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Progress in preventing cervical cancer: Updated evidence on vaccination and screening

Cervical cancer takes the lives of more than 270,000 women every year, over 80 percent of them in less developed countries.[1,2] Deaths from this disease not only cause great personal suffering, but are stark reminders of gender inequity in health care. The loss of mothers, grandmothers, and other essential family members who take care of children, provide income, and work in their communities also causes a significant economic hardship. The highest incidence and mortality rates are in sub-Saharan Africa; Latin America and the Caribbean; and South and Southeast Asia (Figure 1).[3,4] Even in industrialized countries that have experienced dramatic declines, the death rate is still high in regions with poor access to health care or other barriers to cervical cancer screening and early treatment.[5]

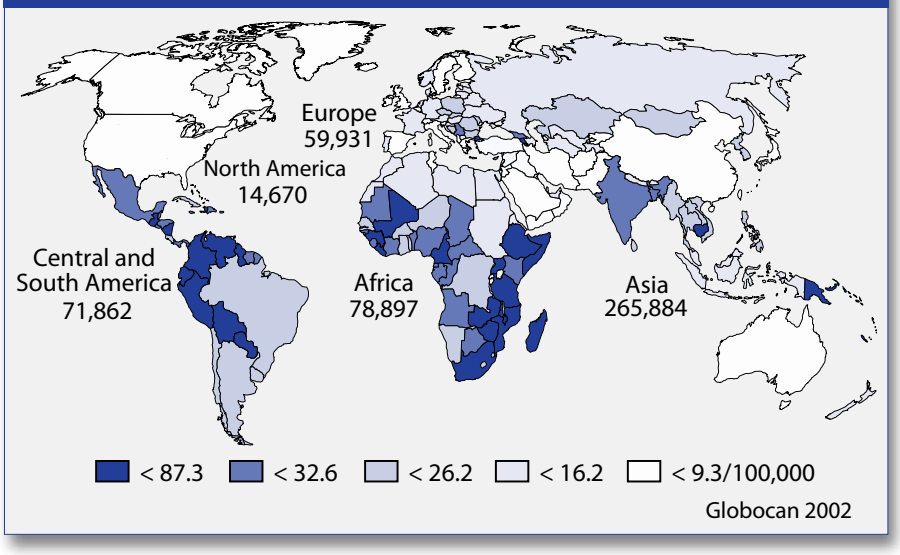
However, we now have efficient, low-cost screening approaches suitable for low-resource areas, and we have vaccines that are efficacious in preventing the precancerous changes that lead to cervical cancer, as highlighted here:[6,7]

- Safe and efficacious vaccines protect against human papillomaviruses (HPV) types 16 and 18, which cause about 70 percent of cervical cancer cases.
- Experience to date using HPV vaccines in demonstration programs in Africa, Asia, and Latin America, as well as in public health programs in Latin America, has been encouraging. Researchers and program managers are finding strong support and interest among decision-makers and in communities.
- New approaches to cervical screening using visual inspection techniques are at least as sensitive as Pap testing and are more sustainable in low-resource areas, especially when paired with cryotherapy for treatment.
- New technologies for HPV DNA screening that are highly sensitive—more sensitive than Pap testing—and suitable for developing countries have the potential to save many lives.
- Comprehensive prevention strategies—those that include both vaccination (when affordable) and screening (either starting or expanding screening and treatment programs)—will save the most lives. Such strategies are endorsed by the World Health Organization, the Pan American Health Organization, the Alliance for Cervical Cancer Prevention, PATH, and many others.

Cervical cancer and HPV

In the early 1980s, Professor zur Hausen and colleagues identified the association between certain human papillomaviruses and cervical cancer, and HPV is now known to be the cause of virtually all cervical cancers.[8] HPV infection, which is sexually transmitted, is necessary for cancer to develop, but additional factors increase the risk for progression to cancer.[1,9,10] Among these co-factors are early age at first sexual intercourse, high number of pregnancies, multiple sexual partners, smoking, long-term use of hormonal contraceptives, and infection with HIV. Clearly, lack of screening and treatment for precancerous lesions also

Figure 1. Estimated number of cases and incidence of cervical cancer[1]



increases the risk that infection will progress to cancer.

HPV infections worldwide

Papillomaviruses are tissue-specific DNA viruses that are easily transmissible and highly prevalent. HPV is the most common sexually transmitted infection, with about 630 million people believed to be infected with HPV worldwide.[11,12] In the United States, about 40 percent of young women become infected with HPV within three years of sexual debut, and globally, 50 to 80 percent of sexually active women are infected by HPV at least once in their lives.[13,14]

Fortunately, the vast majority of HPV infections are transient: they clear as a result of natural immune responses, becoming undetectable after 6 to 18 months.[15-17] However, precancer can develop if infection persists, and precancerous cells can become cancerous over time. HPV vaccination can prevent infection by the HPV types targeted by the vaccines, if given prior to exposure, and for this reason, vaccination is recommended for young adolescent girls before sexual debut.

