Chapter 4

Cervical Cancer

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INTRODUCTION

Cervical cancer, a largely preventable disease, is one of the most common cancers found in women living in low- and middle-income countries (LMICs). A striking reduction in the incidence of and mortality from cervical cancer occurred in the past century in those countries that were able to establish successful national screening programs. These programs relied on cytology-based Papanicolaou smears to identify cervical cancer precursors that can be removed before progressing to invasive cancer. Prevention of up to 91 percent of all invasive cervical cancers has been achieved in countries able to implement widespread cytology-based screening.

However, these programs are expensive and require robust and well-funded health care systems. Few LMICs have initiated or sustained cytology-based cervical cancer prevention programs, and these countries experience very high incidence and mortality rates. The unequal burden of cervical cancer is an example of the impact of unequal access to health care. Fortunately, alternative strategies to prevent cervical cancer have been investigated and extensively evaluated in these settings. The recent introduction of two commercially available vaccines against human papillomavirus (HPV) has offered the possibility of primary prevention of cervical cancer. This chapter focuses on these innovations.

BURDEN OF CERVICAL CANCER[1]

Global Burden of Disease

Cervical cancer, caused by HPV, is the third leading malignancy among women in the world, after breast cancer and colorectal cancer, with an estimated 527,624 new cases and 265,653 deaths in 2012 (Ferlay and others 2013). Incidence and mortality rates have been declining in most areas of the world in the past 30 years, at a worldwide rate of about 1.6 percent per year (Forouzanfar and others 2011). This decline is a result of increased access to health services, reductions in some risk factors (such as fertility rates), improvements in treatment, and successful cytology-based screening programs. However, more than 80 percent of cases and 88 percent of deaths occur in LMICs. Cervical cancer is still the leading cancer in women in many LMICs; some areas report recent increases in rates, including several economies in Europe and Central Asia (Arbyn and others 2011).

A striking characteristic of cervical cancer is its variation by country, with a generally strong inverse correlation between the level of development and the incidence and mortality. Survival once the disease has developed is also much better in richer than in poorer countries. Figure 4.1 shows trends of incidence and mortality in selected countries.

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Figure 4.1 Trends of Age-Standardized Rates of Cervical Cancer Incidence and Mortality in Selected Countries

Source: CI5*plus* (http://ci5.iarc.fr/CI5plus/Default.aspx) and WHO Mortality Database (http://www.who.int/healthinfo/statistics/mortality_rawdata/en/index.html).
Note: Data for the economies in the graphs are for Uganda (Kampala), Thailand (Chiang Mai), Philippines (Manila), India (Chennai and Mumbai), Brazil (Goiâna), Spain (Granada, Murcia, Navarra, and Tarragona), China (Hong Kong SAR, China, and Shanghai), and the United States (Surveillance, Epidemiology, and End Results Program). All available data for these economies are shown.

Regional Burden of Disease

Despite the declining global rates, the number of new cases and deaths has increased constantly by about 0.5 percent per year because of population aging. With no new intervention, the increase will continue, particularly in LMICs where the life expectancy of women is improving. For example, in Latin America and the Caribbean, the estimated number of new cases is likely to increase by 75 percent between 2002 and 2025 if the incidence rates remain at 2002 levels, because of population growth and aging alone (Parkin and others 2008).

The disease is strongly influenced by cultural and religious practices that govern sexual behavior and transmission of HPV. Sub-Saharan Africa has the highest estimated rates of cervical cancer; in Guinea, Malawi, and Zambia, the age-standardized incidence rate is over 50 per 100,000 (Arbyn and others 2011). In contrast, in countries in the Middle East and North Africa, such as Algeria, the Arab Republic of Egypt, Libya, Sudan, and Tunisia, where sexual behaviors are more conservative, the recorded incidence rates are below 10 per 100,000 women. In high-income countries (HICs), rates are even lower, at about 5 per 100,000 women.

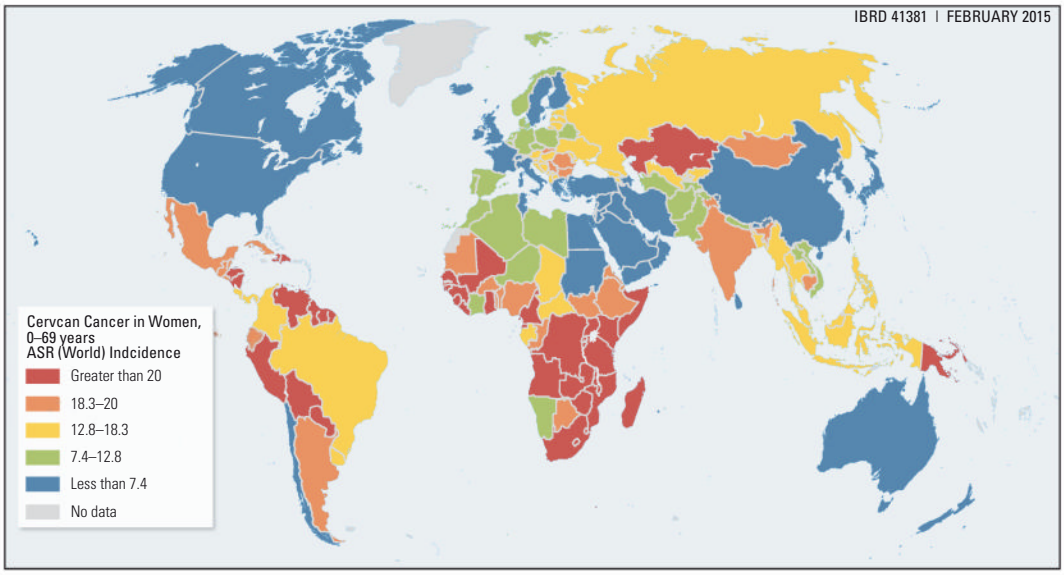
In Latin America and the Caribbean, Guyana, Honduras, Jamaica, and Nicaragua have rates around 40 per 100,000. In Asia, the highest rates are in Bangladesh, Cambodia, India, and Nepal.

