Cervical cancer is the third most common form of cancer among women worldwide, yet it is one of the few cancers that can be detected and prevented at a precancerous stage. Most cervical cancer cases (85%) occur in the developing world, where they account for 13% of all female cancers. Furthermore, cervical cancer rates in developing countries are on the rise. Breast cancer and cervical cancer combined are projected to equal maternal deaths as the leading causes of mortality among reproductive-aged women by 2025. In contrast, in high-resource countries, effective screening for, and management of, precancers has precipitated a decline in the incidence and mortality due to cervical cancer over the past half-century.

Cervical cancer in the developing world is a challenge of education, resources, and competing priorities. Screening for cervical cancer has historically been inadequate in lower-resource settings. In recent years, several developing nations have targeted cervical cancer with renewed focus, establishing new guidelines for prevention and management and directing resources toward increasing screening coverage (Table 1). Prevention of cervical cancer in these settings has been complicated by sociocultural and infrastructural variables. Moreover, the biology of cervical cancer differs for developed versus developing settings, affected by the variable prevalence of high-risk human papillomavirus (HPV) subtypes and by the AIDS pandemic. Programs for cervical cancer prevention and management in developing nations must account for these variables while weighing financial and opportunity costs. This article reviews the current status for prevention and management of cervical precancers in health systems around the world.
EPIDEMIOLOGY OF CERVICAL CANCER

Cervical cancer is the third most common cancer and the fourth leading cause of cancer-related deaths among women worldwide, with an estimated 530,232 cases diagnosed and 275,008 fatalities worldwide in 2008. Cancer rates, however, vary dramatically by whether or not a country has an adequate screening program. In the United States, the disease accounted for only 1.6% of cancer cases and 1.4% of cancer mortality among women in 2008. The incidence rate of cervical cancer in developed nations has decreased steadily over the last half-century. This decline in incidence of cervical cancer is largely the result of improved cervical cytology services and coverage over the period.

In the United States, cervical cancer disproportionately affects racial minorities and women of lower socioeconomic standing. Invasive cervical cancer is more common among black and Hispanic women than among white women. Moreover, survival of the disease is less probable for black women than for white women. Cervical cancer incidence and mortality increase with decreased socioeconomic status among all racial groups.

Internationally, the burden of cervical cancer falls most heavily on developing nations. About 85% of the cases and 88% of the deaths due to cervical cancer occur in developing nations. Women in developing nations are at a 35% greater lifetime risk of cervical cancer than women in high-income countries. Although cervical cancer is most common in women older than 50 years, in developing nations, cervical cancer is becoming increasingly prevalent among women during their reproductive years (ages,

---

<table>
<thead>
<tr>
<th>Country/Organization</th>
<th>Age Range</th>
<th>Interval</th>
<th>Primary Screening Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Obstetricians and Gynecologists</td>
<td>≥21 y</td>
<td>Every 2–3 y</td>
<td>Cytologic examination, optional HPV cotesting at &gt;30 y</td>
</tr>
<tr>
<td>European Guidelines for Quality Assurance in Cervical Cancer Screening</td>
<td>Beginning between ages 20 and 30 y until 60 y</td>
<td>Every 3–5 y</td>
<td>Cytologic examination</td>
</tr>
<tr>
<td>World Health Organization (WHO) Guidelines for Developing Countries</td>
<td>25–49 y, 3-y interval if not resource-limited &gt;30 y, at least 1–3 times lifetime if resource limited</td>
<td></td>
<td>Cytologic examination, other modalities are also acceptable</td>
</tr>
<tr>
<td>South Africa (Department of Health)</td>
<td>≥30 y</td>
<td>3 tests, lifetime</td>
<td>Cytologic examination</td>
</tr>
<tr>
<td>India (Government of India/WHO collaboration)</td>
<td>30–59 y</td>
<td>Every 5 y</td>
<td>VIA</td>
</tr>
<tr>
<td>Peru</td>
<td>25–59 y</td>
<td>Every 2 y</td>
<td>Cytologic examination or VIA</td>
</tr>
<tr>
<td>Thailand</td>
<td>35–54 y</td>
<td>Every 5 y</td>
<td>Cytologic examination nationally, VIA regionally</td>
</tr>
</tbody>
</table>
15–49 years). Because cervical cancer has a greater cure rate when discovered at an asymptomatic early stage, in countries without screening programs, patients are disproportionately diagnosed with advanced stage and thus incurable disease.

