV immunization more affordable by seeking a technology transfer agreement from either GSK or Merck and then manufacturing the vaccine domestically.

“We are very interested in implementing the vaccine here,” he said.

Chile: An Aggressive and Creative Approach to Improved Screening

In the late 1980s, Chile established a National Cervical Cancer Program and embarked on an aggressive and creative effort to increase access to Pap smear exams, said Marta Prieto, the program’s director. The Program has involved everything from upgrading equipment in health care centers and establishing a national reference laboratory for quality assurance to implementing a public education campaign that used inventive techniques such as street theater and raffling a “Pap smile”—offering women who got a Pap smear the chance to win a free dental check-up—in order to encourage more people to seek out screening.

However, over the last few years there has been concern in the sense that the coverage of the Pap Smear has reached a plateau after uninterrupted growth in the 90s and it even decreased slightly to 66% in 2005. Prieto said that this has led to the relaunch of the campaigns that had been left aside in 2004 due to lack of resources.

“We are very interested in implementing the (HPV) vaccine here.”

Claudio Noronha

National Cancer Institute, Brazil
Chile has also taken the unusual step, she said, of providing women with a legal guarantee that they will receive screening, treatment and follow-up care within a fixed time-frame. “If it isn’t provided, the woman has the right to appeal to a court of law,” Prieto said. “She can demand this guarantee.”

For example, Prieto said the law stipulates that a woman was entitled to receive treatment within 20 days of confirmation of an invasive cancer. A recent survey found that this goal is “currently achieved in 78% of the population,” she said.

Regarding progress made, Prieto underscored that in Chile, over the past 20 years, the National Cervical Cancer Control and Prevention Program has increased screening, improved access to treatment and follow-up care and reduced cervical cancer mortality among women between 25 and 64 years old. Between 1987 and 2005, she said deaths from cervical cancer dropped by 58.2% in this group (from 18.2 per 100,000 women to 8.6. among women 25 to 64 years old.

Prieto said there is interest in Chile in the potential of an HPV vaccine, but it is generally viewed as something that should be a “great compliment to a good screening program.”

“We can’t forget that the most important priority is to strengthen screening programs,” she said.

Colombia: Search for alternatives given the lack of efficacy of cytology-based programs

Raul Murillo of Colombia’s National Cancer Institute said there have been “some reductions” in cervical cancer deaths in Colombia, but “far from what we would hope for with 15 years of working on cervical cancer prevention and control.”

He described a concerning situation in which research shows coverage for screening is relatively high—76% in the last three years for cytology—but “again that doesn’t agree with the mortality tendency we are seeing.” But he said the situation is the same throughout Latin America.

“What we found is that there is no relationship between coverage levels and reduction of mortality in the region,” he said.

He said an evaluation in Colombia has suggested that the reasons increased screening may not be affecting mortality rates include:

- a perception among people in the health care system that cervical cancer is not a priority
- decentralization of services that, while it was supposed to improve quality, has diminished technical capacity at the lower levels of the system
- the fact that an early cervical cancer detection program was dismantled and replaced by a system that relies on a series of goals that have not translated into concrete actions

In addition, Murillo said a study of a cytology screening in Bogota, where there was an intensive effort to automate testing and improve quality controls, found that cytology sensitivity was only 30%.

“We can’t forget that the most important priority is to strengthen screening programs.”

Marta Prieto
National Cervical Cancer Program, Chile
“What we found is that there is no relationship between coverage levels and reduction of mortality in the region.”

Raul Murillo
National Cancer Institute, Colombia

“We're talking about a huge effort that's not reflected in the results that we're obtaining today,” he said. “This shows the difficulties of achieving adequate quality control for this test.”

Murillo said there are a variety of efforts now being developed that will seek to remedy the existing deficiencies in screening and detection. As for adopting an HPV vaccine, he said there are no projects “currently underway,” though there has been some data gathered on HPV prevalence and studies conducted on vaccine acceptance.

Mexico: Looking to Improved Screening, Vaccines for New Era of Control

Mexico's Secretary of Health, José Angel Cordoba, said cervical cancer deaths in Mexico have been on the decline, decreasing 25% in the last six years. Nonetheless, he said Mexico still records 6,900 cases—19 a day—and 4,000 deaths from the disease each year. He said the majority of cases occur in “marginalized populations” that have little access to health services.

Cordoba said Mexico's goal is to implement prevention and control measures that get the “maximum benefit” at the “lowest cost and with the lowest risk.” The focus at the moment is to direct more attention to cervical cancer prevention in poor populations that have few health resources. He said there are efforts underway to improve detection and treatment for precancerous lesions for poor women, an initiative that includes a special fund that provides access to testing and treatment for women who lack health insurance.