Map 4.1 shows the incidence of cervical cancer by country in 2012; figure 4.2 shows the contrast between the rates of incidence and mortality between national income groupings.

Even within HICs, the highest incidence and mortality rates are among the poorest or most marginalized women. For example, in the United States, where the average rates are low and cervical cancer has consistently declined in recent decades, strong disparities still exist by race and socioeconomic status (Singh 2012), reflecting the variability in accessibility of services. The other notable characteristic of cervical cancer is that it affects relatively young women who often have many children and are frequently sole providers. The median age at death for women with cervical cancer is 54 years; the burden of disease among women under age 40 years is high compared with other cancers, because of the large numbers of women in these age groups in LMICs and the fact that cervical cancer rates begin to rise at younger ages than other cancers.

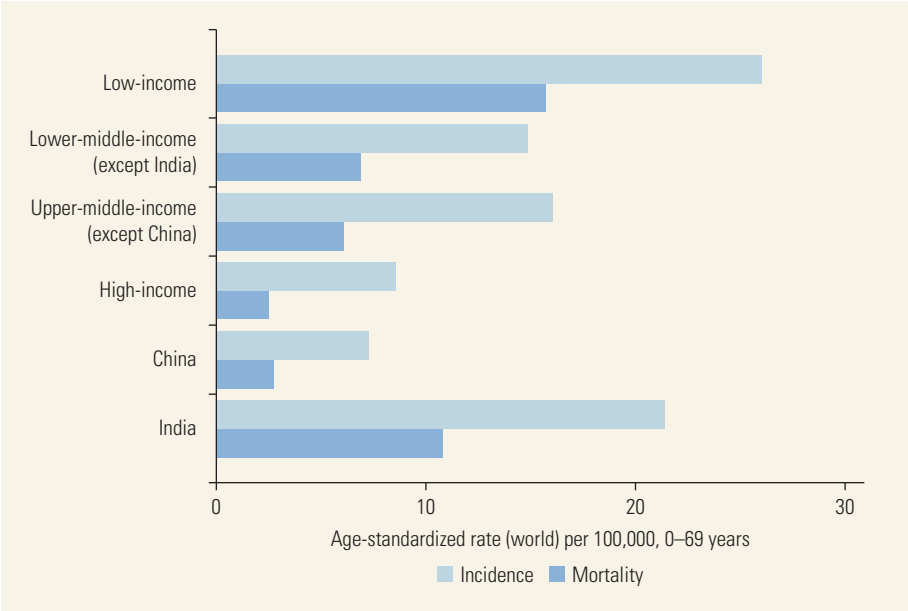
Because cervical cancer affects relatively young women, it ranks highest among cancers according to a disability-adjusted life years (DALYs) metric. In a recent study, DALYs caused by cervical cancer ranged from 84 per 100,000 women in areas with a very high Human Development Index (HDI)[2] to 595 per 100,000 in areas with a low HDI (Soerjomataram and others 2012). Breast cancer DALYs ranged from a high of 566 age-adjusted DALYs per 100,000 in populations with a very high HDI to 387 in those with a low HDI.

Map 4.1 Age-Standardized Cervical Cancer Incidence Rates, 2012



Source: Ferlay and others 2013.
Note: ASR = age-standardized rate.

Figure 4.2 Age-Standardized Cervical Cancer Incidence and Mortality Rates per 100,000 Women, by World Bank Income Group



Source: Ferlay and others 2013.

NATURAL HISTORY OF CERVICAL CANCER

The natural history has been studied extensively, and persistent infection of the cervix with certain high-risk types of HPV has been well established as a necessary cause of cervical cancer (Walboomers and others 1999). HPV is a very common sexually transmitted infection, usually acquired soon after initiation of sexual activity. Most HPV infections clear spontaneously within one to two years; those that persist, particularly high-risk types of HPV (including HPV 16 and 18), may progress to cervical cancer precursors, and ultimately to invasive cervical cancer. High-risk types of HPV are identified in nearly all cancers of the cervix, and the relative risk of cervical cancer associated with persistent, ongoing infection with high-risk types of HPV is higher than the risk of lung cancer associated with smoking. HPV 16 and 18 are responsible for about 70 percent of cases worldwide (http://www.iarc.fr). There is little geographic variation in the predominant HPV types associated with cervical cancer.

A study that evaluated HPV infection in 10,575 histologically confirmed cases of invasive cancer from 38 countries in Asia, Europe, Latin America and the Caribbean, North America, Oceania, and Sub-Saharan Africa over a 60-year period found that 85 percent (n = 8,977) of the cases were positive for HPV DNA (de Sanjose and others 2010). HPV types 16, 18, and 45 were the three most common types in each histologic form of cervical cancer (squamous cell, adenocarcinoma, and adenosquamous carcinoma), accounting for 61 percent, 10 percent, and 6 percent, respectively.

Good evidence suggests that HPV infection precedes the development of cervical cancer by decades and that persistent infection with HPV is necessary for the development and progression of precancerous lesions of the cervix, either to higher grades of precancerous disease or to cancer. Cervical cancer progresses slowly from a preinvasive state to invasive cervical cancer, a process that can take 10–30 years (Wright and Kurman 1994).

However, HPV infections are very common, particularly among young women (Herrero and others 2005), where the majority of infections are likely to regress spontaneously as a result of activation of the immune system.

Cervical Cytology Classification and Terminology

In 1988, the Bethesda classification of cytology was adopted and has been revised several times (National Cancer Workshop 1989). The latest consensus guidelines for the management of abnormal cytology in the United

States were published in 2013 (Massad and others 2013) and can be accessed at http://www.asccp.org.

Cervical Cancer and Infection with Human Immunodeficiency Virus

Women infected with human immunodeficiency virus (HIV) have an increased risk of being infected with HPV and are at increased risk for cervical cancer. Studies have consistently shown higher prevalence of HPV infection, more persistent infections with HPV, greater infections with multiple types of HPV, and higher prevalence of cervical cancer precursors in HIV-infected women (Ellerbrock and others 2000; Harris and others 2005; Palefsky and others 1999). The Rwandan Women's Interassociation Study and Assessment is an observational prospective cohort study of 710 HIV-positive and 226 HIV-negative Rwandan women enrolled in 2005 (Singh and others 2009). The prevalence of HPV was significantly higher in the HIV-positive group overall and in each 10-year age group. Forty-six percent of HIV-positive women had high-risk types of HPV and 35 percent were infected with multiple types, both of which were associated with a higher risk of abnormal cytological findings.

