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Outlook

In this issue

PATH

Preventing cervical cancer: Unprecedented opportunities for improving women's health

Cervical cancer is the second most common cancer in women worldwide and the leading cause of cancer deaths in women in developing countries (Box 1). It is a disease of unfortunate inequities but also of exciting opportunities.

The inequities

The incidence and mortality rate of cervical cancer have declined significantly in industrialized countries in the past 40 or so years, but in developing countries, this disease continues to be an enormous problem. But even in the industrialized world, some women do not receive the care they need. Thus, one inequity is between richer and poorer women. With appropriate health care, wealthy women in poorer countries are likely to be better off than poor women in wealthier countries.

The second inequity is based on gender: cervical cancer is a female disease, and in many countries women do not receive equal information about or access to health care.

The opportunities

A vaccine against cervical cancer is now available. This vaccine can be complemented with improved cervical screening to achieve a substantial reduction in cervical cancer, a disease that shatters families and destroys the lives of women in their prime. The costs of cervical cancer to communities and to individual women and their families are great, but this situation can be improved. To realize the full potential of the human papillomavirus (HPV) vaccine requires universal coverage of adolescent girls before the possibility of HPV contact. Although it will be challenging to reach these girls—many of whom do not routinely see health care providers—once effective systems are in place, they can be used to provide many additional health interventions necessary for older children and young adolescents.

The fight against cervical cancer, a disease that is preventable, can be regarded as both a health issue and a human rights and ethical issue. Current tools can tackle this problem and help to give more women, their families, and their communities a future without cervical cancer.

Cervical cancer and human papillomavirus (HPV)

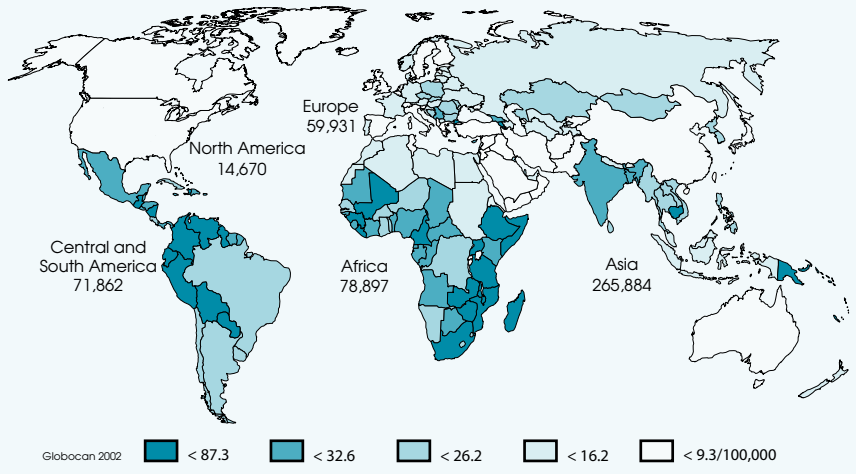
The disease: an unequal burden

Nearly half a million new cases of invasive cervical cancer are diagnosed each year, about half in women who have never been screened. Worldwide, more than a quarter million women die of this disease annually. The highest incidence and mortality rates are in sub-Saharan Africa, Latin America, and South Asia (see Figure 1). Overall, the mortality rates in developing countries are about four times those in industrialized countries; 80% to 85% of cervical cancer deaths occur in developing countries. In these regions, cervical cancer generally affects women with multiple school-age children, and their deaths have a major negative impact on the social fabric of their communities.[1–3,5,6,9–12]

Human papillomavirus (HPV)

Nearly all cases of cervical cancer are associated with HPV, an easily transmissible, highly prevalent, tissue-specific DNA

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



Source: Ferlay et al.[2]

virus. HPV is the most common sexually transmitted infection (STI). There is no treatment for HPV infection.[13–15]

Presently, about 630 million people worldwide are believed to be infected with HPV, more women than men.[13,16] In the United States, about 40% of young women become infected with HPV within three years of sexual debut. Globally, 50% to 80% of sexually active women are infected by HPV at least once during their lives.[17,18] Usually women contract HPV between their late teenage years and early 30s, with the peak of HPV infection coinciding with the onset of sexual activity in girls and young women under age 25. Most often, cervical cancer is found much later, usually after age 40, with peak incidence around age 45. There is a long delay between infection and invasive cancer.[19–22]