**HPV: EPIDEMIOLOGY AND MOLECULAR BIOLOGY**

Infection of the cervix with HPV is necessary, although not sufficient, to cause cervical neoplasia and cervical cancer. HPV is among the most prevalent sexually transmitted viruses in the human population. It is estimated that 50% to 80% of sexually active women contract genital HPV during their lifetime. Around 80% of HPV infections clear within 2 years and do not cause cervical neoplasia and invasive cervical cancers. Persistent infection with HPV is required for the development of cervical dysplasia and invasive cervical cancer.

In the United States, an approximate 6.2 million persons are infected with the virus each year. HPV infection is present in 13.3% of US women with normal cervical cytology, comparable with the global prevalence of 11.4%. HPV is more common in lesser-developed regions. In Eastern Africa, where age-standardized incidence and mortality are greatest, HPV is prevalent in 33.6% of women with normal cervical cytology. HPV is most commonly identified on cervical testing among adolescent women (ages, 14–24 years) and is associated with sexual debut.

Certain HPV subtypes increase the likelihood that an infection of the cervix with HPV will develop into cervical dysplasia and invasive cervical cancer. Fifteen HPV subtypes are classified as high risk for cervical cancer (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82). HPV-16 and HPV-18, the 2 highest-risk subtypes, are present in 71% of cervical carcinoma. The prevalence of HPV-16 and HPV-18 is variable worldwide, ranging from 2.0% among women with normal cervical cytology in Western Europe to 9.7% among women with normal cervical cytologic in Eastern Europe.

Infection with a high-risk HPV subtype is the single greatest risk factor for invasive cervical cancer. Other risk factors include tobacco smoking, high parity, long-term hormonal contraceptive use, and infection with human immunodeficiency virus (HIV). The risk of HPV infection is greater in women with multiple sexual partners, and HPV is a common coinfection with other sexually transmitted infections, including HIV.

**HPV INFECTION, IMMUNE SURVEILLANCE, AND DEVELOPMENT OF NEOPLASIA**

HPV are DNA viruses that infect the human anogenital tract and surface epithelium. HPV are small nonenveloped viruses, consisting of a capsid shell and a 7.9-kilobase genome. The HPV genome carries 8 protein-coding genes, 6 coding for early viral function (E1, E2, E3, E4, E6, and E7) and 2 coding for late viral function (L1 and L2). More than 100 HPV subtypes have been characterized to date. HPV subtypes are distinguished by genotypic diversity in the E6, E7, and L1 coding regions, sharing no greater than 90% genetic similarity in these regions. HPV-16 and HPV-18 are associated with 71% of cervical cancers; types 31, 33, 35, 45, 52, and 58 are found in association with an additional 21% of cervical cancers.

The virus is typically transmitted via sexual intercourse, during which the virus is deposited on the basement membrane of the cervical epithelium. Once present on the cervical epithelium, HPV infection may be transient or may persist and lead to the eventual development of cervical neoplasia and potentially cervical cancer. The course of infection depends on several stages in the natural history of cervical cancer. HPV DNA exists in cervical cells in either an episomal or an integrated state.
Integration of viral DNA into the host genome may be necessary for persistent infection and development of cervical dysplasia.

Most HPV infections resolve within a few years and do not develop into precancerous lesions. A cell-mediated immune response is responsible for clearing viral particles and infected cells. Immunologic memory may protect against future infection, although it is limited to serologic HPV subtype, because women are susceptible to a subsequent infection with a different strain.