Cancer-causing HPV types

Human papillomaviruses comprise a large family of viruses, with more than 100 types known. Some infect the genital tract and of these, some have a high potential for causing cancer (oncogenic types), whereas others cause non-cancerous conditions.

- Oncogenic HPV types cause a variety of anogenital and other cancers, such as oral cancer.
- Nononcogenic HPV types cause genital warts, abnormal cervical cytology, recurrent respiratory papillomatosis, or infections that go unnoticed and eventually clear up.[11]
- HPV 16 and 18 are oncogenic types associated with about 70 percent of all cervical cancer cases.[18,19] At least 11 other HPV types cause cancer, though less commonly. Among these, HPV 45 and 31 each account for about 4 percent of cervical cancer cases.

Cervical cancer begins with infection of cells on the surface of the cervix by an oncogenic HPV type. As mentioned above, most HPV infections clear up spontaneously, but a small percentage of women infected with oncogenic HPV types develop persistent infections, and this can lead to precancerous changes, or lesions.[19,20] Neither short-lived nor persistent infections have symptoms, so women must be screened periodically to determine if a persistent infection has occurred or if lesions have developed.

Some lesions resolve spontaneously, but others progress to invasive cervical cancer (Figure 2).[21] Progress from infection to precancer and cancer is slow,[16,18,22] so most often cervical cancer is found in women of middle age. Because of this long period of progression, there are good opportunities to identify and treat early stages of the disease—either HPV infections or precancerous lesions. If lesions are treated early, success rates are very high and cancer typically does not develop.

Preventing cervical cancer

Women can lower their risk of developing cervical cancer by both primary and secondary prevention methods. Primary prevention means avoiding initial infection with oncogenic HPV types, and this can be accomplished, for the two viruses that cause most cervical cancer, by HPV vaccination before beginning sexual activity. If infection has already occurred, secondary prevention—screening and treatment of precancerous lesions—can prevent development of cervical cancer. Abstinence or mutual monogamy can also prevent HPV infection; however, these are not realistic options for many women.

Vaccines against HPV

In 2006, the first vaccine against HPV infection was approved by the US Food and Drug Administration—Merck & Co., Inc.'s Gardasil®. Since that time, Gardasil and the GlaxoSmithKline vaccine, Cervarix®, first approved in Australia and the European Union in 2007, have been licensed in more than 100 countries worldwide. Both vaccines consist of virus-like shells containing no DNA, along with compounds called adjuvants that stimulate the immune system. The vaccines cannot cause HPV infection.

Both Gardasil[23] and Cervarix[24] protect against the most common cancer-causing types of HPV—types 16 and 18. Gardasil also protects against HPV types 6 and 11, which cause about 90 percent of genital warts. Both vaccines are given in a series of three 0.5-mL intramuscular injections

over six months, with slightly different schedules.

Efficacy of HPV vaccines

HPV vaccines prevent infection and lesions

Clinical trials of the two HPV vaccines used cervical lesions (usually high-grade lesions, such as cervical intraepithelial neoplasia 2 and higher—CIN2+) as their primary endpoint; that is, they compared the number of cases of precancerous lesions in vaccinated and control groups to determine how efficacious the vaccines were at preventing the lesions that can progress to cancer.[25,26] This progression can take decades, so it was not feasible in the trials to wait so long for cases of cancer to occur, and more importantly, it would have been unethical to allow patients to develop cancer if lesions were detected.

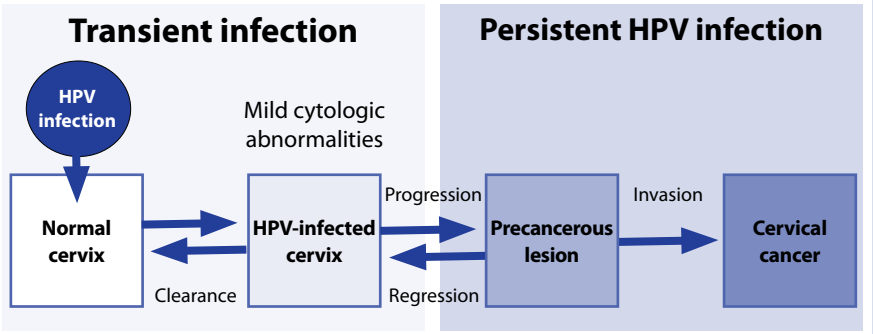
The World Health Organization[27] and other scientific bodies agreed that the CIN2+ endpoint was a logical, ethical choice to assess vaccine efficacy, and that prevention of CIN2+ strongly suggests prevention of eventual cancer. It will take time to see the effect on actual cervical cancer cases.

Efficacy in preventing precancerous lesions caused by HPV 16 or 18 for both vaccines is very high—greater than 92 percent in women who have not been previously infected with these viral types.[25,26,28] (Note that this efficacy applies to the 70 percent of cancers caused by these two viruses, not all cervical cancer.) Thus it is important to vaccinate young adolescent girls before they are exposed to the viruses through sexual activity.