HPV types

HPV is a common family of viruses.[14] More than 100 types of HPV are known. Some types have a high potential for causing cancer (high-risk types), whereas others have a lower potential for causing cancer (low-risk types). High-risk types cause most anogenital cancers, whereas low-risk types can cause genital warts, abnormal cervical cytology, recurrent respiratory papillomatosis, or, most commonly, asymptomatic infections of no clinical consequence.[13] At least 13 of the HPV genotypes are high-risk. Two types of high-risk HPV are associated with about 70% of all cases of cervical cancer: HPV-16 and -18. HPV-45 and -31 are also associated with cervical cancer, accounting for about 4% of cases each. Studies have shown some regional variations with respect to which HPV types are predominant in an area.[22,23]

Progression from HPV infection to cervical cancer

Cervical cancer begins with HPV infection. Most infections resolve spontaneously, without symptoms, but persistent infection with high-risk types can lead to precancerous cervical abnormalities and low-grade cervical intraepithelial lesions. Of women infected with high-risk HPV types, 5% to 10% develop persistent HPV infection and thus have an increased risk of developing precancerous cervical lesions. If not treated, precancerous lesions can progress to invasive cervical cancer.[23–25]

Both precancer and cancer usually arise in the "transformation zone" of the cervix, which is larger during puberty and pregnancy. Normally, the top layers of the cervical epithelium die and slough off, with new cells constantly forming. With persistent HPV infection, however, this process is disrupted; cells tend to keep on multiplying, first becoming abnormal (precancerous), and then invading the underlying tissue (invasive cancer). Because progression from HPV infection to invasive cancer is slow, usually taking decades, it is seen more frequently in women in their 40s and 50s.[2,6,26–30] See Figure 2 for age-specific rates of cervical cancer deaths.

Risk factors

For women, the risk of contracting HPV infection is affected primarily by sexual activity, in particular the sexual behavior of their partner or partners. HPV infection differs from other STIs, however, in that HPV infection can occur even with nonpenetrative sex (after ejaculation just outside the vagina, for example). Early age at first sexual intercourse is a risk factor for HPV infection because an underdeveloped cervix has an immature epithelium, which can be penetrated more easily by the virus. Co-factors include early age at first parity and infection with HIV or other STIs (e.g., herpes virus or *Chlamydia trachomatis*). For men, risk factors for HPV infection include having a high number of sexual partners, having same-sex partners, and being uncircumsized.[10,13,14,23,31,32]

The need for improved prevention methods

Primary prevention

Prevention of cervical cancer can be achieved in one of two ways: preventing infection initially or detecting the precursors to cervical cancer and providing treatment. The former method is called primary prevention and can be accomplished by avoiding exposure to the virus through abstinence from sexual activity or through mutual monogamy forever, provided both partners—not just one—are consistently monogamous and were not previously infected. Condoms provide only about 70% protection against HPV when used all of the time. Another mode of primary prevention is vaccina-

tion against HPV.[32,33] The new vaccines are discussed in a later section.

Secondary prevention: screening, diagnosis, and treatment

Screening

Secondary prevention is achieved through screening and treatment of identified precancerous lesions. Cervical cancer screening is directed toward sexually active—or formerly active—women to determine whether they are at increased risk of developing cervical cancer. This determination can be made by examining the exfoliated cells of the cervix using the Papanicolaou (Pap) smear, examining the surface layer of the cervix through visual inspection, or detecting HPV DNA.[34,35] The Alliance for Cervical Cancer Prevention recently made ten recommendations for effective cervical cancer screening programs (see Box 2).

Cytologic screening

Since its introduction more than 50 years ago, the Pap smear, also known as the cervical smear, has been used throughout the world to identify precancerous lesions for treatment or follow-up. The results of routine Pap smear screening in the industrialized world have been impressive, and the procedure has contributed to the 70% to 80% reduction of cervical cancer incidence in developed countries since the 1960s. Even in industrialized countries, however, the level of success can vary. For example, in the United States, where an overall decline in the number of cervical cancer cases has occurred, rates nonetheless remain high in impoverished areas.[9,39–41]

Lack of similar success in developing countries is largely attributable to limited resources (i.e., supplies, trained personnel, equipment, quality control, health care infrastructure, and effective follow-up procedures).[5] As noted earlier, screening programs in developing countries either do not exist or are ineffective.[1] One estimate is that about 75% of women in industrialized countries have been screened within the preceding five years. By contrast, studies in India and estimates in Kenya found that only 1% of participants had ever undergone any screening, despite numerous efforts to improve screening programs.[42,43] Compounding the problem is that both women and health care workers often lack information about cervical disease and cost-effective ways to prevent it.[3,42–48]