Cervical dysplasia typically begins in undifferentiated keratinocytes in the cervical transformation zone, where proliferating subcolumnar cuboidal reserve cells replace columnar cells with squamous epithelium. This site of epithelial metaplasia is at risk for dysplastic growth. Most invasive cervical cancers arise from the squamous epithelium in the transformation zone. However, between 10% and 25% of cervical cancer patients, are found to have adenocarcinoma of the glandular epithelia.

Growth at the precancerous stage is gradual and may progress to a higher level of dysplasia but may also regress and eventually clear. Levels of dysplasia diagnosed on cervical biopsy are roughly categorized into 3 levels of dysplasia: low-grade dysplasia (with minimal risk for progression to cancer) and moderate or severe levels of dysplasia (categorized as high-grade dysplasia). There is a fair amount of interobserver variation as to the diagnosis of the different levels of dysplasia and, to date, no reproducible way to predict which of these high-grade precancers will progress to invasive cancer.

An HPV infection in general progresses more rapidly from transmission to precancerous lesions than from precancerous lesions to cancer. Cervical lesions persist for years before progressing to cancer, which allows for time to intervene and prevent progression to cancer. Even in the absence of treatment, only a minority of cervical intraepithelial neoplasias (CINs), an estimated 1% of low-grade lesions and 5% to 12% of high-grade lesions, progress to invasive carcinoma. The progression of an infection to precancerous lesions and to invasive cancer is more probable and more rapid in women infected with high-risk subtypes HPV-16 and HPV-18. At the cellular level, HPV-16 and HPV-18 have greater transforming potential than lower-risk HPV subtypes. The oncogenicity of high-risk HPV-16 may further relate to its suppression of immune responses. However, 80% to 90% of women infected with HPV-16 and HPV-18 will not develop precancerous lesions.

HPV infection is more likely to persist in immunocompromised patients. Most notably, HIV coinfection is a risk for HPV infection and for the development of CIN and invasive cervical cancer. HIV broadly suppresses immune system function by killing macrophages and CD4+ T cells. The virus may also increase the risk of malignancy with HPV infection by altering interactions between cancer cells and lymphocytes.

SCREENING AND DIAGNOSIS OF CERVICAL PRECANCERS

At the time that cervical cytologic examination was being introduced by Papanicolaou and Traut in 1943, cervical cancer was the leading cause of cancer mortality among US women. As of 2008, cervical cancer was the 15th most common cause of cancer mortality among US women. Organized cervical cancer prevention programs have precipitated a decline in cervical cancer rates in the developed world. When compared against historic cohorts, such programs have reduced the incidence of cervical cancer by as much as 75%.

Successful cervical cancer prevention programs integrate screening with management of cervical precancers. Three screening modalities, cervical cytologic testing
(Papanicolaou test), cervical HPV testing, and visual inspection of the cervix, are commonly used for cervical screening. Women with positive test results may be referred for colposcopy, in which the transformation zone is visualized under magnification, and abnormal lesions may be biopsied. Histologically confirmed precancerous lesions may be treated by various excisional or ablational techniques. Specific recommendations for screening and management vary according to national and institutional guidelines. In developed nations, a 3-visit model for cervical precancer management is generally used in which screening, colposcopy with directed biopsy, and treatment proceed in 3 separate steps. Alternatively, either a 1-visit approach, in which a rapid screen is followed by immediate treatment, or a 2-visit approach, in which an abnormal Papanicolaou test result is triaged to evaluation and treatment in 1 visit (both known as see and treat), may also be used.

The Papanicolaou test, or Pap smear, has been the standard screening test for much of the past half-century. The test checks for morphologic abnormalities in fixed and stained cells from cervical epithelial sampling. Conventional cytologic testing has a specificity of 94% to 97% in distinguishing high-grade CIN. However, with a sensitivity of approximately 70% to 80%, false-negative results are frequent with Papanicolaou testing alone. Uneven sampling of cervical epithelia and sample loss and manipulation during preparation of cytology slides limit the sensitivity of the technique.