The association with HIV is important because integrating cervical cancer prevention strategies with chronic care for HIV-positive women is essential to maximizing the health-giving benefit of antiretroviral therapy. In many countries in Sub-Saharan Africa, antiretroviral therapy is free, but cervical cancer screening and treatment are not.

SECONDARY PREVENTION OF CERVICAL CANCER THROUGH SCREENING

Historically, cervical cancer screening, also known as secondary prevention of cervical cancer, was based on examining cells collected from the surface of the cervix by Pap smear (cytology), followed by colposcopy for women with abnormal smears and histological assessment, followed by surgical treatment for histologically proven cancer precursors. This approach resulted in dramatic reductions in cervical cancer incidence and mortality in health systems that were robust enough to support relatively complex screening programs effectively. However, very few LMICs have been able to initiate or sustain cytology-based screening programs because of lack of adequate resources or health care or laboratory infrastructure.

For screening and treatment of precancerous lesions, several new tools have been developed that are better suited to low-resource settings. Depending mainly on the target age group and frequency of screening, these tools may be effective in reducing cervical cancer rates. The new interventions include the following:

- Screening with visual inspection with acetic acid (VIA)
- Screening with HPV DNA testing
- Treatment with ablative techniques (cryotherapy and cold coagulation)
- Treatment using excisional techniques, called loop electrocautery excision procedure (LEEP), also known as large loop excision of the transformational zone (LLETZ), and cone biopsy.

Impact of Cervical Cytology-Based Screening Programs

Cytology-based cervical cancer screening, which began in the early 1960s in the Scandinavian countries, was not evaluated in randomized trials to assess the impact of screening on cervical cancer incidence or mortality. The marked reduction in cervical cancer incidence and mortality after cytology-based screening programs were initiated in a variety of LMICs was interpreted as strong nonexperimental support for organized cervical cancer screening programs.

The International Agency for Research on Cancer (IARC) conducted a comprehensive analysis of data from several of the largest screening programs in the world in 1986; the analysis showed that well-organized, cytology-based screening programs were effective in reducing cervical cancer incidence and mortality (Hakama 1986). In the Nordic countries, following the introduction of nationwide screening in the 1960s, mortality rates from cervical cancer fell between 84 and 11 percent, respectively, corresponding to the country with the shortest screening interval and widest age range (Iceland) and to the country with only 5 percent population coverage by an organized screening program (Norway) (Laara, Day, and Hakama 1987).

Further, the age-specific trends indicated that the *target age range* of a screening program was a more important determinant of risk reduction than the *frequency* of screening within that age range. This finding was in agreement with the estimates of the IARC Working Group on Cervical Cancer Screening that for interscreen intervals of up to five years, the protective effect of organized screening exceeded 80 percent throughout the targeted age group (IARC Working Group on Cervical Cancer Screening 1986a, 1986b). It is clear that the extent to which screening programs have succeeded or failed

to decrease the incidence of and mortality from cervical cancer is largely a function of three factors:

- The extent of screening coverage of the population at risk
- The target age of women screened
- The reliability of cytology services in the program.

Gakidou, Nordhagen, and Obermeyer (2008) evaluated screening programs in 57 countries and found that the levels of effective screening coverage using cytology vary widely across countries, from over 80 percent in Austria and Luxembourg to less than 1 percent in Bangladesh, Ethiopia, and Myanmar. Many women in low-income countries (LICs) had never had a pelvic examination. This proportion of women is largest in Bangladesh, Ethiopia, and Malawi, where more than 90 percent of women report never having had a pelvic examination, compared with 9 percent of women living in the richest global wealth decile. Although crude coverage rates are high for women in the richest wealth deciles, effective coverage rates are overall low, with rates of around 60 percent and less than 10 percent in the poorest countries.

Screening efforts have failed to produce the expected reductions in cervical cancer mortality in many places, even when large numbers of Pap smears were performed, because the wrong women have been screened (for example, younger women attending antenatal clinics), coverage of the most at-risk population was too low (that is, women ages 35–64 years), the quality of cervical smears was poor (Irwin, Oberle, and Rosero-Bixby 1991; Lazcano-Ponce and others 1994; Sankaranarayanan and Pisani 1997), and follow-up of screen-positive women was incomplete. In all cases, funds were spent for little gain.

Alternative Approaches to Cytology for Cervical Cancer Screening

Visual Inspection with Acetic Acid

VIA involves applying a 3–5 percent acetic acid solution to the cervix and then examining it with the naked eye using a bright light source. No expensive equipment or supplies are needed, and screening takes less than five minutes. A well-defined aceto-white area close to the transformation zone indicates a positive test.

VIA is inexpensive and simple and can be carried out by primary care staff. Most important, VIA provides an immediate result that can be used to decide on treatment, usually with cryotherapy, which requires training but no surgery or anesthetic.

It is difficult to recommend VIA unconditionally, however, because its sensitivity and specificity are lower than those of other screening methods (table 4.1). VIA sensitivity and specificity are variable, because they are highly dependent on the training and skill of the staff carrying out the examinations. The accuracy of the test decreases with the increasing age of the women screened. In cross-sectional studies, the sensitivity and specificity of VIA compared favorably with cytology in detecting high-grade cervical cancer precursor lesions and cervical cancer. Sensitivity has varied from 49 to 96 percent, and specificity has varied from 49 to 98 percent (Denny, Quinn, and Sankaranarayanan 2006). However, many of these studies suffer from verification bias, where the true status of disease in test-negative women is unknown. Sauvaget and others (2011) performed a meta-analysis of 26 studies of VIA with confirmatory testing, using high-grade squamous intraepithelial lesions (HSIL) as the disease threshold. Sauvaget and others (2011) report a sensitivity of 80 percent specificity (range 79–82 percent) and 92 percent specificity (range 91–92 percent) for