Limitations of cytology

A single cytologic screening results in a high rate of false-negatives—that is, it lacks sensitivity, making repeat screening necessary. Pap smear failure can be a consequence of the health care provider's sampling technique or the monotony of subjectively processing many samples. In addition, the need for follow-up medical appointments to present the results and manage any abnormalities can negatively affect treatment rates.[20,35]

Box 1. Cervical cancer facts[1–8]

- Invasive cervical cancer affects an estimated 490,000 additional women worldwide each year and leads to more than 270,000 deaths annually.
- About 85% of women who die of cervical cancer reside in developing countries. Each year, 75,000 women die of the disease in India alone.
- If current trends continue, by the year 2050, there will be more than one million new cases of invasive cervical cancer annually.
- Cervical cancer can be prevented if precancerous lesions are identified early through screening and then treated.
- Most women in the developing world do not have access to cervical screening and treatment programs, making routine vaccination an important potential disease-control strategy.


PATH, Molly Mort

- New rapid screening methods may make screening more widely available.
- The new HPV vaccines appear to be safe and effective in preventing HPV infections and type-specific cervical lesions when given prior to infection.

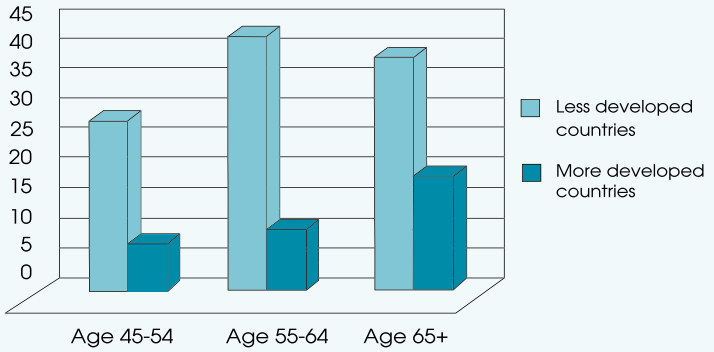
Cervical cancer screening update

In addition to Pap smears, several new types of screening methods are either available now or under development. Ideally, the most effective screening method would be inexpensive, painless, simple to perform, socially and culturally acceptable, accurate, with no adverse effects, and able to provide immediate results. Some promising new screening methods appear to be on the near horizon and may bring cervical cancer screening closer to this "ideal."[40,42,49]

Developments in cytology

Efforts to improve Pap smears in the last ten years include the development of liquid-based cytology, which uses a small amount of fluid to preserve cells collected from the cervix and automates the process of preparing smears. This method has greater laboratory efficiency and reduces a number of

Figure 2. Age-specific cervical cancer mortality rates per 100,000 women



Cervical cancer mortality is much more common in the developing world, in part due to lack of screening programs.

Source: Ferlay et al.[2]

problems such as poor fixation, uneven thickness of the cell spread, debris, and air-drying artifacts. But in some countries, it adds to the cost of the Pap smear, has not been shown to have better accuracy, and requires additional instruments, which means it may not be well suited for use in many low-resource settings.[40,42,49]

In addition, computers are now being used to identify the most abnormal areas on a Pap smear slide, thereby reducing the subjectivity of assessments and increasing the test's sensitivity, but this technology is quite expensive.[40]

Visual inspection with acetic acid (VIA)

VIA, also known as direct visual inspection or cervicoscopy, can be an alternative to cytologic testing or can be used along with Pap screening. VIA involves applying 3% to 5% acetic acid (vinegar) to the cervix using a spray or a cotton swab and observing the cervix with the naked eye after one minute. If characteristic, well-defined aceto-white areas are seen adjacent to the transformation zone, the test is considered positive for precancerous cell changes or early invasive cancer. VIA does not require a laboratory or intensive staff training. The results are immediately available, allowing treatment during a single visit and thus reducing loss to patient follow-up. An additional advantage of VIA not offered by Pap or HPV DNA tests is that it allows providers to identify the small proportion of positive lesions that are unsuitable for treatment with cryotherapy, a mode of treatment well suited to limited-resource settings. An implication of this is that even if testing is done by Pap or by HPV DNA tests, the decision not to treat with cryotherapy can be made only with VIA. VIA's sensitivity is as good as or better than that of the Pap smear, but like the Pap smear, visual inspection is subjective, and supervision is needed for quality control of visual inspection methods. VIA might not work as well in postmenopausal women because the transformation zone recedes into the cervical canal at menopause.[26,48,49–52]