Duration of vaccine protection

Published clinical trial results show that HPV vaccines are efficacious in preventing infection and high-grade lesions for at least five years (Gardasil[29]) to more than six years (Cervarix[30]) and preliminary results from a trial of the HPV 16 component of Gardasil indicate that it is effective for up to 8.5 years.[31] This is the duration reported to date, based on follow-up data from the major trials. It is encouraging that protection has not been shown to diminish over time, and the vaccines may prove to be effective for much longer, as data accumulate.[29,32] Definitive results will become available only when clinical trial participants have been followed for a longer period of time. Researchers in Finland are following 22,000 young women for at least 15 years to help answer this question.[33]

Figure 2. How cervical cancer develops



Adapted from Wright TC Jr., Schiffman M[21]

Limited protection against additional HPV types

Both Gardasil and Cervarix appear to offer some protection against cancer-causing HPV types that are not targeted by the vaccines, mainly against type 31, which is related to type 16 (current HPV vaccines target types 16 and 18). Cervarix has also shown efficacy against type 45.[26,36] However, the clinical trials reported to date were not designed to show efficacy in nonvaccine types, and protection does not reach the levels demonstrated for types 16 and 18.[34-36]

Co-administration of vaccines

Adolescents typically do not interact with health care systems as frequently as when they are younger. If HPV vaccines could be administered at the same time as other recommended adolescent immunizations or health interventions, programs might achieve higher coverage rates. At least three studies have shown that co-administration of HPV vaccine and other vaccines is safe. In these studies, researchers gave HPV vaccine during the same visit as either hepatitis vaccines (two of the studies) or a diphtheria-tetanus-pertussis-polio vaccine. In each case, the regimen was well-tolerated and, for the two studies where antibody data were available, the immune responses were good.[37, 38, 39]

Safety of HPV vaccination

The safety of drugs, including vaccines, is assessed in two ways: from data in clinical trials and from post-marketing surveillance reports from the public after medicines have been approved and are in use. Data from large, randomized clinical trials are usually very reliable, since reports of serious adverse events can be investigated and verified, and there is a built-in control group for comparison. However, extremely rare serious adverse events may not be detected until hundreds of thousands of doses of vaccines have been administered. For this reason, post-marketing surveillance is important for monitoring the safety of all drugs, including HPV vaccines.

As of August 2009, more than 50 million doses of Gardasil had been distributed worldwide,[40] (over 23 million in the United States as of December 2008[41]) with a very low rate of serious side effects and with no deaths confirmed to be associated with vaccination.[42] In Australia, as of December 2009, 6 million doses of Gardasil had been distributed with few side effects and the great majority of them mild.[43] From September 2008 to September 2009, 1.4 million doses of Cervarix were administered across the United Kingdom[44] and approximately

9 million doses worldwide,[45] also with a low rate of serious side effects and with no indication that any deaths were associated with vaccination.

Safety data from clinical trials

In clinical trial reports for Gardasil[23] and for Cervarix,[24] the most common side effect was discomfort at the injection site. With Gardasil, about 60 percent of recipients had pain, swelling, itching, bruising, or redness at the injection site; however, about 50 percent of participants in the control group, who received the vaccine adjuvant (a mixture of aluminum salts), also had these symptoms. Other common side effects were headache, fever, nausea, dizziness, vomiting, and fainting. Most side effects were of short duration (from several hours up to a few days).

In addition to these side effects, vaccines and other medicines can cause serious adverse events (SAEs), which are defined by regulatory bodies as events that result in death, are life-threatening, require or prolong hospitalization, result in significant disability or birth defects. Some SAEs have been linked to the HPV vaccines. For example, out of nearly 30,000 participants in Gardasil clinical trials, 0.04 percent reported SAEs that were judged by study investigators to be related to the vaccine.[23] Among these were three severe headaches, three cases of gastroenteritis, and one case of severe injection site pain. While 126 Gardasil recipients reported SAEs, 129 placebo recipients also reported SAEs.

After more than five years of follow-up, no deaths have been shown to have been caused by HPV vaccines in the clinical trials. The number of deaths occurring during the trials and follow-up was very small, and was similar in the vaccine and control groups, indicating that deaths following vaccination occurred by chance and were not caused by vaccine.[44,46,47]

Side effects for Cervarix are similar to those reported for Gardasil. In clinical trials, injection-site reactions were the most common side effect. Other frequent effects were headache, nausea, vomiting, and muscle aches. In regard to SAEs, throughout the large trials with control groups, there were no apparent imbalances in the rates of these events between vaccine and control groups. The number of deaths in the trials was nearly identical in the vaccine and control groups.[47]

Safety reports from post-marketing surveillance

Reports of suspected side effects from providers and the public after vaccine approval can be made to the Vaccine Adverse Event Reporting System (VAERS) in the United States; to a similar system, the Yellow Card Scheme, in the United Kingdom; and to regulatory agencies in other countries. Events reported cannot be interpreted as confirmed side effects of the vaccines; rather, these accounts only document problems that occurred sometime after vaccination (even weeks or months later). Further, because these events are reported from a population of uncertain size, it is not possible to estimate their frequency reliably. The reports are useful because they may expose patterns of post-vaccination events, which can trigger further monitoring or other action.