Table 4.1 Performance and Characteristics of Screening Methods

Screening test	Sensitivity	Specificity	Characteristics
Conventional cytology	Moderate (44–78%)	High (91–96%)	Adequate health care infrastructure required; laboratory based; stringent training and quality control required
HPV DNA testing	High (66–100%)	Moderate (61–96%)	Laboratory based; high throughput; objective, reproducible, and robust; currently expensive
Visual inspection methods			
• VIA	Moderate (67–79%)	Low (49–86%)	Low technology; low cost
• VIAM	Moderate (62–73%)	Low (86–87%)	Linkage to immediate treatment possible; suitable for low-resource settings
Colposcopy	Low (44–77%)	Low (85–90%)	Expensive; inappropriate for low-resource settings

Source: Ranges of sensitivity and specificity adapted from Cuzick and others 2008.
Note: HPV = human papillomavirus; VIA = visual inspection with acetic acid; VIAM = magnified visual inspection with acetic acid.

VIA, with a positive predictive value of 10 percent. They conclude that in very low-resource settings where the infrastructure for laboratory-based testing is not available, VIA is a reasonable alternative to cytology. However, in more recent randomized studies, VIA has performed less well.

Despite its limitations, the possibility of immediate diagnosis and treatment makes VIA the only possible alternative in many low-resource settings. One potential use of VIA that would have a significant impact is following an HPV test, for HPV-positive women only, to make treatment decisions. The utility of VIA in this context is promising but yet to be proven.

Case Study of Upscaling VIA

From 2005 through 2009, the World Health Organization (WHO) sponsored a VIA demonstration project in six Sub-Saharan African countries: Madagascar, Malawi, Nigeria, Tanzania, Uganda, and Zambia (WHO 2012). In all, 19,579 women were screened with VIA. Of these, 1,980 were VIA-positive (11.5 percent); cancer was suspected in 326 (1.7 percent). Of the VIA-positive women, 1,737 were eligible for cryotherapy (87.7 percent); of these, 1,058 (60.9 percent) were treated, 601 (34.6 percent) were lost to follow-up, and 78 women were not treated. Of the women treated, 243 (39.1 percent) were treated during the same visit as the screening.

No information was available for 230 of the 326 women in whom cancer was suspected (70.5 percent); of the 96 women investigated, cancer was confirmed in 79, but no staging information was recorded; 77 of the women were treated, mostly with radiation.

This is an interesting study of "real world" VIA screening, with all of the difficulties of any screening program, even with a test as simple as VIA. These difficulties range from achieving adequate coverage; to losing to follow-up the large number of women needing treatment (only 60 percent of eligible women were treated); to treating women on the same day as screening ("screen and treat"), which occurred for less than 40 percent of the women. The failure to refer over 70 percent of women with suspicious lesions for further evaluation—possibly because cervical biopsy is not a free service in any of these countries and most women could not afford to pay—is disturbing. The greatest utility of VIA in countries that cannot afford any alternative is to establish the necessary infrastructure to provide health care services to older women. Once VIA becomes successfully implemented, it should be relatively easy to introduce more sensitive methods of screening into the system. In many LMICs, establishing a sustainable and appropriate infrastructure is most likely the priority.

HPV Testing

Highly sensitive and reproducible laboratory techniques to detect oncogenic HPV and cervical cancer have been developed and are being used or considered in place of cervical cytology for primary screening, in addition to other potential uses (Cuzick and others 2008). The cervix is sampled with a brush, which is inserted into the endocervix and then removed and placed in a tube containing special transport media. The U.S. Food and Drug Administration has approved five of the many tests available for routine laboratory service:

- ***Hybrid Capture 2*** detects 13 oncogenic types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).
- ***Cervista HPV HR*** detects 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).
- ***Cervista HPV 16/18*** detects only HPV 16 and 18.
- ***Aptima*** (transcription–mediated amplification test) detects RNA from 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).
- ***Cobas 4800*** (real-time polymerase chain reaction [PCR]–based test) detects 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).

Other tests that use PCR technology are being used in many clinical studies.

HPV testing is an excellent alternative to cytology for cervical cancer screening (Arbyn and others 2012). In meta-analyses of cross-sectional studies, the sensitivity of the Hybrid Capture 2 (HC2) DNA test, the most commonly used test, was 90 percent to detect CIN2+ and 95 percent to detect CIN3+, with more heterogeneity in studies from LMICs. Compared with cytology, the sensitivity of HC2 is 23–46 percent higher on average, and the specificity is 3–8 percent lower (note we are using the terminology as reported by the authors, hence the switch between cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesion (SIL) terminology).

Another advantage of HPV testing is the possibility of linking screening to treatment without colposcopy or prior histological sampling, particularly once either simplified or point-of-care HPV tests are developed. A randomized screening trial to evaluate safety investigated the acceptability and efficacy of screening women and treating those with positive tests without colposcopy and histological sampling (Denny and others 2010). A total of 6,555 previously unscreened women, ages 35–65 years, were tested for high-risk types of HPV using HC2 (Qiagen, Gaithersburg, MD, United States) and VIA, performed by nurses in primary care settings. This study found that the HPV screen-and-treat arm was associated with a 3.7-fold reduction in the cumulative detection of CIN2 or greater by 36 months;

VIA was associated with a 1.5-fold reduction. For every 100 women screened, the HPV and screen-and-treat strategy averted 4.1 cases of CIN2 and greater compared with VIA-and-treat strategies, which averted 1.8 cases.

A further advantage of HPV testing is that specimens can be obtained by self-collection, with almost complete preservation of the sensitivity and specificity of the screening method. Self-collection, which can be done at home, is accepted by women and could significantly increase participation in screening, particularly by women who are reluctant to undergo a gynecological examination or who live in remote areas.

Another landmark study was a cluster randomized trial of villages and centers where 131,746 women ages 30–59 years were recruited and randomly assigned to one of four groups: HPV testing; cytologic testing; VIA; or the standard of care, which involved no organized or opportunistic screening (Sankaranarayanan and others 2009). The incidence rate of cervical cancer stage 2 or higher and death rates from cervical cancer were significantly higher in the cytologic, VIA, and control groups compared with the HPV testing group. Further, the age-standardized incidence rate (ASIR) of invasive cancer among women who had negative test results on cytological or VIA testing was more than four times the rate among HPV-negative women.