Visual inspection with Lugol's iodine (VILI)

VILI is similar to VIA but involves applying Lugol's iodine to the cervix and then examining for mustard-yellow areas. The results of VILI are immediately available, which offers the advantage of follow-up care without delay. The accuracy of VILI testing was evaluated in India and Africa by colposcopy and biopsies with good results.[42,48,50,51] As part of the Latin American Screening (LAMS) study, four centers (three in Brazil, one in Argentina) evaluated the accuracy of VIA and VILI in 11,834 women. The findings did not match previous results but did show that these visual methods can be combined with Pap smear or Hybrid Capture® 2 testing for improved accuracy over any of these tests alone.[52] However, data on VILI's sensitivity and specificity remain limited, and further studies of VILI's accuracy are warranted.

HPV DNA testing

New tests can detect DNA from high-risk HPV types in vaginal or cervical smears. A sample of cells is collected from the cervix or vagina using a small brush or swab; then, the specimen is sent to a laboratory for processing. One advantage of HPV DNA testing is that when conditions are ideal, it is not as subjective as visual and cytologic screening. It can identify women who already have cervical disease in addition to those who are at increased risk for developing it.[53] A review of 14 studies concluded that HPV DNA testing is particularly valuable in detecting high-grade precancerous lesions in women over age 30 because HPV infections in women under 30 are likely to be transient.[18,53–58]

The Hybrid Capture® 2 test (hc2)

The HPV DNA detection assay Hybrid Capture® 2, developed by Digene Corporation, is currently the only US Food and Drug Administration HPV test approved for clinical use. The hc2 test can detect 13 types of HPV and is more sensitive than visual inspection methods and cytology, but it is expensive and presents some of the same challenges as cytologic screening in low-resource areas. For example, the test requires laboratory facilities, special equipment, and trained personnel; takes six to eight hours for results; and requires follow-up visits for results and treatment.[42,59,60]

The Fast*HPV test*

The *Fast*HPV test is being developed specifically for use in low-resource settings. This test will be able to detect DNA from 14 high-risk types of HPV, and test results are available in two to two and a half hours. Development is expected to be completed in 2007, and

the *Fast*HPV test is anticipated to be available commercially sometime in 2008. If it proves to be simple, rapid, accurate, and affordable, it may be a suitable screening tool for low-resource settings.[59,60] One issue regarding both the *Fast*HPV test and the hc2 test is that they are usually batched, which might affect how programs will use them. Other commercial HPV tests are under development and are likely to be approved soon for clinical use.

Diagnosis

In industrialized countries, women who test positive during screening by either Pap smear or HPV DNA tests then undergo diagnostic testing, with colposcopy, for example. Colposcopy usually involves examination of the vagina and cervix using a magnifying device with a powerful light source to identify abnormal areas on the cervix and to guide sampling of cervical tissue (biopsy). Colposcopy must be performed by trained providers, and colposcopes can be expensive, complex instruments. In addition, the biopsy samples must be transported to a histopathology laboratory staffed by a pathologist, which is often impractical or impossible in low-resource countries. If a woman has an abnormal Pap smear but no abnormal areas are seen by colposcopy, or the colposcopic examination is inadequate (i.e., the entire transformation zone is not seen), cells from the cervical canal can be sampled and sent to the laboratory. This procedure is called endocervical curettage.[27,61,62]

Screen-and-treat programs

In developing countries, a new approach called screen-and-treat is being used. Women who test positive on visual or HPV DNA tests do not undergo further diagnostic testing; instead, they are treated immediately.[27] The screen-and-treat approach is especially appealing in low-resource countries, where transportation, time, and other access issues make follow-up visits difficult. The main benefit is that women are less likely to be lost to follow-up before being treated.[63] Screen-and-treat programs have been evaluated in Thailand, South Africa, and Ghana with good results. The data show that VIA and cryotherapy, in one or two clinical visits, without an intermediary colposcopic diagnostic step, is one of the most cost-effective alternatives to conventional multi-visit strategies.[64–67]