Recently, liquid-based cytologic examination has emerged as an alternative to conventional cytologic examination. Improvements in sample preparation limit the number of unsatisfactory Papanicolaou tests, although they do not appreciably raise the sensitivity of cervical cytologic examination. The high frequency of false-negative results with cytologic testing necessitates repeated screening. Cervical cytologic examination has been effective with screening at regular intervals because of the long lead time of cervical precancers, although such screening requirements place a larger burden on patients and health systems.

Modern techniques in molecular biology allow detection of genital HPV infection with probes for HPV DNA and RNA, HPV proteins, and cellular markers. Hybrid Capture 2 (HC2; Qiagen), which is the most widely used of these tools, uses DNA hybridization probes for type-specific detection of HPV DNA and can detect 13 high-risk HPV subtypes, including HPV-16 and HPV-18. The sensitivity of detection with HPV testing for high-grade cervical lesions is approximately 95%. However, the technology does not discriminate between transient HPV infections and HPV-associated cervical lesions. As such, interpretation of test results is complicated by the moderate specificity of the technique, reported between 61% and 96% in various studies. The specificity of HPV testing is greatest among populations in which the prevalence of HPV is low and the incidence of cervical precancer is high. In a Finnish study of primary HPV testing (N = 33,100), the specificity of the test ranged from 93.4% to 95.6% in women aged 35 years and more, who have lower HPV prevalence yet higher CIN incidence than younger cohorts, as compared with 84.4% among women aged 25 to 34 years.

In clinical studies involving side-by-side comparison of cervical cytologic examination and HPV testing, sensitivity is consistently higher with HPV testing and specificity is consistently higher with cytologic examination. Because of the complementary strengths of each technique, HPV testing has been incorporated as an adjuvant test with cytologic examination. The Canadian Cervical Cancer Screening Trial, which examined conventional cytologic examination and the HC2 HPV test in a randomized controlled trial (N = 10,154), reported 100% sensitivity and 92.5% specificity for simultaneous Papanicolaou and HPV cotesting. However, a large number of additional colposcopies were required for diagnosis of each additional case of high-grade
dysplasia when using combined testing than when using either test alone or when using either test only as a downstream test for abnormal screens, a process known as reflex testing. Colposcopy and biopsy adds significant additional cost as well as pain and anxiety to a screening program; thus, combined testing becomes viable only if offered at a less frequent interval than either test alone.

In much of the developed world, cervical cytologic examination remains the primary screening test. Several large-scale studies have evaluated HPV screening as a cotest along with primary cervical cytologic examination or for triage after cytologic examination, reporting greater predictive values than for cytologic examination alone. Nevertheless, as recently as 2010, the European Guidelines for Quality Assurance in Cervical Screening maintain cytologic examination as the standard, noting the risk of overdiagnosis and inconclusive evidence on adjuvant HPV testing. Specifics of screening programs vary amongst European Union nations. Recent guidelines issued from several major US organizations, including US Preventive Services Task Force, American Society of Colposcopy and Cervical Pathology, American Cancer Society, and American College of Obstetrics and Gynecology recommend Papanicolaou test alone starting at age 21 years, with reflex HPV testing for Papanicolaou tests showing atypical squamous cells of undetermined significance. These organizations have different opinions about the data suggesting that all women should undergo Papanicolaou and HPV cotesting starting at age 30 years, although they do all agree that if both tests are obtained and both show negative results, they should not be repeated before 3 years. They all agree that for regular-risk women, Papanicolaou testing alone every 3 years is acceptable for women aged 30 years and older.

MANAGEMENT OF SCREENING ABNORMALITIES

Patients with abnormal cervical cytology are typically triaged to a secondary screening evaluation, although in some nations, particularly in Central and Eastern Europe, colposcopy is used in routine cervical examination. Colposcopy involves the visualization of abnormal lesions of the cervix under magnification, often with direct biopsy for histologic diagnosis. Independently, colposcopy has a sensitivity reported between 44% and 77% and a specificity reported between 85% and 90% in various studies. Biopsy enables histologic diagnosis of mild, moderate, or severe dysplasia or invasive cervical cancer. Colposcopy requires equipment (a working colposcope and sterile instruments), experienced trained practitioners to perform the biopsies, and easily available pathology services to read the biopsies, relay results, and then track patients to return for repeat visits for treatment or reassessment. Such a system is costly and impractical in many lower-resource settings. Thus, easier, more practical solutions for screening and diagnosis that can be applied by lesser-trained clinicians or health care workers, which do not require easily accessible pathology services and often allowing for one see-and-treat visit, have been evaluated extensively.