In VAERS reports on Gardasil, the most commonly reported adverse events following HPV immunization have been similar to those found in clinical trials. Serious side effects accounted for only six percent of all VAERS reports—and these have not been confirmed to be caused by the vaccine. US Centers for Disease Control and Prevention investigators published a review of the data available from the time of Gardasil approval in 2006 through December of 2008 and concluded that the quadrivalent HPV vaccine is safe and effective, and its benefits continue to outweigh any risks.[41]

The most common side effects reported for Cervarix in the UK Yellow Card Scheme have been similar to those in the clinical trials. According to the Medicines and Healthcare products Regulatory Agency in the United Kingdom, the number and nature of suspected side effects are in line with what was expected. The Commission on Human Medicines reviewed the data in September of 2009 and stated that following substantial usage, no new or serious risks were identified during use of Cervarix in the United Kingdom, and that the balance of benefits and risks remained positive.[48]

Safety in pregnant women

Manufacturers of both vaccines along with regulatory agencies recommend against vaccinating pregnant women, because no randomized controlled trials have been done to assess safety in this population. While contraception was required and urine pregnancy tests were required before every injection in all clinical trials, some women did become pregnant during the three-dose course of the vaccination regimen. Women

who were discovered to be pregnant during the course of clinical trials were not scheduled for further vaccinations until the pregnancy ended.

Gardasil

In a combined analysis of five clinical trials of Gardasil, the quadrivalent vaccine, data showed that out of more than 20,000 women in the trials, there were approximately 1,800 pregnancies in the vaccine groups and a similar number in placebo groups. Researchers reported no significant differences overall between groups for the proportions of pregnancies resulting in live birth, fetal loss, or spontaneous abortion.[49]

Separate analyses were conducted for the small number of women who became pregnant within 30 days of receiving an injection. In this analysis, there were numerically more congenital abnormalities in the vaccine group, but the difference was not statistically significant and total numbers were very small. While reviewers concluded that the anomalies were unlikely to be related to vaccination, they have recommended continued close attention to outcomes in this group.[50] The rate of spontaneous abortion in women becoming pregnant within 30 days of receiving an injection was the same for vaccine and placebo groups.[49]

In addition to publications on clinical trial results, a report has been published on pregnancy outcomes from a registry that collected data on Gardasil vaccinations in the general public for two years.[51] The rates of spontaneous abortion and major birth defects were not greater than the rates for the unvaccinated, general population.

Cervarix

The clinical trials for Cervarix were similar to those of Gardasil in taking precautions to avoid vaccination of pregnant women. Nevertheless, combined results of thirteen clinical trials showed that out of a total of approximately 38,000 women, around 3,600 in the vaccine group and a similar number in the placebo group became pregnant.

In an overall analysis of all pregnancies, no imbalances in the rates of any specific pregnancy outcome (e.g. normal births, stillbirths, spontaneous abortions, congenital anomalies, etc.) were seen between the HPV vaccine and control groups.[47]

Investigators also performed a number of analyses of pregnancy outcomes for the small proportion of women who became pregnant close to the time of vaccination. In one of these analyses, the rate of spontaneous abortion was found to be numerically higher in the vaccine group than in the control group. While the difference was not statistically significant, investigators are being cautious and cannot completely rule out the possibility of a very small effect of the vaccine in the first 90 days of pregnancy. As more data are gathered from clinical trials, the question will be clarified. In addition, GlaxoSmithKline has also set up a registry to follow pregnancies in women who receive Cervarix inadvertently during pregnancy outside of clinical trials.

World Health Organization position on HPV vaccination

The World Health Organization (WHO) provides policy advice, strategy recommendations, and several forms of guidance for the use of vaccines in the global context. WHO position papers are one form of guidance: they provide background information on vaccines and the diseases they target. The papers also detail the WHO policy on such topics as vaccine delivery issues, appropriate target populations for vaccination, and the conditions under which vaccine introduction is recommended.

According to the WHO position paper on HPV vaccines,

> "WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and recommends that routine HPV vaccination should be included in national immunization programmes, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered. HPV vaccines are most efficacious in females who are naïve to vaccine-related HPV types; therefore, the primary target population should be selected based on data on the age of initiation of sexual activity and the feasibility of reaching young adolescent girls through schools, health-care facilities or community-based settings. The primary target population is likely to be girls within the age range of 9 or 10 years through to 13 years…"[27]

In addition to providing policy advice and guidance for HPV vaccine introduction, WHO provides a service to UN agencies that purchase vaccines, called prequalification,[52] to determine acceptability in principle of vaccines from different sources. The process includes a review of the general production methods and quality control procedures at manufacturers' facilities as well as site visits and testing of different lots of vaccine. After the prequalification process by WHO, UN agencies play an indispensable role by negotiating bulk prices with manufacturers and securing considerable discounts compared with private-market rates.