The high negative predictive value of HPV testing (nearly 100 percent) allows the extension of the screening interval, with consequent savings that can offset the possibly higher cost of the test compared with cytology. Screening with HPV testing under age 30 is not recommended, as HPV infection in this group of women is common, and most infections are likely to be transient with a low likelihood of developing into cancer. Screening younger women will add to the costs of the program and may result in significant overtreatment that may be associated with reproductive morbidity, in addition to significant emotional and social problems.

The HPV test is already in use for primary screening in several countries, although in the United States, primary HPV testing has been recommended only in combination with cytology in primary screening or for triage of cytologic abnormalities. A recent study including more than 300,000 women in the United States concluded that HPV testing without cytology might be sufficiently sensitive for primary screening (Katki and others 2011).

Triage of Positive HPV Tests

Even among women over age 30 years, most HPV infections regress; only a minority of women develop persistent infection with high-risk types of HPV that progresses to cervical cancer precursors and cervical cancer. HPV testing identifies women at risk, but not those HPV-positive women who are most likely to have or to develop in the near future significant disease requiring treatment. The challenge is to triage these women by further testing with visual methods, cytology, molecular biomarkers, or a combination of techniques.

Among the visual methods, colposcopy with subsequent biopsy and treatment of visible lesions is the usual procedure in cytology-based programs. However, this method requires highly specialized training and relatively costly equipment. More importantly, the colposcopic impression, colposcopically guided biopsy, and histologic diagnosis are poorly reproducible and have important limitations to the point of reducing the potential of highly sensitive screening tests. The current practice of selecting the most worrisome lesion for biopsy misses up to one-third of prevalent small HSIL lesions. The collection of multiple biopsies from aceto-white lesions can increase the sensitivity of colposcopy (Pretorius and others 2011).

Cytology of HPV-positive women is under strong consideration as a triage method in screening programs, given the high specificity of cytology and ample expertise and infrastructure existing in some areas. This method has the advantage of being highly specific, but it suffers from limited sensitivity. Sensitivity of cytology is influenced by many factors and is complex, but used as a triage test for women already identified as high risk, cytology may suffice. The reduction in the number of cytology tests required and the restriction to HPV-positive women may improve the quality of cytology by reducing the workload and the number of negative slides.

Using DNA biomarkers, limiting further follow-up to women infected with HPV 16 and 18, which are responsible for about 70 percent of cervical cancer and precursors, can reduce the number of women referred to colposcopy while maintaining adequate sensitivity (Castle and others 2011). Overexpression of certain oncoproteins is a marker for increased risk of progression to cervical cancer and may be a better predictor of cancer risk than HPV DNA testing alone, although this is yet to be confirmed (Dockter and others 2009). One biomarker under intensive study is $p16^{ink4a}$, which is overexpressed in cancerous and precancerous cervical cells. In a meta-analysis of studies using several detection methods, the proportion of smears overexpressing $p16^{ink4a}$ increases with the severity of cytological abnormalities (12 percent of normals and 89 percent of HSIL) and histological abnormalities (2 percent of normals and 82 percent of CIN3) (Sahasrabuddhe, Luhn, and Wentzensen 2011). A rapid test for the E6 oncoproteins

of HPV types 16, 18, and 45 is undergoing clinical trials (Schweizer and others 2010).

PRIMARY PREVENTION OF CERVICAL CANCER: HPV VACCINES

Vaccines that prevent infection with certain types of HPV are a major breakthrough in preventing cervical cancer. Monovalent (against HPV 16), bivalent (against HPV 16 and 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium), and quadrivalent (against HPV 6, 11, 16, and 18; Gardasil, Merck and Co., Inc., West Point, Pennsylvania) vaccines have been tested in randomized placebo-controlled trials and shown to be safe, immunogenic, and highly efficacious at preventing HPV infection for up to eight years after vaccination. The bivalent and quadrivalent vaccines are delivered by intramuscular injection at zero, one, and six months, with the first dose between the ages of 9 and 13 years.

Efficacy of HPV Vaccines

Evidence from well-conducted, randomized, placebo-controlled trials demonstrates that these vaccines prevent both persistent cervical infection with the types included in the vaccines in women not previously exposed to HPV infection, as well as preinvasive lesions of the anogenital tract associated with the types present in the vaccines in males and females. In addition, the quadrivalent vaccine prevents genital warts caused by types 6 and 11 (both associated with benign disease) in males and females (The Future II Study Group 2007; Harper and others 2006; Koutsky and others 2002; Mao and others 2006; Roteli-Martins and others 2012; Villa and others 2005).

Bivalent and quadrivalent vaccines appear to offer full protection against types 16 and 18, which together cause an estimated 70 percent or more of cervical cancers worldwide, and a slightly lower fraction of cervical cancer precursors. Some evidence suggests that the immune response to vaccination against types 16 and 18 also provides some cross-protection against types 45 and 31, which are important in the etiology of cervical cancer, thereby increasing the projected protection from vaccination to 75–80 percent.

However, both vaccines are prophylactic and should be administered to individuals prior to infection. HPV is the most common sexually transmitted infection in the world. Ideally, the vaccine should be administered to girls and possibly boys prior to the onset of sexual activity, the age of which varies considerably by country and culture. Vaccination of girls ages 9–12 years with high coverage will most likely be the most clinically effective and cost-effective strategy for cervical cancer prevention.

Public Health Challenges to Implementing HPV Vaccination

From the point of view of developing countries, introducing the HPV vaccine poses many challenges. The most obvious is cost. The current price of both bivalent and quadrivalent vaccines is high, although the costs have decreased considerably as a result of initiatives to enable implementation of HPV vaccination in low-resource settings. However, cost is only one aspect. Unlike the development of a platform for vaccinating infants and children against a range of diseases (the Extended Program for Immunization [EPI]), few LMICs have established pubescent/adolescent health platforms or school health systems from which to vaccinate young girls and possibly boys. The infrastructure will have to be created; for this to happen, a great deal of political will must be generated. Studies supporting the efficacy of HPV vaccines involve adolescents, so they are effective in that age group; however, no completed studies have included infants, so it would be premature to consider adding an HPV vaccine to infant EPI. Several studies including young children are ongoing.