TREATMENT OPTIONS

There are 2 main approaches to treatment of cervical precancers: excisional and ablative. In countries with greater resources, an excisional procedure, either a loop excision or a cold knife cone biopsy, is commonly performed. The loop procedure uses a wire loop and electrocautery and local anesthesia to excise a small area of the cervix containing an abnormality that can then be sent off for pathology review. If cancer is diagnosed, a larger therapeutic surgery can be performed. This treatment can be performed both in a 3-visit approach (screen with Papanicolaou test or HPV, followed by
colposcopic-directed biopsy, followed by treatment if pathologic examination shows a high-grade precancer), or it can be performed in a 2-visit approach (abnormal Papanicolaou test result followed by evaluation and treatment at next visit).

Another treatment, cryotherapy, ablates the cervix by freezing it. This technique applies a cold probe to the external cervix and is best when used for smaller less-advanced lesions. For the treatment to be successful, the lesion must be fully visible and cannot involve the endocervical canal or the vagina. Furthermore, cryotherapy does not treat cancer and has limited efficacy (70%–92%) against CIN 3.7 Because it is low cost and rarely results in major complications, cryotherapy is an ideal treatment when resources are scarce or when a less-trained worker is performing many see-and-treat examinations.

SCREENING IN DEVELOPING SETTINGS

Simultaneous or sequential Papanicolaou and HPV screening require additional resources, making such combination testing impractical in developing settings. HPV may be preferable to Papanicolaou testing as a stand-alone primary cervical screen in resource-limited settings. Because of the high sensitivity for the detection of moderate or severe dysplasia, HPV testing is more appropriately suited for settings in which women have few lifetime examinations.41 Moreover, HPV tests have a higher positive predictive value in these settings because of the higher incidence of cervical cancer.42

Visual inspection of the cervix (visual inspection with acetic acid [VIA] or Lugol iodine [VILI]) offers an alternative screening test to Papanicolaou and HPV testing. The screen involves application of acetic acid (VIA) or Lugol iodine reagent (VILI) to the cervix, followed by examination with the naked eye or with magnification to detect well-defined lesions in the vicinity of the squamocolumnar junction. The sensitivity of VIA/VILI for detection of high-grade lesions varies widely in studies in different settings (55%–96%), although it is most frequently reported in the 70% to 85% range, roughly comparable with cervical cytologic examination.18,32,43 However, VIA/VILI is less specific than cervical cytologic examination, with reported specificities ranging from 49% to 86% for VIA and from 73% to 93% for VILI.32

Cervical screening programs with VIA/VILI are likely most compatible with the available infrastructure in developing countries. VIA/VILI does not require laboratory capacity, and medical personnel can be trained in the technique in less than 10 days.44 Moreover, VIA is the most cost-effective method of cervical screening, as measured in cost per year of life saved. In representative models based in Thailand comparing primary Papanicolaou, HPV, and VIA screening, VIA screening costs approximately $200 to $300 per year of life saved and HPV and Papanicolaou screening cost approximately $1000 to $4000 per year of life saved ($2002).42

Loss to follow-up is a challenge with cervical cancer screening in middle- and low-income countries. The course of care is taxing on patients and health systems, requiring multiple visits for primary screening, directed biopsy, and treatment. Thus, VIA/VILI or HPV testing can be used in combination with same-day treatment, often using low-cost cryotherapy, wherein screen-positive women are immediately triaged to treatment without colposcopy or histologic examination. See-and-treat cervical cancer prevention programs using VIA/VILI or HPV testing with cryotherapy have proven efficacious in reducing the incidence of moderate or severe dysplasia and invasive cancer in a variety of developing settings.45–47 In a large (N = 6555) randomized trial of the approach in South Africa, participants randomized to the see-and-treat cohort with VIA/VILI and HPV screening had a 46% and a 77% lower prevalence of
See-and-treat approaches using same-day screening and cryotherapy are liable to overtreat participants. However, the technique has been generally highly acceptable to study participants, and major complications with cryotherapy are infrequent. Moreover, see-and-treat approaches are more cost-effective than multiple-visit screening designs for resource-limited settings. Models of see-and-treat programs in Kenya, Thailand, Peru, India, and South Africa produce a cost per year of life saved that is below the respective national per capita gross domestic products (GDPs).