Patricia Uribe, director of the National Center for Gender Equality and Reproductive Health in Mexico, said a recent high point occurred in 2006 when health authorities in Mexico guaranteed “free treatment for every woman” regardless of income.

Uribe said Mexico screening programs continues to struggle with low coverage, particularly in less populated regions, and with deficiencies in test quality that produce “many false negatives.”

Mexico is now embarking on a new cervical cancer prevention and control effort, she said, one that seeks to provide Pap smears for 85% of women combined with HPV testing. She said HPV testing is being incorporated into the effort because it has the potential to improve screening in areas that lack the laboratories or infrastructure to conduct Pap smears.

Also, depending on the price of vaccines, Mexico would like to offer HPV immunization.

Uribe said researchers have been conducting a variety of studies to decide the most effective and affordable approaches to fighting cervical cancer. For example, she said that at $20 a dose, a vaccine is a cost-effective method of cervical cancer control compared to interventions such as Pap smears and HPV testing.

Mexican health officials have received funding to launch a pilot project that will seek to provide HPV immunizations to pre-adolescent girls in Mexico’s 125 poorest municipalities.

“This pilot project will allow us to see acceptability, obstacles, and operative issues that we need to consider in the event that, at some point, the countries decide together to initiative vaccination,” she said.
In Peru, Going Low Tech in an Effort to Achieve High Coverage

Carlos Santos Ortiz of Peru’s National Institute of Neoplastic Communicable Diseases added his voice to the chorus of experts who are unhappy with the Pap smear. He said in many Latin American countries, the “failure” of the Pap smear to make a difference in disease incidence and deaths “has been the rule more than the exception”

“This is because the cytology-based system is very demanding in terms of laboratories and trained staff and requires a number of visits before a woman is in a position to receive treatment,” he said.

Santos is a proponent of an approach that involves utilizing a low-tech screening methods followed by immediate treatment of suspicious lesions.

In 2000, he and his colleagues worked with PAHO, the Peruvian Ministry of Health, and PATH to develop a pilot program called TATI to test this approach. It has involved using relatively simple “visual inspection” techniques to detect suspect lesions followed by cryotherapy treatment (destruction of the lesions by freezing them) with CO2, which is cheaper than the more commonly used nitrous oxide.

The goal was to find a way to provide effective screening and treatment of suspicious lesions that would be practical for areas with poor populations that lack the health care resources required for conventional approaches.

The study focused on enhancing the availability and quality of cervical cancer screening and treatment services for the 100,000 women in the San Martin region of Peru who are between 25 and 49 years old.

One important result was that the simple, inexpensive approaches to screening, which involved applying an acetic acid solution to the cervix and then inspecting either with the naked eye or with a special magnifying device, were better than Pap smears at picking up abnormalities. By one measure, the sensitivity of the visual inspection method for detecting potentially troublesome lesions was 54.8% compared to 26% for the Pap smear.

Equally important, said Santos, is that the visual inspection offered immediate results, which allowed physicians participating in the study to offer screening and treatment in the same visit. For example, in one part of the study, more than 90% of patients who tested positive for suspicious lesions were treated on the same day with cryotherapy.

Also, Santos said patients who required a follow-up visit appeared to be much more likely to return when given immediate results of their visual screening tests compared to those who had to wait days or weeks for the results of a Pap smear. According to Santos, only about 9% of women who underwent visual inspection failed to return for their follow-up appointment compared to 44% who “were subjected to classic management.”

“One of the virtues of the visual inspection is that by providing immediate results the amount of women who disappear decreases,” he said.

Santos also found that the cost of visual inspection was about half the cost or less than conventional screening via Pap smear.

FIGURE 14

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<th>TATI PROJECT: VIA vs. VIAM by physician</th>
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<tr>
<td>• Aviscope had no discernable advantage over VIA</td>
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<td>• Triage can be done by physician with naked eye</td>
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From Carlos Santos Ortiz, National Institute of Neoplastic Communicable Diseases, Peru
Santos said the project demonstrates that low-tech, low-cost approaches to screening can provide a satisfactory and even superior alternative to conventional screening. Achieving better coverage of at-risk women remains a challenge, he said, as the project did not come close to achieving its objective of providing screening for 85% of the targeted group. Coverage was only 35%.

“We have to campaign and get more commitment from the community,” Santos said.