Treatment

Precancerous lesions

Women who are treated for preinvasive lesions have a survival rate of nearly 100%. Currently, the usual treatment of women with cervical lesions involves colposcopically controlled excisions using loop electrosurgical excision procedure (LEEP) or ablation (destruction) of abnormal epithelium by cryotherapy, both of which are outpatient procedures (see descriptions in Table 1). If cryotherapy is restricted to lesions that are small (i.e., ≤19 mm), efficacy is near 100%. Both cryotherapy and LEEP are less radical than the previous standard treatment, cold-knife cone biopsy. Although no longer the standard, it is still used for precancerous lesions that cannot be otherwise treated or for rigorous evaluation of the cervix and cervical canal when squamous carcinoma or adenocarcinoma is suspected.[9,27,42,49,61,68,69]

Cervical cancer treatment

If detected early, invasive cervical cancer can also be treated successfully; five-year survival for women with cancer in the earliest stage (stage 1A, in which the cancer has had minimal spread to the inside of the cervix) is estimated at 92%.[9] Hysterectomy and radiotherapy are the recommended

Table 1. Treatment of precancerous lesions[20,27,35]

Treatment	Description	Effectiveness	Common adverse effects	Comments
Cryotherapy	Freezing tissue using a metal cytoprobe that has been cooled by nitrous oxide or carbon dioxide gas circulating within the probe.	85%	Slight cramping, watery discharge, risk of infection.	Can be performed by nonphysician, in a single visit; simple equipment; advisable only when the affected area is small; no anesthesia required.
Loop electrosurgical excision procedure (LEEP)	Removal of the diseased area of the cervix using electrically heated wires; sample is then further evaluated.	90%–98%	Bleeding, either immediately or later.	Fast (5–10 min); must be performed by a physician; complex procedure; requires local anesthesia.
Cold-knife conization	Removal of cone-shaped area from the cervix.	90%–94%	Bleeding, infection, stenosis, cervical incompetence, possible decreased fertility.	Requires anesthesia, hospitalization, and highly skilled staff.

Box 2. Ten key findings and recommendations for effective cervical cancer screening and treatment programs

Since 1999, the partners of the Alliance for Cervical Cancer Prevention (ACCP) have been assessing screening and treatment approaches for low-resource countries and working to increase awareness about cervical cancer and improve delivery systems.[36–38] In April 2007, the ACCP made ten key recommendations for effective cervical cancer screening and treatment programs:

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

*It is important to note that subsequent to screening using an HPV DNA test, triage using VIA is still necessary to identify those patients for whom cryotherapy is not appropriate.

primary treatments for cervical cancer but should not be used to treat precancerous lesions. For advanced disease, radiotherapy is frequently used for palliation of symptoms, but in developing countries it is not widely available or accessible. Radiotherapy aims to destroy cancer cells while preserving normal cells insofar as possible. Adverse effects include vaginal bleeding and discharge, diarrhea, and nausea. Its effectiveness depends on the extent of the cancer, that is, whether it has spread beyond the cervix. Chemotherapy may also be used with hysterectomy and radiotherapy.[20,27]

Adjunctive nonmedical care can include traditional or cultural practices, provided they do not cause harm (e.g., massage, prayer, counseling, emotional support). Pain control for women with advanced cervical cancer is often inadequate in developing countries. There are, however, effective and inexpensive options for providing pain control. This palliative aspect of patient care should be a priority for implementation by both clinical and home care providers.[20,70]

Current and future vaccines

Current prophylactic vaccines

In June 2006, the first vaccine against HPV infection was approved and marketed—Merck's Gardasil®—and, as of April 2007, it had been registered in more than 70 countries. Gardasil®

prevents infection with two of the most common cancer-causing types of HPV, types 16 and 18. Around 70% of cervical cancer cases are associated with these two HPV types. This vaccine also protects against two types of HPV that do not cause cancer—types 6 and 11—but cause about 90% of genital warts. The quadrivalent vaccine is given in a series of three 0.5-mL intramuscular injections over six months, with the second dose given two months after the first and the third about six months after the first.[71]

The second vaccine, GlaxoSmithKline's Cervarix™, also protects against infection with two of the most common cancer-causing types of HPV, types 16 and 18, and is also given in a series of three 0.5-mL injections. In this case, the second dose is given a month after the first and the third given six months after the first. Licensing for this vaccine is expected to be approved sometime in 2007.[71] See Table 2 for further information on the two vaccines.