The efficacy and cost-effectiveness of see-and-treat screening with HPV testing may be augmented by cervicovaginal sample self-collection. In various settings, sample self-collection has been acceptable to the local population, and invitation for self-collection has increased compliance and overall screening coverage versus invitation for clinician-directed sampling. The approach is limited by poorer specimen quality and sensitivity for detection of moderate or severe dysplasia, reported between 55.0% and 82.5%. However, self-collection is more cost effective than clinical sample collection.

See-and-treat and self-collection with cervical screening are confined to pilot programs and study trials in much of the developing world. Conventional cytologic examination remains the standard in South Africa, Brazil, and Sudan, although many nations, including India and Kenya, have shifted the focus to VIA/VILI with referral to secondary screening.

LIMITATIONS OF SCREENING SERVICES WORLDWIDE

Cervical cancer is the second most common cancer among women in low-income countries, although it accounts for only 0.6% of the overall mortality in low-income countries. The design of, and resource allocation to, cervical cancer programs must be made in the context of the demands of such competing health priorities as HIV, maternal mortality, and diarrheal diseases. The standard of care in developed nations for the management of cervical precancers requires laboratory capacity for cytologic and histologic examinations and time and resource available for multiple visits for screening, colposcopy with directed biopsy, and ultimately treatment. Comparatively, see-and-treat programs, 1- or 2-visit models involving VIA/VILI or HPV screening with cryotherapy, can produce a cost per year of life saved that is below the respective national per capita GDPs at which point see-and-treat screening can be considered very cost effective.

Effective prevention and management of cervical precancers has yet to be realized in many developing nations and resource-poor settings. In developing nations, 65.3% of women have never received a pelvic examination. Lifetime screening coverage may be as low as 10% in poorer nations, including Zambia, Ethiopia, and Bangladesh. Even in developing nations that, in recent years, have committed to cervical cancer prevention programs, screening coverage is markedly depressed as compared with coverage in developed nations. Moreover, follow-up diagnosis and treatment of cervical precancers have been complicated by inefficiencies in referral networks and care provision. Efforts to address cervical cancer in developing nations are further complicated by particular regional variables, including the HIV/AIDS pandemic. Nevertheless, within controlled settings in developing nations, cervical cancer screening and management can function with comparable efficacy to programs in developed nations. A host of economic, logistical, and sociocultural factors may...
impede the accessibility and availability of preventative and treatment services for cervical precancers. Such limitations include fragmented health care systems, inadequate health infrastructure for cervical cancer care, and a lack of training of clinicians for cervical cancer prevention and management.\textsuperscript{59–61} In an example from an Ugandan study, 87\% of final-year medical students had never performed a Papanicolaou test\textsuperscript{59}; in Lagos, Nigeria, a study found that only 11.8\% of general practitioners informed their patients about Papanicolaou tests.\textsuperscript{62} Numerous developing nations are severely lacking in capacity for colposcopy, cryotherapy, or other vital screening or treatment infrastructure.\textsuperscript{40}

Social and cultural barriers may also limit patient access to care. Low levels of awareness about cervical cancer pose a common barrier in many developing settings to uptake of preventative services.\textsuperscript{60,63–65} Cultural notions of modesty and attitudes about screening further impede uptake of these services.\textsuperscript{59,66} In a survey of attitudes about Papanicolaou testing among Kenyan women, participants did not recognize the rationale for early detection, opining, “if you are not in pain, why [do] you need a test?” and adding that “even if we went for such a test, we do not want to be told that we have cancer.”\textsuperscript{57} The utility of cancer treatment is viewed with skepticism in some settings in which cancer is regarded as a disease without a cure or as the result of witchcraft or infidelity.\textsuperscript{61} Such patient limitations to cervical cancer screening and treatment are prevalent among lower-income and immigrant populations in developed nations as well.\textsuperscript{66,67}