The study also revealed that using magnification technology to conduct the visual inspections was no more effective than simply examining the cervix with the naked eye.

Santos said the encouraging results from the project has prompted the creation of the Latin American School for the Management of Cervical Cancer, which has become a regional training center for teaching alternative techniques for screening and treatment.

There were questions for Santos about whether the lack of coverage and the sensitivity of the screening techniques justified their use in low resource settings. Santos acknowledged that coverage needs to be improved and that sensitivity of 60%, even though it is better than what is achieved with cytology, is “not perfect.” But he asserted that if coverage can be improved to 80%, visual inspection is sufficient to “diminish the amount of invasive cancer by about half” in the targeted groups. That’s a significant achievement compared to the status quo, he said.

“It’s diminishing invasive cancer by 50% versus nothing, which is what they have now,” he said.

SIDEBAR

Introducing HPV Vaccines in Latin America: the MINSA/PATH Project in Peru

As part of an international effort to facilitate the adoption of HPV vaccine in developing countries, the health NGO PATH has been working with the Peruvian Ministry of Health (MINSA) on a pilot project that's exploring the challenges and opportunities involved in providing HPV immunizations to young girls in Latin America.

Irma Ramos of PATH said the project has been executed in three phases:

- The first phase involved education, communication and dialogue with parents, children and teachers.
- The second phase explored issues related to vaccination coverage and vaccination strategies.
- The third phase, which was still ongoing at the time of the conference, has involved a demonstration project to understand how HPV vaccination could perform as a routine immunization implemented through schools.

The demonstration project is focused on vaccinating 5th grade girls in several areas, including girls who live in “very poor” regions, Ramos said, with three doses of Merck’s Gardasil vaccine. It was expanded in 2008 to include more than 7,000 girls.

Ramos said a number of factors have emerged that have a potential to affect coverage rates in the targeted group. For example:

- Consent can be a problem, Ramos said. There have been instances in the project, she said, in which parents did not agree to the vaccination or the girls simply did not return the form. There were also situations in which girls from rural areas were going to school far from home and not living with their parents and so could not obtain parental consent.

- Since the vaccinations were done as part of a pilot project, the forms noted that the immunizations were “investigational,” and Ramos said that bothered many parents. “Even though we explained over and over that it was not a clinical trial, many parents could not get the idea out of their heads that their daughters were being used as guinea pigs,” she said.

- Some girls felt like they were not getting enough information and were intimidated by health care professionals, which Ramos said prompted the creation of an “information exchange” between teachers, parents and children. There was also an effort to educate teachers about the vaccine.

With 2500 Peruvian women dying every year from cervical cancer, Ramos said the hope is that the pilot project will lay a foundation for a future in which HPV immunization is a part of routine care for young girls.
Elizabeth Unger, Team Leader for the HPV Laboratory at the US CDC, described a wide range of technical issues and complex laboratory practices that can play a role in the quality and usefulness of conducting HPV surveillance with a test that detects HPV DNA. These challenges are getting a lot of attention today, she said, as the WHO moves to create a network of laboratories that can use HPV DNA tests to carefully monitor the effectiveness of HPV vaccination.

She said establishing a network that allows for “inter-laboratory” comparisons is crucial first step to ensuring epidemiological studies of HPV worldwide are adhering to a shared set of standards.

“When we come together as a group, and we compare the results of HPV worldwide and we have differences regionally, we want to know that those are real differences and not just differences in the kind of assay or the kind of sample that was collected or the kind of laboratory that was doing” the work, she said.

One of the difficulties in determining the effectiveness of testing for HPV DNA, she said, is that, strictly speaking, the test is not a definitive measure of the main cause of concern, which is cervical cancer. The test only indicates the presence of HPV DNA, not cancer. In fact, Unger said a positive result is not necessarily a reason for alarm.

She said the DNA detected by an HPV test could be “a totally inactive infection, it could be one that’s been essentially cleared...it could be the DNA from a partner. All we know is that we can find the DNA.”

Additional complicating factors, she said, include the fact that there are more than 100 HPV viruses, but only about 40 that cause concern “in the genital tract.” Yet all HPV viruses are “closely related,” Unger said, which poses a “logistical nightmare” when it comes to a test that could “detect all of them sensitively and selectively.”

But even with all the challenges involved, Unger said HPV DNA remains “our closest surrogate to infection.”

Overall, Unger said adequately monitoring the state of HPV as a public health problem will require “a very large scale testing program,” that utilizes sensitive and relatively sophisticated detection methods that “have a very high cost.”

“So not only is the vaccination expensive but the testing procedures (to monitor effectiveness) are very expensive,” she said.