Both Cervarix and Gardasil were prequalified by WHO and thus are eligible for purchase by UN agencies for implementation in national immunization programs in developing countries.

Vaccination strategies

Recommended ages for vaccination

Many countries have adopted policies that support vaccination of female adolescents before sexual debut (approximately ages 9 to 13, though policies vary by country), as recommended by WHO, the US Centers for Disease Control and Prevention, and the Medicines and Healthcare products Regulatory Agency in the United Kingdom. France has approved vaccination for females aged 15 to 23; Germany, 12 to 17; Mexico, 9 to 26; and Australia, 9 to 45. Although vaccination even earlier in life poses no theoretical risk, no studies have yet been published to support vaccination of very young girls or infants.

While regulatory bodies in many countries have approved the use of the vaccines in women up to their mid-twenties and beyond, thus far it is not recommended that public health programs—especially those in the developing world—allocate resources to vaccinate sexually experienced, older women, since both vaccines show much lower efficacy after HPV infection. Rather, cervical screening is considered the best approach for this group.[27,53]

Screening when vaccination programs are in place

Although HPV vaccines are expected to significantly reduce the risk and incidence of cervical cancer, they will not replace screening; rather, use of the vaccines along with screening will maximize overall effectiveness.[54-56] Screening is needed for the millions of women age 30 or older in whom HPV infection has likely occurred if they have been sexually active sometime in their lives. Because the vaccines are not therapeutic, they cannot benefit already-infected women (although women infected, for example, by type 16 but not 18, would receive partial protection). Further, because current vaccines target the two HPV types known to cause 70 percent of cervical cancer, screening for lesions and cancer caused by other types must continue.

WHO,[27] PAHO,[57] and other agencies concur that countries with screening programs already in place should continue to support screening and to improve the quality and coverage of screening, even if vaccination programs are instituted.

Vaccination programs in high-resource countries

Several industrialized countries have introduced government-funded HPV vaccination programs, and in other countries the vaccines are approved and available in the private sector. The United Kingdom began a national program in September 2008 for 12- to 13-year-old school girls. By September 2009, 87 percent of eligible girls had received the first dose of the regimen and 70 percent had received all three doses.[58]

In the United States, while vaccination is not covered by a national program, it is recommended for all girls 11 to 12 years of age, and may be started in girls as young as 9 years. A 2009 survey reported on coverage for girls aged 13 to 17 at the time of the survey. Coverage for those who had received at least one dose of HPV vaccine was about 37 percent, and coverage for the recommended three doses was about 18 percent.[59]

Australia started a national school-based vaccination program in April 2008 for girls aged 11 to 12, with catch-up vaccination for women up to age 26 for the subsequent two years. HPV vaccine coverage among school-aged female adolescents has been estimated at up to 80 percent.[60]

While several other countries have also introduced HPV vaccines into national public health programs, the experiences are early and information is not yet widely publicized.

Vaccination programs in low-resource settings

In 2006, PATH began a program to explore the most effective strategies for vaccinating young adolescent girls in middle- and low-resource countries and to assess acceptance, feasibility, and costs associated with implementing such strategies.[61] Projects initiated in regions of four countries (India, Peru, Uganda, and Vietnam) were intended to simulate, on a small scale, national HPV immunization programs and to provide a basis for later policy decisions. By late 2009, immunizations had been completed for groups of girls in several districts in Peru, Vietnam, and Uganda, and were well along in India. The four demonstration projects have shown that HPV vaccination is acceptable and feasible in these areas, and that high coverage can be attained.

Before starting to distribute HPV vaccines through these projects, teams carried out extensive research to identify the best ways to communicate about and to deliver the vaccine in each country.[61] In all four countries, results indicated that cervical cancer and its HPV connection were not well known, so comprehensive community education—outreach to teachers, parents, girls, health workers, and the media—was recommended. Further, because HPV vaccination sometimes has been presented as controversial in the lay press and among interest groups, it was important to address community concerns in advance.

In all four countries, vaccination programs achieved very high coverage rates—that is, a high percentage of the eligible girls in the targeted districts received all three doses of the vaccine. While vaccination programs conducted at schools were very successful and some regions used these exclusively, programs were also held at other community locations and were also found to work well. In these projects, all vaccinations were provided free of charge; coverage might have been lower if families had to pay for HPV vaccination.

Some other low-resource countries have initiated or are planning to initiate HPV vaccination, but they have not yet published their experience or data.