In addition to the need to create a new infrastructure, both vaccines require a cold chain and thus a reliable source of electricity, which is absent in many LMICs, particularly in Sub-Saharan Africa. The need for three injections and follow-up poses its own challenges, as does the necessity for intramuscular injection, which requires skill and medical waste disposal. However, recent data indicate that the immunogenicity and efficacy of two doses of the vaccine may be comparable to three doses, a promising development that could simplify the logistics and reduce the cost of HPV vaccination programs. Furthermore, the vaccine is administered to young girls to prevent a disease that will manifest itself only after 30 years or more. Developing a national strategy will require those familiar with vaccination, including pediatricians and public health officials, to communicate with those who work in the adult oncology field; these two worlds rarely intersect.

A new pubescent or adolescent health platform could be used beyond HPV vaccination. Such a platform would provide an excellent opportunity to offer a range of services to young people, including booster vaccinations against hepatitis B and tetanus; possibly an anti-HIV vaccination in the future; antihelminthic medication; nutritional assessment; and education about drug, tobacco, and alcohol use and pregnancy prevention and sexuality.

Case Studies of HPV Vaccine Implementation

Rwanda, a country of 11 million people, introduced an HPV vaccination program in partnership with Merck, the manufacturer of the quadrivalent vaccine, in 2010. Merck guaranteed three years of vaccinations at no cost and concessional prices for future doses. In April 2011, 93,888 Rwandan girls in primary grade 5 received their first dose of the HPV vaccine, which represented 95 percent coverage of all Rwandan girls in the first round, followed by 94 percent in the second and 93 percent in the third (Binagwaho and others 2012). The success of this program is attributed to the school-based vaccination and community involvement in identifying girls absent from or not enrolled in school.

On World Cancer Day 2013, Gavi, the Vaccine Alliance, announced that it would provide support for the rollout of HPV vaccination in eight developing countries: Ghana, Kenya, the Lao People's Democratic Republic, Madagascar, Malawi, Niger, Sierra Leone, and Tanzania; the price has since been established at US$4.50 per dose (http://www.gavi.org). Further, Gavi plans to have one million girls vaccinated by introducing the HPV vaccine in 20 countries by 2015 and hopes to reach 30 million by 2020 by introducing the vaccine in 40 countries.

Ladner and others (2012) report on the Gardasil Access Program, managed by Axios Healthcare Development, which received a large donation of the quadrivalent vaccine from Merck. Participating projects received free vaccine and were responsible for the costs related to the importation, transportation, storage, and distribution of the vaccine, as well as the costs of community outreach, program management, and data collection. Eight programs were implemented in seven countries: Bhutan, Bolivia, Cambodia, Cameroon, Haiti, Lesotho, and Nepal. The eight programs targeted 87,380 girls, of whom 76,983 (88 percent) received three doses of the vaccine. Three vaccine delivery models were used: health facility–based, school-based, and mixed (health facility– and school-based). The mixed model resulted in the best coverage (96.6 percent); the school-based model was intermediate (88.6 percent); and the health facility model was the least effective (79.9 percent). The estimated coverage was 94.9 percent for the five programs that targeted girls ages 9–13 years, and 80.0 percent for the three programs that vaccinated girls outside that age range.

These data, which show high coverage in low-resource settings, are encouraging. They suggest that with sufficient political will, the implementation of HPV vaccination in low-resource settings should be possible in the near future.

Whether countries introduce the vaccine into the public health sector will be determined by several factors:

- Burden of HPV-associated disease in the country
- Ability to convince politicians and health officials, particularly those who work with children and vaccination, that it is worthwhile to invest in vaccinating children to prevent a disease of adulthood
- Creation of the appropriate infrastructure for the administration of the vaccine
- Cost

TREATMENT OF CERVICAL CANCER

As a result of screening, particularly at long intervals, some more advanced cancers will be detected, and some women will come for treatment because of symptoms, commonly abnormal vaginal bleeding (postcoital, irregular, or postmenopausal), offensive vaginal discharge, pelvic pain, dysuria, or symptoms of local or advanced metastatic disease.

As for all cancers, treatment of cervical cancer is determined by the stage of the disease at presentation. Cervical cancer is staged clinically, for example, through a pelvirectal examination combined with some basic tests as part of the metastatic work-up. Most institutions rely on the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging.

Treatment options for most stage 1 cancers favor surgery alone and usually are curative. For women with later stage 1, stage 2, and early stage 3 cancers, primary treatment is chemotherapy and radiotherapy, with curative intent but lower success rates than for earlier stages. For stage 4 disease, treatment is usually palliative and may involve chemotherapy, radiotherapy, and surgery, although few women in LMICs are likely to have access to these services.

COST-EFFECTIVENESS ANALYSIS

Model-Based Cost-Effectiveness Analysis

In addition to the strong evidence of the clinical effectiveness of primary and secondary prevention of cervical cancer worldwide, a critical factor in decision making, particularly in resource-poor settings, is the financial impact and cost-effectiveness of alternative strategies. Most economic evaluations of cervical cancer prevention approaches have utilized mathematical models to project the long-term public health and economic impacts of prevention strategies in different populations. State-of-the-art methods, as well as the limitations of modeling, have been discussed extensively in published review papers (Brisson, Van

de Velde, and Boily 2009; Canfell and others 2012; Kim, Brisson, and others 2008).

