

Cervical Cancer Update

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OUT LOOK

Preventing Cervical Cancer in Low-Resource Settings

Cervical cancer is an important women's reproductive health problem, especially in developing countries, where over 80 percent of the 231,000 yearly deaths from cervical cancer occur.¹ Yet cervical cancer—caused by infection with a sexually transmitted agent, human papillomavirus (HPV)—can be readily prevented by identifying and treating women with HPV-induced precancerous lesions of the cervix. Strategies for preventing HPV transmission also may decrease disease incidence among women in some settings. Although efforts to reduce the health impact of cervical cancer have been initiated all over the world, most attempts in developing countries have not been successful due to factors such as lack of awareness of the problem, limited access to necessary health interventions, inability to provide Pap smear services to women who need them, and ineffective use of available resources. Lessons learned from program experience combined with emerging information from research and policy assessments now make development of cost-effective, integrated programs in low-resource settings much more feasible.

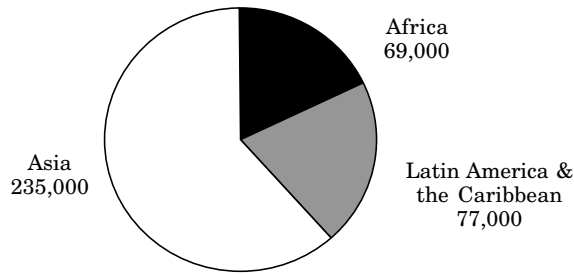
This updated edition of *Outlook* outlines the issues that must be considered when providing cervical cancer prevention services, and summarizes experiences and lessons learned from programs in developing countries. Much of the information has been adapted from the second edition of PATH's *Planning Appropriate Cervical Cancer Prevention Programs*.²

Scope of the Problem

Cervical cancer is the third most common cancer worldwide and the leading cause of death from cancer among developing-country women. The most recent compilation of global data indicates that an estimated 466,000 new cases of cervical cancer occur annually among women worldwide; about 80 percent occur in developing countries. Of these, over half occur in Asia (see Figure 1). Rates are highest in Melanesia, Southern and Eastern Africa, and Central America.¹

An important reason for the sharply higher cervical cancer incidence in developing countries is the lack of effective screening programs aimed at detecting and treating precancerous conditions. Compared with women in developed countries, very few women in developing countries have access to screening for precancerous cervical lesions.

Figure 1. Estimated Number of New Cervical Cancer Cases in Some Developing Regions, 2000



Source: Parkin, 2000.¹

Basic Principles of Cervical Cancer Control

The vast majority of cervical cancer cases are caused by HPV, a sexually transmitted agent that infects the cells of the cervix and slowly causes cellular changes that can result in cancer.³ A 1999 study estimated that over 99 percent of cervical cancers worldwide contained HPV DNA.⁴ Women generally are infected with HPV in their teens, twenties, or thirties, although cervical cancer can develop 20 years or more after HPV infection (see Figure 2). Various studies have looked at other risk factors associated with cervical cancer, including sexual activity, obstetric history, and health behaviors (such as smoking and nutrition). Most of these factors probably are proxies for HPV infection, although smoking, parity, and perhaps nutritional status likely are independent cofactors in HPV progression.

The pathway to preventing cervical cancer deaths is simple and effective. If the precancerous changes in cervical tissue (which can linger for years) are identified and successfully treated, the lesions will not develop into cervical cancer. Treating the abnormal, dysplastic tissue also seems to protect women from developing cervical cancer in the future.⁵

Screening and dysplasia treatment are cost-effective interventions when compared to expensive, often futile hospital-based treatment of invasive cancer. A World Bank analysis suggested that, in 1993, cervical cancer screening (defined as screening women every five years, with standard follow-up for identified cases) cost about US\$100 per disability-adjusted life year (DALY) gained, compared with about US\$2,600 per DALY for treatment of invasive cancer and palliative care.⁶

Of course primary prevention of cervical cancer through preventing HPV infection also will contribute to reducing cancer mortality. Primary prevention of HPV presents greater challenges than prevention of most other sexually transmitted infections (STIs), however. HPV generally is asymptomatic and easily transmitted. While treatments for the genital warts caused by some types of HPV are available, there are no therapies that eliminate the underlying infection. The virus can remain infectious

for years and can exist throughout most of the anogenital area (including areas not covered by condoms). The standard STI prevention recommendations (for example, regular use of condoms or other barrier methods and reducing the number of sexual partners) may help women reduce the chance of HPV infection, but the degree to which they will affect the overall incidence of cervical cancer is unclear.