Future vaccines

A key goal for the future is to develop preventive vaccines that are more suitable to resource-limited areas. Desirable characteristics for use in

these areas are lower cost, efficacy with fewer doses, efficacy when given orally or nasally, and stability at a range of temperatures. Vaccines that prevent infections with multiple oncogenic HPV types are also needed. Investigators are working on second-generation prophylactic vaccines that may address some of these needs.[62,63]

Currently, no therapies are available for eliminating persistent HPV infections, but researchers are working on such vaccines. Other therapeutic vaccines could potentially eliminate preexisting lesions and tumors by generating immunity against HPV-infected cells expressing viral DNA or proteins. Though development of such vaccines has been challenging, some have been shown to induce HPV-specific antitumor immune responses in animal models and several promising strategies have been applied in clinical trials.[64,65]

Screening and treatment

Screening

Even following introduction of HPV vaccination programs, screening will continue to be necessary for a considerable time because current vaccines provide protection only against infections that cause about 70% of cervical cancer cases. Until new vaccines can prevent infections by oncogenic types in addition to types 16 and 18, and until vaccines are 100 percent effective and can confer life-long immunity, prevention programs must include screening. It will also take time for vaccination programs to attain high coverage rates. Further, because clinical trials of the current vaccines have shown little benefit for women already exposed to HPV 16 and 18, screening will be necessary for this large population.

Screening of sexually active or formerly active women can determine whether they are at risk of developing cervical cancer. This determination can be made in several ways:[54,66]

- Pap testing—examining cells gently scraped from the cervix.
- Visual inspection—examining the surface of the cervix after applying a staining solution.
- HPV DNA tests—detecting the genetic material of oncogenic viruses in samples collected from the vagina or cervix.

Cytologic screening in low-resource settings

While Pap tests have reduced cervical cancer incidence and deaths dramatically in industrialized countries, this has not been true in low-resource countries.

> The most efficient and effective strategy for finding and treating precancerous lesions in low-resource settings is screening with either VIA or HPV DNA testing, and treating immediately using cryotherapy.

Pap screening, whether conventional or liquid-based, has proven difficult to implement and sustain in these countries because of the lack of supplies, trained personnel, equipment, quality control, health care infrastructure, and effective follow-up procedures.[66,67] Thus, creating, staffing, and maintaining cytology laboratories country-wide in low-resource regions is not feasible.

Even where it is feasible and in broad use, cytology has low sensitivity, which means that the test misses a good number of precancer and cancer cases. In North America and Europe[68] as well as in urban centers in Latin America,[69] sensitivity is estimated at approximately 53 percent, while a study in rural Peru[70] found the sensitivity to be 26 percent. In high-resource settings, the low sensitivity is overcome by repeated screening every year or every few years. But in low-resource areas, the vast majority of women has never been screened and would be fortunate to have one or two opportunities for screening in their lifetimes. Even then, often they would be unable to return for treatment appointments if abnormalities were found.[22,54]

Visual inspection with acetic acid

Visual inspection with acetic acid (VIA) has sensitivity comparable to or greater than that of cytology. The sensitivity has been found to range from about 41 to 79 percent in large-scale field studies from a wide range of countries[70,71,79-81] including South Africa, China, India, and Peru. VIA involves swabbing the cervix with three to five percent acetic acid (vinegar) during a speculum exam, waiting for one minute, and then observing the cervix. If characteristic, well-defined white areas appear, the test is considered positive for precancerous cell changes or early invasive cancer.

Visual inspection of the cervix requires simple equipment and relatively brief training and can be performed by midlevel health personnel. Because visual inspection is subjective, refresher training sessions are helpful and supervision is needed for quality control. Results are immediately available, and if indicated, treatment can be provided at the same visit (see the "Screen-and-treat programs" section), thus reducing loss to patient follow-up.

HPV DNA testing

Molecular tests can detect DNA from cancer-causing HPV types in vaginal or cervical smears collected using a small brush or swab. Trained providers must collect cervical samples, but women can collect vaginal samples themselves. While self-sampling has sometimes been shown to be less sensitive than provider-collected samples, the fact that a speculum exam is not required may raise acceptability and increase access for some populations.[66] A review of studies concluded that HPV DNA testing is particularly valuable in detecting high-grade precancerous lesions in women older than 30.[72,73] HPV infections in women younger than 30 are likely to be transient, so testing young women (with HPV DNA tests or other screening methods) can lead to unnecessary referrals or treatment of lesions that would regress spontaneously.


David and Lucile Packard Foundation

Current approved HPV DNA tests are more sensitive than visual inspection methods or cytology, but so far are unaffordable in low-resource areas. Sensitivity ranges from 66 to 95 percent, with most studies reporting values greater than 85 percent among women aged 30 or older.[70,71,74,75] Specimens must be evaluated in laboratories with special equipment and trained personnel in a process that takes several hours. The cost and laboratory requirements represent barriers to access in developing countries, similar to Pap tests.[71,76]

A new test, *care*HPV (Qiagen, Inc.), has been developed and field-tested for use in low-resource settings.[74,76] The *care*HPV test can detect DNA from 14 cancer-causing types of HPV, with test results available in about 2.5 hours without extensive laboratory facilities. However, one issue regarding both the *care*HPV test and some high-cost tests is that they are designed to test many samples at the same time, which might affect how programs will be able to use them. The *care*HPV test should become available commercially sometime in 2011 or 2012. If it proves to be simple, rapid, accurate, and affordable, it may become a suitable screening tool for low-resource settings.[74,76]