Clinical trials have found that both vaccines have been at least 95% effective in preventing HPV-16 or -18 persistent infection and 100% effective in preventing type-specific cervical lesions when given to girls prior to sexual activity or to women without prior infection with these HPV types. Widespread use of the vaccine alone has the potential to reduce cervical cancer deaths by 50% over several decades, and some estimates anticipate an even higher prevention rate of 71%, depending on immunization coverage.[73–77] In countries able to do so, vaccination of adolescents combined with a screening program that targets women over age 30 will be the most effective approach.[73–80]

Vaccination strategies

Potential strategies will include vaccination of schoolgirls (which may miss the more vulnerable out-of-school girls) and/or through mother-daughter initiatives or other existing community outreach programs.

The current recommendation in the United States is to vaccinate all adolescents routinely before their sexual debut. Although vaccination earlier in life poses no theoretical risk, no studies are yet published to allow earlier vaccination. There is also a catch-up program that allows vaccination for women aged up to 26 years. At this time, it is not recommended that sexually active older women be vaccinated. Rather, cervical screening is the best approach for this group.[71,72]

For low-resource countries, vaccination with current vaccines will be possible only with substantial vaccine subsidies. Although the new HPV vaccines are expected to result in impressive reductions in the risk and incidence of cervical cancer, they will not replace screening; rather, use of the vaccines in partnership with screening will maximize effectiveness.[35,81] For the millions of women aged 20 or older, infection with HPV has likely occurred already if they have been sexually active sometime in their lives. The new vaccines are not therapeutic, so they cannot benefit these women. Furthermore, only two of the cancer-causing types of HPV are included in the currently available vaccines (i.e., HPV-16 and -18), and protection has been demonstrated so far against only those types. Screening will continue to be necessary because the vaccine does not prevent cancer caused by non-16 and -18 cancer-causing types of HPV.

Countries with screening programs already in place should continue to support screening even if a vaccination program is instituted. In countries without screening programs, policymakers should consider initiating screening of women aged 30 and older at least once or twice in their lifetime in conjunction with vaccination of older girls and women who are not yet sexually active. [20,81–84]

Vaccinating boys

Although boys do not develop cervical cancer, they can become infected with HPV and can develop other HPV-associated disease such as penile, anal, and oral cancers and genital warts. Some experts believe that vaccinating both males and females would benefit women because women are infected by male sexual partners, but the cost-effectiveness of vaccinating both genders is under investigation. Furthermore, there is still no evidence that vaccinating males reduces the risk of HPV transmission to their female partners.[85,86]

Table 2. Characteristics of current HPV vaccines[7, 71,72]

Gardasil® (Merck)	Cervarix™ (GlaxoSmithKline)
Quadrivalent (HPV types 6, 11, 16, 18)	Bivalent (types 16, 18)[a]
Made in yeast	Made in baculovirus
Aluminum adjuvant	ASO4 (alum and MPL) adjuvant
0-, 2-, 6-month schedule,	0-, 1-, 6-month schedule
0.5-mL injection volume	0.5-mL injection volume
Licensed in >70 countries	Licenses expected in 2007
Clinical trials with 25,000 women aged 15–26 worldwide	Clinical trials with 18,000 women aged 15–25 worldwide
Efficacy against developing precancerous lesions nearly 100%[b]	Efficacy against developing precancerous lesions nearly 100%[b]
Duration: at least 5 years	Duration: at least 5 years

[a] Preliminary evidence shows that Cervarix™ might also provide some protection against HPV types 45 and 31. This cross-protection is being confirmed by new analyses of the original studies as well as in the first data from Phase 3 studies.

[b] A few women developed precancerous lesions associated with other HPV types.

Duration of effectiveness

Clinical trials show that HPV vaccines are effective for four and a half to five years at a minimum (the duration to date of the trials), but they very well might be effective for much longer.[78] During the past five years, there has been no evidence of waning immunity or decreased efficacy for prevention of infection. Also, an antigen challenge of the HPV vaccine stimulated a response similar to vaccines that provide long-lasting protection, such as the hepatitis B vaccine. These findings suggest that the duration of effectiveness could be long-lasting, but data will become available only with time.[87]

Cross-protection

At present, it is not certain whether and to what degree the HPV vaccines will provide cross-protection against HPV types not included in the vaccines. Evidence has been found that some cross-protection occurs against HPV-45 and -31, and ongoing studies are addressing this issue.[7,77,78]

Adverse events

The most common known adverse events following HPV immunization are discomfort at the injection site, pain, swelling, redness, headache, or low-grade fever. No serious adverse events have been reported in any of the clinical trials, even after five years' follow-up.[71,72,77,88,89]

Unanswered questions

Other issues pertaining to the vaccine itself include the following:

- Will booster shots be necessary and, if so, when and how often?
- What is the optimal dosing regimen? Can protection be achieved with fewer than three doses?
- Are the vaccines safe in pregnant and breastfeeding women?
- Is co-administration with other adolescent vaccines safe and effective?