A more promising approach to primary prevention—vaccines against HPV—is some years away. A number of private companies and public-sector agencies worldwide are exploring various candidate HPV vaccines. While research to date is encouraging, much remains to be clarified regarding the safety, effectiveness, and program implications of potential HPV vaccines.⁷

It is important to take into account the current understanding of the natural history of cervical cancer in deciding when to initiate screening, how often to screen, and when to recommend treatment and/or follow-up evaluation (see Figure 2).

- *When to initiate screening:* Cervical cancer most often develops in women after age 40, and high-grade dysplasia generally is detectable up to 10 years before cancer develops, with a peak dysplasia rate at about age 35. Therefore, where program sources are limited, screening initially should focus on women in their thirties and forties.
- *How often to screen:* Cervical cancer generally develops slowly from precursor lesions; therefore, screening can take place relatively infrequently and still have a significant impact on morbidity and mortality. Screening every three years has almost as great an impact as screening every year. Even screening every 10 years or once in a lifetime can have a significant impact.^{8,9} The emphasis of screening programs, therefore, should be on coverage of high-risk women rather than on frequency (see Table 1).
- *Whom to treat and follow up:* Because most low-grade dysplasia regresses spontaneously, treatment

Cervical Dysplasia Classification Systems

Two formal classification systems are used for cytological identification of cervical cancer precursor conditions. In the Cervical Intraepithelial Neoplasia (CIN) system, mild cervical dysplasia is categorized as CIN I, moderate dysplasia as CIN II, and severe dysplasia (including carcinoma *in situ* [CIS]) as CIN III. The Bethesda Classification System includes atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesions (LSIL), which include CIN I; and high-grade squamous intraepithelial lesions (HSIL), which include CIN II and CIN III.

generally should focus on high-grade dysplasia, with follow-up mechanisms in place for women with lower-grade lesions. About one-third of untreated high-grade lesions will progress to cancer within 10 years, whereas approximately 70 percent of low-grade dysplasia regresses spontaneously or does not progress.^{10,11}

Screening

To date, cervical cancer prevention efforts worldwide have focused on screening at-risk women using Pap smears and treating precancerous lesions. Pap smears involve scraping cells from the cervix, fixing and staining them on a glass slide, and having them evaluated by a trained cytologist. Where screening quality and coverage have been high, these efforts have reduced invasive cervical cancer incidence by as much as 80 percent.¹²

Effective Pap screening faces challenges. Although Pap smear-based screening efforts have been introduced in several developing countries, many have achieved only limited success. Problems have included:

- screening is offered opportunistically (often for a fee) to younger, relatively low-risk women;
- cytology services are limited and/or of poor quality;
- follow-up diagnostic and treatment services are unavailable to most women; and
- clients often do not understand that having a Pap smear is important to cancer prevention.¹³

In most countries, developing systems to ensure access to high-quality cytology services is a challenge.

“In countries where resources are limited, the aim should be to screen every woman in the target group once in her lifetime at about the age of 40 years.” —WHO, 1992⁹

In Mexico, for example, the low quality of cytology services has been a major barrier. A study of 13 cytology centers found a range of problems from poor-quality services to inadequately trained technicians; the false-negative rate for Pap smears in these centers was as high as 54 percent.¹⁴ In Colombia’s cervical cancer prevention program, a shortage of cytotechnicians has been a key barrier to achieving screening goals.²

Efforts to improve the quality of the Pap smear itself are ongoing. For example, the ThinPrep® slide system uses a liquid-based cytology system to produce slides that, in general, are easier to read with fewer difficult-to-

interpret slides. The slides can be read either by a cytologist or an automated Pap smear reading machine. This approach adds considerable cost to Pap smear-based programs, however, and requires technical capability that is difficult to maintain in many settings.

Several alternative approaches to screening women at risk of cervical cancer currently are being investigated. These include visual screening to identify cervical lesions and HPV tests to identify women at high risk for dysplasia.

Visual inspection: an alternative to Pap smears. Given the difficulty of ensuring high-quality cytology-based services in many settings, there is significant interest in new approaches to screening for precancerous lesions. Of these, visual inspection of the cervix is a promising option, especially for low-resource settings.