HPV Vaccination

The economic evaluations of HPV vaccination have focused primarily on vaccination of preadolescent girls prior to sexual initiation; only a handful of evaluations have addressed HPV vaccination of other targeted groups, such as preadolescent boys or older women (Tsu and Murray 2011; Tsu, Murray, and Franceschi 2012). Several regional reports published as part of an HPV monograph series have projected health benefits (for example, cancer risk reduction and life expectancy, adjusted or unadjusted for disability or quality of life) and economic outcomes of HPV vaccination of preadolescent girls in all countries in the following regions:

- East Asia and Pacific (25 countries) (Goldie, Diaz, Kim, and others 2008)
- Europe and Central Asia (28 countries) (Berkhof and others 2013)
- Latin America and the Caribbean (33 countries) (Goldie, Diaz, Constenla, and others 2008)
- Middle East and North Africa (20 countries) (Kim, Campos, and others 2013)
- Sub-Saharan Africa (48 countries) (Kim, Sharma, and others 2013)

A related analysis evaluated HPV vaccination in 72 countries eligible for support from Gavi (Goldie, O'Shea, and others 2008). A handful of country-specific analyses in these regions and economies have also been conducted, including Brazil (Goldie and others 2007; Vanni and others 2012); China (Canfell and others 2011); India (Diaz and others 2008); Malaysia (Aljunid and others 2010; Ezat and Aljunid 2010); Mexico (Reynales-Shigematsu, Rodrigues, and Lazcano-Ponce 2009); Taiwan, China (Demarteau and others 2012); and Thailand (Sharma and others 2011).

The overwhelming majority of these studies has concluded that HPV vaccination of preadolescent girls has the potential to reduce substantially the morbidity and mortality associated with cervical cancer, under assumptions of sustained, high vaccine efficacy and reasonable uptake. For example, when assuming vaccination coverage of 70 percent and complete, lifelong protection against HPV 16/18 cervical cancer, HPV vaccination was estimated to avert more than 670,000 cervical cancer cases in Sub-Saharan Africa alone over the lifetimes of women in five consecutive birth cohorts vaccinated as young adolescents (Kim, Sharma, and others 2013).

Measures of Cost-Effectiveness

Not surprisingly, HPV vaccination was cost-effective in more countries as the cost of the vaccine decreased. Consistently across the regional and country-specific studies cited, the results have suggested that for a cost per vaccinated girl (CVG) of US$50 or less, HPV vaccination of preadolescent girls was good value for money in most of the countries evaluated. In countries with a relatively lower disease burden and/or lower per capita gross domestic product, the vaccine cost threshold at which HPV vaccination was cost-effective was lower, at US$10 or US$25 CVG. One study, published by the manufacturers of the quadrivalent HPV vaccine, included strategies of vaccinating males and females up to age 24 years in Mexico; the study found that the most cost-effective strategy was vaccinating 12-year-old girls alone (Insinga and others 2007).

Generally, the factors with the greatest influence on the cost-effectiveness results were the vaccine cost and discount rate, which reflect the time preference for health benefits and costs and are important to capture, given the long time horizon between vaccine expenditure and expected cancer benefits. Vaccine efficacy and the length of vaccine protection—and the requirement for booster doses—also influence the results, with the cost-effectiveness profile diminishing greatly, assuming protection lasts only 10–20 years and/or requires at least one booster dose. Variations in cancer incidence moderately influenced the cost-effectiveness ratios.

In interpreting cost-effectiveness results, a critical distinction must be made between value for resources and affordability. Affordability will be a critical determinant for success in preventing cervical cancer in LMICs with high cervical cancer incidence (Natunen and others 2013). Despite the high value that HPV vaccination can provide at US$25–US$50 per vaccinated girl, the immediate financial expenditures required for adoption of HPV vaccination at this cost may not be attainable in many countries. For example, the financial requirements for vaccinating five birth cohorts over five years at 70 percent coverage in all of Sub-Saharan Africa will range from US$110.0 million (US$0.55 per dose) to US$2.8 billion (US$19.50 per dose) (Kim, Sharma, and others 2013). At least one HPV vaccine manufacturer has offered a price as low as US$5 per dose to Gavi, undoubtedly diminishing the financial barrier to accessing HPV vaccines. Study results suggest that the upfront financial investments in HPV vaccination may be offset by downstream savings in costs of cancer care averted at such a low vaccine price. Careful planning to ensure the sustainability of an HPV vaccination program will be as important as the decision to implement it.

Recent publications on the incremental program costs of introducing and scaling up HPV vaccination suggest that integrating HPV vaccination into existing immunization services is feasible but will likely incur an additional financial burden to countries above the cost of the vaccine (Hutubessy and others 2012; Levin and others 2013). The support by Gavi not only to fund HPV vaccines directly, but also to develop country HPV vaccination programs through demonstration projects, will be instrumental in creating sustainable programs; to date, at least 14 countries have applied for demonstration projects.

Future Directions for Cost-Effectiveness Analysis of HPV Vaccines

Head-to-head comparisons of the bivalent and quadrivalent vaccines are lacking for LICs, but such comparisons may be more relevant in the future. Economic evaluations in HICs that have introduced the HPV vaccine have been conducted comparing the bivalent and quadrivalent vaccines. To date, the results have been conflicting; three studies find that the quadrivalent vaccine is more cost-effective than the bivalent vaccine (Dee and Howell 2010; Jit and others 2011; Lee and others 2011). In contrast, two studies (Demarteau and others 2012; Ezat and Aljunid 2010) find that the cost-savings from reducing more cases of cervical cancer (bivalent vaccine) outweigh the cost-savings from reducing cases of genital warts (quadrivalent vaccine). Current studies have not yet explored the potential added benefits from broad-coverage HPV vaccines that target additional oncogenic HPV types and are anticipated to be available in the near future; these second-generation vaccines are expected to yield even greater cancer reductions and are likely further to impact optimal screening, but the efficacy and costs are unknown.

Cervical Cancer Screening

Studies evaluating screening strategies alone have primarily assessed screening tests (for example, cytology, HPV DNA tests, and VIA), frequencies (for example, one to three times per lifetime, at 3- to 10-year intervals), and ages at screening (for example, 30–50 years). In a seminal study, Goldie and others (2005) assess the cost-effectiveness of screening strategies in five LMICs with heterogeneous epidemiologic, demographic, and economic profiles. They find that strategies that required the fewest visits—and thereby minimized loss to follow-up—were consistently the most cost-effective. The reduction in lifetime cervical cancer risk was 25–36 percent, with only one screening per lifetime; 47–52 percent, with two screenings per lifetime; and 57–60 percent, with three screenings per lifetime. Taking into consideration the direct medical and patient costs associated with screening, the authors conclude that HPV DNA testing and VIA, requiring one or two clinic visits, two to three times per lifetime, at age 35 years, are attractive alternatives to traditional three-visit, cytology-based testing programs. In a more recent study, Levin and others (2010) find that increased coverage levels of cervical cancer screening using rapid HPV tests were cost-effective for a two-visit strategy for screening and treatment of precancerous lesions in China.