The preceding questions as well as others are being addressed in current research projects.[55,90]

Future vaccines

Work is ongoing to improve prophylactic vaccines and develop therapeutic vaccines to eliminate existing HPV infections and associated lesions.[3,7]

Future prophylactic vaccines

Improved prophylactic vaccines may involve using different development approaches, such as protein and peptide recombinant live-vector, bacteria-based, plant-based, DNA, and prime-boost vaccine strategies. A key goal is to develop vaccines more suitable to resource-limited areas, that is, vaccines that are cheaper to produce, have a longer shelf-life, require only a single dose or two doses, confer long-lasting immunity not requiring boosters, can be given nasally or orally, are stable at a range of temperatures, and are effective against multiple HPV high-risk types.[3,7,91]

Future therapeutic vaccines

It is hoped that future vaccines will be able to prevent cancer in women who have already contracted persistent HPV. Currently, no therapeutic vaccines are available for HPV infection, but work has begun to develop such vaccines. These vaccines may be used alone or in combination with other therapies, and they would be designed to stop the progression of low-grade lesions to invasive cancer or to prevent the recurrence of previously treated lesions or cancer. Unlike current and past treatments, therapeutic vaccines would likely treat the underlying infection.[7,86]

Therapeutic vaccines for women with high-grade (i.e., advanced) lesions may be more difficult to formulate because these lesions are genetically unstable, meaning that HPV gene expression can vary within a single patient and from one patient to another. The efficacy of therapeutic vaccines presently in development is not yet established.[7,86]

Getting vaccines to those who need them most

Implementation of effective vaccine programs might seem straightforward and obvious in light of the vaccines' efficacy and lack of serious adverse events to date; nonetheless, significant challenges remain.

Knowledge and acceptability

Accurate information is essential to improving understanding of both HPV and cervical cancer among health care workers, educators, policymakers, parents, and patients. Many do not comprehend the cause and burden of cervical cancer and may not be able to understand the value of HPV vaccines for improving the current situation. Without such understanding and strong advocacy, individuals are unlikely to support vaccination.[12,54,92]

To achieve this goal, it is first necessary to determine how best to "frame" the information by considering socio-cultural realities. Might the stigma of STIs complicate acceptance of the vaccines in some societies? Should vaccination be presented mainly as a women's issue? Effective framing can help to avoid social resistance from, for example, groups who fear that HPV vaccines will promote promiscuity (even though studies have shown that sex education has the opposite effect).[12,54,93,94]

Community readiness and acceptance will help to ensure access to vaccine, so community leaders should be involved in the design and implementation of a vaccination program. Because clinicians are often a source of information for both parents and adolescents, educating clinicians helps parents to understand the benefits of any vaccine.[12,45]

Cost and financing

It is expected that costs for delivering the HPV vaccine will be greater than that of existing infant vaccination programs. Financing for health care in developing countries is already limited; therefore, financing for HPV vaccine programs will require sustained, strong advocacy efforts and innovative strategies.[95]

At present, the price for the vaccine in developing countries is not known and might not be known for some time.

The usual course of introduction of a new vaccine involves availability in the private sector first and then, after prices fall, into the public sector. Efforts are being made to shorten the time until the price drops and HPV vaccines are widely available in the developing world. The ultimate price will be determined by such factors as the number of doses to be purchased and the duration of the purchase agreement.[7,96]

The price of the vaccine itself is not the only cost: there are programmatic costs as well. Most adolescents do not routinely participate in health care to the same extent as younger children and infants, and new strategies aiming to reach young adolescents need to be developed. The cost-effectiveness of vaccination programs in developing countries will be influenced by the cost of instituting programs for widespread coverage of young adolescents, a group not usually included in vaccination programs; the duration of protection the vaccine provides; and the degree of participation in the program.[92,97–102] An important component in the cost-effectiveness consideration will be the eventual savings in treatment of cervical cancer and other HPV-related diseases.[98]