Early studies of visual inspection involved simply looking at the cervix for any signs of early cancer. Also known as “downstaging,” this approach was not effective

Figure 2. Natural History of Cervical Cancer and Program Implications

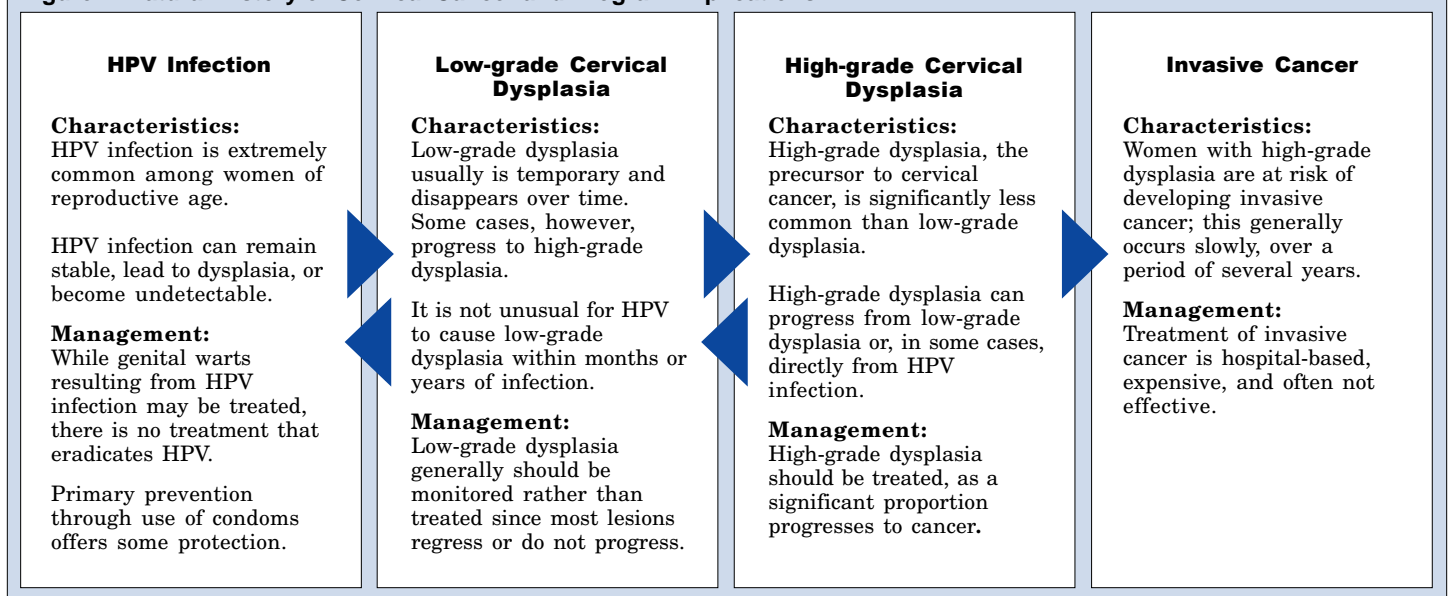


Table 1. Potential Reduction in Cumulative Cervical Cancer Rate With Different Frequencies of Screening

Frequency of Screening [†]	Percent Reduction in Cumulative Rate
1 year	93
2 years	93
3 years	91
5 years	84
10 years	64

[†]Screening all women aged 35-64 who have had at least one previous negative screen. Adapted from IARC, 1986.⁸

in identifying precancerous conditions.¹⁵ By contrast, visual inspection after swabbing the cervix with an acetic acid (vinegar) solution highlights differences in cell structure and absorption rates, and causes precancerous cells to turn white. One study found that when combined with Pap smear screening, visually inspecting the cervix after a one-minute acetic acid wash improved detection of cervical disease by 30 percent.⁵

Visual inspection with acetic acid (VIA). VIA is defined as visual inspection of the acetic acid-swabbed cervix without any magnification. The cervix is illuminated with a light source and examined with the naked eye by a trained health care worker. Although protocols have varied, results of several studies in developing countries suggest that VIA is as sensitive as Pap smears in detecting high-grade dysplasia in many settings, although not as specific.

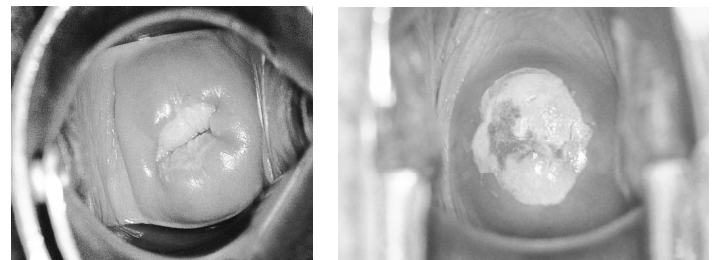
A 1996 study of 2,426 women in South Africa found that VIA detected more than 65 percent of high-grade lesions and invasive cancer and, according to the study authors, warranted consideration as an alternative to cytologic screening.¹⁶ A 1999 study in Zimbabwe used nurse-midwives to perform the screening exam. The study reported that the sensitivity (proportion of true positives identified as positives) and specificity (proportion of true negatives identified as negatives) of VIA in detecting HSIL were 77 and 64 percent, respectively, compared to 43 percent and 91 percent for Pap smears.¹⁷ A study of 1,351 women in India found that VIA performed by trained nurses detected 96 percent of moderate-severe dysplasia and cancer, while Pap smears (obtained by trained nurses and examined by a cytopathologist) detected 62 percent. The specificity of VIA for detecting these lesions was 68 percent.¹⁸