Treatment

Women with precancerous cervical lesions (CIN2+) who receive treatment have an excellent chance of avoiding progression to cervical cancer. Several treatment methods exist, and one, cryotherapy, is very suitable for low-resource settings. With cryotherapy, the affected area of the cervix is frozen with a cold probe, which destroys the precancerous cells. The equipment and procedure are relatively simple, and if the use of cryotherapy is restricted to cases where lesions are small (about 20 millimeters) and entirely visible (do not extend into the cervical canal) treatment efficacy is 85 to 95 percent.[75] There are some cases where cryotherapy is not indicated; for example, when the affected area is too large or is not reachable by the cold probe, or there is suspicion of invasive cancer. Technical problems with some cryotherapy equipment have prompted studies to improve cryo-devices so they will work more robustly in low-resource settings.[77,78]

Screen-and-treat programs

A promising strategy is becoming available for developing countries—the "screen-and-treat" or "single-visit approach." In this method, women who test positive on VIA or HPV DNA tests do not undergo further diagnostic testing; instead, they are treated immediately or shortly after screening.[75] If treatment is offered at the same visit, rather than at a referral site, it is known as a single-visit approach. According to a recent review, the most efficient and effective strategy for finding and treating precancerous lesions in low-resource settings is screening with either VIA or HPV DNA testing, and treating immediately using cryotherapy, without further diagnostic confirmation.[66]

While VIA followed by cryotherapy where indicated has been shown to be effective in some settings,[79] two large studies, in South Africa[80] and in India,[81] showed a greater reduction in the incidence of cervical lesions after HPV DNA testing and cryotherapy than after visual inspection and cryotherapy. However, HPV DNA testing still requires triage to determine the best treatment option (cryotherapy or a more advanced treatment) and VIA can fill this role. Thus, an HPV DNA test followed by VIA for women who test positive may prove to be a reasonable approach.

Unfortunately, because screening is limited in low-resource areas and because HPV infection and precancer have no symptoms, women may seek medical aid only when they already have symptoms such as bleeding, weight loss, or pain, indicating that the malignancy is advanced and that treatment is less effective. If detected early, invasive cervical cancer can be treated successfully; five-year survival for women with cancer in the earliest stage is estimated at 95 to 98 percent, but in advanced stages, the five-year survival falls to 5 to 10 percent.[75]

New paradigms for screening in the age of HPV vaccination

Once HPV vaccination gains momentum and more sensitive tests than Pap or VIA are in widespread use, it is likely that the screening strategies common today, such as Pap tests repeated every two to five years as in some high-resource countries, will change. One proposed scenario is to vaccinate prior to sexual debut, then screen only a few times when a woman is in her 30s and 40s, using HPV DNA

testing (or other future molecular tests that may give a better indication of which women are at highest risk of precancer).[82] Such a strategy would be feasible in low-resource settings[83] and would save considerable costs in wealthier countries. In countries without screening programs, policymakers should consider initiating screening of women aged 30 and older at least once or twice in their lifetimes, in conjunction with vaccination of girls and young women who are not yet sexually active.[22,55,84]

Cost-effectiveness and financing

Mathematical modeling studies show that vaccinating girls for HPV can be cost-effective under various assumptions about the price of vaccine, associated program costs, incidence of cervical cancer in the population, coverage that can be attained, effectiveness of the vaccine, and duration of immunity.[85,86] One model found that vaccinating 70 percent of 12-year-old girls against HPV 16 and 18 each year for ten years in 72 of the world's poorest countries could prevent more than 3 million deaths over the lifetimes of the vaccinated women.[86] Less optimistic scenarios utilizing country-specific assumptions (e.g., income level, past immunization experience, educational attainment of girls) yielded more conservative results; for example, 2 million lives saved by vaccinating girls over the course of 10 years. Provided the cost per vaccinated girl through a public-sector program is less than US$10 in some countries, or less than US$25 in others, adolescent HPV 16 and 18 vaccination would be cost-effective even in relatively poor countries. Clearly, the more expensive the vaccine, the less cost-effective vaccination programs become. Until prices come down or less expensive vaccines enter the market, vaccination programs in many countries will be possible only with substantial subsidies. The GAVI Alliance[87] has made providing HPV vaccine at a reduced cost to the poorest countries a priority.

Cost-effectiveness research on screening has also been done. Studies in India, Kenya, Peru, South Africa, and Thailand found that screening women once in their lifetimes, at the age of 35 years, using either VIA or HPV DNA testing and requiring only one or two clinical visits, reduced the lifetime risk of cancer by approximately 25 to 36 percent, and was cost-effective. Relative cancer risk declined by an additional 40 percent with two screenings, at 35 and 40 years of age.[88]

Cervical cancer prevention programs will include costs in addition to the prices of vaccines and screening tests. Program costs for vaccination include injection supplies such as syringes, needles, and waste cleanup materials; personnel costs estimated from staff time spent in delivering vaccines; and shares of capital costs such as cold chain systems and vehicles for delivery. For screening and precancer treatment, providers must be trained and transported to clinics; supplies and cryotherapy equipment must be purchased; and clinic time must be negotiated.