Unger said that given the complexities of DNA testing, there could be a tendency to just consider reduction in cervical cancer as proof of the vaccine’s effectiveness. But she said that if countries achieve their stated goal of adopting HPV immunization while simultaneously improving screening, “it’s going to be hard to tease out whether it was the vaccination or the screening” that achieved the change.

“I think we just have to accept that would be a good problem to have,” she said.

Unger said that it might not be necessary for every country that uses the vaccine to “specifically evaluate vaccine efficacy.” Some countries, she said, could contribute to the overall assessment by focusing on vaccine uptake.

“So not only is the vaccination expensive but the testing procedures (to monitor effectiveness) are very expensive.”

Elizabeth Unger
Centers for Disease Control and Prevention, US
Conclusion: A New Commitment to Cervical Cancer Control

Dr. Ruiz of PAHO said that at a press conference on the first day of the meeting, the most common question was “when do we start the introduction of this vaccine?”

“The start of the vaccine introduction has already begun; it started with this discussion,” he said.

Sabin’s Ciro de Quadros said that judging from discussions in the formal sessions and also “in the hallways and during the coffee breaks” he was confident that attendees left Mexico City “energized and enriched, enriched technically, scientifically, and emotionally.”

“It’s so great to know that the cervical cancer control programs are definitely going to improve extraordinarily in the future, even before the vaccine is introduced; there’s no doubt about that,” he said. “The dialogue that started during these two days here between the different communities that we mentioned this morning will definitely have a spectacular result in the coming years.”

Dr. de Quadros also believes that the approach to cervical cancer control that took shape at the conference is one “I think we should emulate for other vaccines that will come in the future.”

“I always say that we’re living in the era of vaccines,” he said, “and if we aren’t prepared to launch these vaccines, we’re going to miss the opportunity to truly improve health around the world.”

The meeting also concluded with the issuance of a declaration calling for governments to “promote the integration among programs responsible for immunization, prevention, control, and adolescent and reproductive health with the goal of strengthening efforts toward the prevention and control of cervical cancer.” The full text of the declaration is below.

“The dialogue that started during these two days here between the different communities that we mentioned this morning will definitely have a spectacular result in the coming years.”

Ciro de Quadros
Sabin Vaccine Institute, US
DECLARATION
of the HUMAN PAPILOMAVIRUS MEETING
Mexico City 12–13 May, 2008

Recognizing that cervical cancer is one of the most common causes of death among women in Latin America and the Caribbean (LAC);

That 33,000 women die each year of cervical cancer in Latin America and the Caribbean.

That it is estimated that, if this trend continues, the number of deaths from cervical cancer will double by 2030.

That it primarily affects vulnerable populations such as poor women and indigenous populations.

Expressing concern for the high burden of this disease, with the highest mortality rates in the world and its economic impact in Latin America and Caribbean.

That now we know HPV causes virtually 100% of cervical cancers.

That today there are vaccines against HPV, which offer great hope towards the prevention of 70% of the infections by this virus.

That the primary limitation for its use is the high cost.

That vaccines against HPV do not replace screening programs, diagnostics and treatment.

That with the introduction of this vaccine we have an opportunity to strengthen prevention and comprehensive control through improving coverage and quality of screening, diagnostics, and treatment services.

The participants resolve to:

▷ Promote the integration among programs responsible for immunization, prevention, control, and adolescent and reproductive health with the goal of strengthening efforts toward the prevention and control of cervical cancer.

▷ Take the opportunity with the introduction of the vaccine against HPV to strengthen sexual and reproductive education, training of personnel, as well as screening services, diagnostics and treatment.

▷ Continue considering immunization programs as a regional public good with high political priority.

▷ Consider the introduction of a vaccine against HPV based on technical, programmatic and operational criteria of individual countries, taking into consideration the need to strengthen the cold chain, epidemiological surveillance systems, and the laboratory network in countries.

▷ Work together and with PAHO’s Revolving Fund to obtain affordable prices for HPV vaccines so that all the countries in the region can introduce the vaccine in their national immunization programs as soon as possible.

▷ Generate mechanisms and negotiating processes with high-level financing stakeholders at the national level, which will ensure the sustainability of vaccination programs, prevention and control of cervical cancer.

COUNTRY PARTICIPANTS: Argentina, Barbados, Brazil, Canada, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, México, Nicaragua, Panamá, Peru, United States, Paraguay, Venezuela.
Speakers

Beryl Irons
Trinidad
Carlos Santos
Peru
Ciro de Quadros
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