The most influential factors in determining the relative value of different screening strategies include the assumptions regarding loss to follow-up between clinic visits, the clinical performance of the screening test (that is, the sensitivity/specificity), and the relative costs of the test. Patient time spent receiving interventions and traveling to clinics are also found to be influential, given the long distances to the clinics, lack of paved roads, and limited public transportation in some settings. Treatment of precancerous lesions can range from inexpensive cryotherapy to more complex and costly LEEP, cold knife conization, and simple hysterectomies. However, these costs are rarely the main drivers affecting the cost-effectiveness of cervical cancer screening strategies.

Remaining challenges include improving the acceptability and accessibility of these services among previously unscreened women. Even with the strong momentum toward introducing HPV vaccination programs, investing in expanded quality screening and treatment services and increasing demand for these services among older women remain critical, given that screening rates are very low in Asia, Latin America and the Caribbean, and Sub-Saharan Africa, irrespective of income, and that these women are not the target group for HPV vaccination.

Combined Vaccination and Screening

Increasingly, analyses are considering the potential synergies between preadolescent HPV vaccination followed by screening in adulthood. The majority of recent studies are set in upper-middle-income countries, such as Malaysia (Aljunid and others 2010; Ezat and Aljunid 2010), Mexico (Insinga and others 2007; Reynales-Shigematsu, Rodrigues, and Lazcano-Ponce 2009), Peru (Goldie and others 2012), South Africa (Sinanovic and others 2009), and Thailand (Praditsitthikorn and others 2011; Sharma and others 2011; Termrungruanglert and others 2012). Only a handful of such studies are in LICs and lower-middle-income countries, such as countries in Eastern Africa (Campos and others 2012), India (Diaz and others 2008), and Vietnam (Kim, Kobus, and others 2008).

The findings suggest an opportunity to improve on cervical cancer prevention by following preadolescent

HPV vaccination with screening (HPV DNA testing) of women one to three times per lifetime, starting at about age 40 years. For example, in Thailand, preadolescent HPV vaccination combined with screening in older women reduced the risk of cervical cancer by over 50 percent (Sharma and others 2011). In Mexico, HPV vaccination combined with cytology screening every three years reduced cancer incidence and mortality by 75 percent (Reynales-Shigematsu, Rodrigues, and Lazcano-Ponce 2009). Similar to findings in studies that explored the cost-effectiveness of HPV vaccination alone, this set of literature generally finds that adding HPV vaccination for preadolescent girls to existing or modified screening programs has the potential to be a cost-effective strategy, with the vaccine price being a key factor in determining cost-effectiveness. Despite finding that HPV vaccination is cost-effective, these studies reiterate the concern over affordability (Canfell and others 2011; Praditsitthikorn and others 2011; Sharma and others 2011).

Conclusion of Cost-Effectiveness Analysis

The findings from recent cost-effectiveness analyses clearly indicate that there are promising opportunities to prevent cervical cancer in different world settings. HPV vaccination for preadolescent girls and screening of adult women, even only three times per lifetime, can avert a significant proportion of cervical cancer cases in a cost-effective manner. In addition to many other critical inputs to health decisions, such as political will and cultural acceptability, evidence on the cost-effectiveness and affordability of HPV vaccination and screening from rigorous model-based analyses can help to inform decision makers and stakeholders in their deliberations on how best to prevent cervical cancer worldwide.

CONCLUSIONS

Cervical cancer remains one of the most common cancers among women living in LMICs, yet it is a preventable and treatable cancer. Resource-constrained countries have been unable to initiate or sustain cytology-based cervical cancer screening programs because of weak health care infrastructure and prohibitive cost. There are two new avenues for cervical cancer prevention:

- Primary prevention through prophylactic vaccination against the most common HPV types causally associated with cervical cancer.
- Use of alternative screening tests and strategies for cervical cancer prevention, namely, HPV DNA testing and VIA. Both tests have their advantages and disadvantages, but the development of a highly reproducible, reliable, and accurate point-of-care HPV DNA test (or an alternative test yet to be developed but fulfilling these criteria) will enable women to be screened and treated in one visit and without the need for colposcopy and laboratory infrastructure. HPV DNA testing has shown very promising results; however, issues of specificity, overtreatment, and effective triage still need to be resolved.

Screening and vaccinating either separately or together are shown to be highly cost-effective public health interventions.

NOTES

The World Bank classifies countries according to four income groupings. Income is measured using gross national income per capita, in U.S. dollars, converted from local currency using the World Bank Atlas method. Classifications as of July 2014 are as follows:

- Low-income countries = US$1,045 or less in 2013
- Middle-income countries are subdivided:
  - Lower-middle-income = US$1,046–US$4,125
  - Upper-middle-income = US$4,126–US$12,745
- High-income countries = US$12,746 or more

1. The map and figures in this chapter are based on incidence and mortality estimates for ages 0–69 years, consistent with reporting in all DCP3 volumes. Cancer statistics are estimates for 2012 and have been provided by the International Agency for Research on Cancer from its GLOBOCAN 2012 database. Observed population-based cancer incidence rates were derived from *Cancer Incidence in Five Continents*, 10th edition, and for trends over time from CI5*plus* (http://ci5.iarc.fr/CI5plus/Default.aspx). The discussion of burden (including risk factors), however, includes all ages unless otherwise noted. Interventions also apply to all age groups, except where age ranges or cutoffs are specified.
2. HDI is a composite of three dimensions of human development: a long and healthy life (life expectancy at birth), access to knowledge (adult literacy and enrollment at different educational levels), and standard of living (gross domestic product adjusted for purchasing power parity).

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