> HPV vaccination programs can build other health interventions into vaccination sessions. These can include giving advice on sexual violence, family planning, and preventing HIV and STIs.

Because most developing countries do not routinely vaccinate older children and adolescents, HPV vaccination programs will have to be integrated into existing immunization programs and other outreach activities such as Child Health Days,[56] or new systems will need to be created. Such systems may offer many positive opportunities for other health interventions such as de-worming; malaria intermittent preventive treatment; provision of bed nets or nutritional supplementation; general health and life skills education; and education about hand washing, tobacco, and drugs. Young adolescents can also benefit from information and advice on sexual violence, family planning, and preventing HIV and STIs.[89,90] Using one system to deliver multiple interventions should lower the costs of all the interventions.

Given that financing for health care is already limited in so many places, financing for HPV vaccine and for precancer screening and treatment programs will require sustained, strong advocacy efforts and innovative strategies in the years ahead.[54,88,91]

Communication and advocacy

Outreach to communities

Accurate information is essential for improving the understanding of HPV infection and cervical cancer among health care workers, educators, policymakers, parents, and patients. Many are unaware of the cause and the burden of cervical cancer and need help to understand the value of HPV vaccines and cervical screening. Without such understanding, individuals, communities, and governments are unlikely to support interventions.[5,7,61,92,93]

Outreach to decision-makers and communities in support of cervical screening, HPV vaccination, or both, can take many forms. As with all health education, understanding audiences and crafting appropriate messages, based on cultural background and educational levels, is crucial. It is important to create easy-to-understand action items ("make an appointment for screening to protect yourself against this disease" or "make sure your daughter receives all three doses of vaccine") while also explaining details of the interventions (how they work, for example) according to the audience's interest and education level. Some vaccination programs in low-resource countries found that for the general public, using the phrase "cervical cancer vaccine" worked best, while health professionals understood "HPV vaccine."

Educating health care workers

Because health care providers are often the primary source of information for both parents and adolescents, educating providers helps families understand the benefits of any vaccine or other health service.[92,93] Health care workers in many developing countries might not have a clear understanding of HPV infection and its relationship to cervical cancer development and prevention. This situation is exacerbated by the "silent nature" of HPV infection and cervical cancer—the fact that symptoms are not present until the cancer is at an advanced stage. Health workers need to be educated about how to help patients understand the enormous advantages offered by both screening and vaccination.[93–95]

In both industrialized and developing countries, it is unclear which types of providers will deliver the vaccines—community health workers, general physicians or nurses, pediatricians, nurse midwives, or obstetricians and gynecologists. Obstetricians and gynecologists have not traditionally administered vaccines. Conversely, the immunization community may have limited knowledge of cervical cancer and HPV. Therefore, additional training with both groups will be necessary to implement HPV vaccination programs.[66,96,97]

Implications for policy and programs

Three relatively recent events have been crucial to propelling forward the fight against cervical cancer: the discovery that this cancer is caused by an infectious agent, the development of vaccines against HPV infection, and research demonstrating the effectiveness of alternatives to Pap screening. The challenge now is to build momentum in low-resource regions, where the burden of disease is most concentrated. Essential points for comprehensive prevention programs are:

- HPV vaccination cannot reach people in developing countries unless the vaccines become affordable, health infrastructures can support vaccination programs, and governments institute national HPV immunization programs.
- Prevention strategies must include screening for cervical lesions or HPV infection among adult women, because vaccines do not protect against all cancer-causing types and because many women are not vaccine candidates.
- Integrating cervical cancer prevention programs with other health interventions will lead to better care for girls and women and can improve cost-effectiveness.
- Preventing cervical cancer is an integral part of the broader agenda of meeting women's health needs, and it is essential for women's rights and health equity. With vaccination for girls, screening for women, and the political will and resources to create strong health systems, communities can slow and ultimately halt this disease.

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Cervical cancer prevention and adolescent health resources

World Health Organization (WHO) cervical cancer publications
www.who.int/reproductivehealth/topics/cancers

WHO position paper on HPV vaccines
www.who.int/wer/2009/wer8415.pdf

Pan American Health Organization
new.paho.org/hq/index.php?option=com_content&task=view&id=292&Itemid=386

GAVI Alliance
www.gavialliance.org

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

Cervical Cancer Action coalition
www.cervicalcanceraction.org

RHO Cervical Cancer library
www.rho.org

Cervical Cancer Prevention Action Planner
www.rho.org/actionplanner

United Nations Population Fund
www.unfpa.org/adolescents/

WHO/Institut Català d'Oncologia HPV Information Center on HPV and Cervical Cancer
www.who.int/hpvcentre

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