In-country demonstration projects are planned to collect data on overall costs and delivery strategies. Discussions are also ongoing to identify international financing mechanisms that might subsidize vaccination programs in low-resource areas.[101]

Access

Young adolescents do not routinely interact with health systems in most developing countries, and ensuring access will be a challenge. One promising suggestion is to strengthen school health programs, especially given the recent increase in primary school attendance. Where many young girls drop out of school at an early age, community programs might help to fill the gap.[101]

Once effective strategies have been developed to reach these girls, they can be used to provide many different health interventions appropriate for older children, such as tetanus, rubella, hepatitis B, measles, and eventually HIV immunization; deworming; malaria intermittent preventive treatment; treatment of schistosomiasis, filariasis, and trachoma; iron and/or iodine supplementation; provision of bed nets; nutritional supplementation; and education about handwashing, tobacco, drugs, body awareness, and life-choice decision-making. Using the same system to deliver multiple interventions—at the same time as HPV vaccination or at different times—will increase the cost-effectiveness of all the interventions.

Training and supporting health providers

Effective training of health care workers—with clear, realistic, and practical goals—is crucial in any health program. 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 cervical cancer. Health workers need to be educated about how to help patients understand the enormous advantages offered by both screening and vaccination.[45,50,65,103]

In both industrialized and developing countries, it is unclear which types of providers will deliver the vaccines (i.e., general physicians or nurses, pediatricians, nurse midwives, or obstetricians/gynecologists). Obstetricians and gynecologists have not traditionally administered vaccines. Conversely, the immunization community may have limited knowledge of cervical cancer and HPV. It can be anticipated, therefore, that some additional training will be necessary to implement HPV vaccination programs.[96,104,105,106]

Documenting experience with HPV vaccine in low-resource settings

Lessons learned from demonstration vaccination programs will help give countries the tools they need to develop effective local programs. Forecasting and delivery strategies (in schools or community programs) can also be guided by this information.[12,95]

PATH is collaborating with four countries—India, Peru, Vietnam, and Uganda—on formative and operational research to test strategies for introducing the HPV vaccine. In conjunction with these demonstration projects, PATH is interacting with policymakers, health care providers, parents, and young adolescents to determine the extent of knowledge about HPV and cervical cancer and to investigate ways to introduce HPV vaccine. The projects will address how to ensure vaccine coverage for the targeted age group of girls and will collect data on costs, sociocultural acceptability, resource use, financing, supply, and vaccine demand. Data from initial formative research will become available in late 2007 and 2008, with operations research findings in 2009 and 2010.

Conclusions

By combining HPV vaccination with improved screening, diagnosis, and treatment, cervical cancer mortality rates in developing countries could conceivably be reduced to the low levels achieved by industrialized countries—or even lower. This goal will not be reached without:

- Cooperative efforts by both private- and public-sector partners and community leaders.
- Strengthened health systems, including routine screening for cervical cancer.
- Data and experience on which to facilitate evidence-based decision-making.
- Availability of a vaccine supply that is affordable and can meet demand.
- A supportive social and political climate.

A variety of strategies will be needed for different settings. These strategies must be designed with full acknowledgment of present-day realities, including the burden of disease and relevant knowledge, behavior, and sociocultural

attitudes. Ensuring that evidence-based secondary prevention (screening) strategies either continue or are established in conjunction with vaccination will also be crucial.

Communication and advocacy with influential religious, medical, and political leaders can positively affect the community's trust and willingness to participate in cervical cancer prevention programs. Several agencies and organizations are conducting studies and projects aimed at gathering the information and evidence to aid policymakers in their decisions about improving cervical cancer control.

The challenges presented by HPV and cervical cancer are substantial—some might say overwhelming. However, with the improved screening, diagnostic, and preventive technologies described herein—and yet to come—the world has an opportunity to make a real difference in women's lives and to enhance the strength and survival of families and communities.

For additional information on HPV and cervical cancer, please visit the following websites:

RHO Cervical Cancer
www.rho.org

PATH cervical cancer prevention
www.path.org/cervicalcancer

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

International Agency for Research on Cancer Screening Group
www.iarc.fr/cervicalindex.php

World Health Organization—cancers of the reproductive system
www.who.int/reproductive-health/publications/cancers.html

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