Cervical cancer prevention programs have used multiple strategies in efforts to overcome patient limitations. Interventions commonly incorporate a public educational component, which may consist of posters, pamphlets, television, or radio advertising. In regions with low literacy, person-to-person and group health education may be most important to overcoming barriers of lack of awareness. Sample self-collection by patients for HPV testing may allow screening programs to circumvent specific barriers associated with pelvic examination.

Cervical cancer programs have succeeded in developing settings in which they have addressed both provider limitations and patient limitations. In a pilot project for mass cervical cancer screening in Soweto, South Africa, laboratory capacity was organized to conduct 90,000 Papanicolaou tests annually. The project, however, garnered a low level of participation among the target population because it failed to incorporate a public awareness campaign.\textsuperscript{65} By contrast, an intervention in Sarawak, Malaysia, that addressed both infrastructural and social barriers succeeded in reducing the late-stage presentation of both breast cancer and cervical cancer cases by approximately one-half.\textsuperscript{68} The program trained health staff in early detection and strengthened referral systems, while also engaging an active public awareness campaign.

### HPV Vaccination

As an alternative to screening and management of cervical precancers, HPV vaccination provides primary prevention against precancers and invasive cancer. At present, 2 vaccine formulations are commercially available, the quadrivalent HPV 6/11/16/18 vaccine (Gardasil) and the bivalent HPV-16/18 vaccine (Cervarix). Both vaccines protect against infection from HPV-16 and HPV-18, which are associated with approximately 70\% of cervical carcinoma.\textsuperscript{10} Both the bivalent and quadrivalent vaccines are highly effective in protecting against HPV-16/HPV-18 infection (92\%–100\% efficacy) and the development of HPV-16/HPV-18–related CIN 2/3 (>90\% efficacy) among HPV-naive women.\textsuperscript{69–71} However, the vaccines are not effective in women with
previous HPV exposure. In the United States, vaccination is recommended for girls aged 9 to 18 years. Under certain guidelines, catch-up vaccination is recommended for women aged 18 to 26 years, who are more likely to have had previous HPV infection. Cervical screening is still recommended in vaccinated women because the current HPV vaccines cover the 2 highest-risk HPV subtypes but not the remaining 13 high-risk HPV subtypes that cumulatively account for approximately 30% of cervical cancers.

Although currently affordable only in middle- and high-income nations, HPV vaccination has the potential to close the gap in cervical cancer incidence and mortality between developed and underdeveloped nations. Various models of HPV vaccination campaigns in developing countries highlight potential reductions in lifetime risk of cervical cancer ranging from 30.1% (Senegal) to 60.1% (Ethiopia) and 60.8% (Brazil). HPV vaccination in combination with see-and-treat HPV screening provides a 1.5- to 2-fold lifetime risk reduction versus screening alone. At present, however, the cost of the vaccine is prohibitively expensive for resource-poor settings. Vaccination is most cost effective in nations with the greatest cervical cancer burden, including much of Eastern Africa, Haiti, and Bolivia. Several global health care organizations are currently working with vaccine manufacturers to lower the cost of the vaccine to be affordable in the poorest countries.

**SUMMARY**

Cervical cancer incidence and mortality have decreased dramatically over the past 50 years in countries with access and resources to provide frequent screening, evaluation, and treatment of high-grade cervical cancer precursors. For countries with fewer resources and many competing health concerns, cervical cancer remains one of the most lethal and common cancers among women. With the advent of newer technology, such as low-cost HPV vaccines and self-administered HPV tests, followed by simple well-known techniques such as VIA and cryotherapy, cervical cancer rates may well start to decrease worldwide.

**REFERENCES**