Some studies of VIA have added low-power magnification to the procedure. This approach—called VIA with magnification (VIAM)—currently uses a low-power (4x), hand-held visual inspection device with a built-in light source (an Aviscope™) to examine the cervix after application of acetic acid. A small Indonesian evaluation

of an earlier version of the device indicated that VIAM may be acceptably sensitive and specific (over 90 percent) in identifying moderate to severe cervical lesions. It is not yet known if use of the Aviscope offers a significant advantage over VIA without magnification, although the potential for increased specificity is of particular interest. Several studies in developing countries are underway to assess its ability to provide accurate results.

Many aspects of VIA make it an attractive approach for use in low-resource settings. VIA is a relatively simple, low-tech approach that is minimally reliant upon infrastructure for performance. Non-physicians can perform the procedure, provided that they receive adequate and ongoing training. Furthermore, results of the procedure are available immediately, making it possible, in principle, to provide treatment during the same visit (see page 5). However, VIA is less effective for screening postmenopausal women because physiological changes make observation of cervical lesions difficult. This limitation should be taken into consideration by all screening programs using VIA. Pap smears also can be more difficult to obtain in postmenopausal women.

As countries begin to evaluate broad-scale use of VIA, it is important to consider the issue of false-positives and determine the balance between false-positives and false-negatives that is consistent with local health policy and programmatic capabilities. Regular training of health care providers is an important component of any cervical cancer prevention program. Because VIA is an entirely provider-dependent screening method, clear standards for identifying the precancerous lesions that should be treated are essential, along with approaches for ensuring that



Left: Small, flat, dull acetowhite lesion. Right: Large, thick, dull acetowhite lesion. Both are examples of high-grade squamous intraepithelial lesions (HSIL). Photo courtesy of JHPIEGO Corporation. *Atlas of Visual Inspection with Acetic Acid (VIA)*. JHPIEGO Corporation: Baltimore, MD (1999).

providers make appropriate judgments, both after initial training and throughout routine service provision.

Other visual inspection approaches also are being used. For example, Cervicography® involves taking photographs of the cervix through a specially equipped camera. Once developed, the photographs (called cervigrams) are projected as slides and interpreted by specially trained colposcopists. While the sensitivity of Cervicography can be comparable to cytology, as with other visual inspection approaches, specificity appears to

be lower.¹⁹ Cervicography is relatively expensive and requires a reliable logistics infrastructure.

HPV testing. There is growing interest in the potential for using HPV testing in cervical cancer prevention programs. While epidemiological and technical barriers remain, several scenarios have been suggested. The most commonly proposed approaches are to use positive HPV tests to (1) identify women with low-grade dysplasia who should be managed more aggressively; (2) determine which women treated for high-grade dysplasia should be monitored more closely; and (3) determine which women aged 35 and older are at greatest risk of high-grade dysplasia.

Recent data point to the potential for using HPV testing as a primary screening strategy in older women. For example, one study evaluated the use of the Digene Corporation's Hybrid Capture® II (HC II) test (which detects the presence of 18 high-risk HPV types in cervical/vaginal specimens) to identify women likely to have high-grade lesions and cancer. The study involved more than 9,000 sexually active women aged 18 and older in Guanacaste Province, Costa Rica, and found that HPV testing detected 88.4 percent of high-grade lesions and cancers. The HPV test demonstrated greater sensitivity than Pap smears in this setting (88 versus 78 percent) but lower specificity (89 versus 94 percent). When results were calculated by age group, specificity was highest (94 percent) in women aged 41 and older.²⁰

A second study evaluated the HC II test's ability to identify women likely to have high-grade lesions and cancer among more than 1,400 previously unscreened black South African women aged 35 to 65. HPV testing (using self-collected vaginal samples) was more sensitive than Pap smears (66 versus 61 percent) in this population, but less specific (as the false-positive rate was 17.1 percent for HPV testing, and 12.3 percent for Pap smears). These differences, however, were not statistically significant.²¹

Key barriers to further exploration of HPV test protocols in low-resource settings are cost and technical requirements. In the U.S., the current HC II test retails for about US\$22 per test, takes six to seven hours to process, and requires access to laboratory equipment and a computer. A simpler, less-expensive, but equally accurate test will be required before screening protocols utilizing HPV testing can be initiated in most developing countries.

Treatment

Any screening program must be accompanied by adequate treatment options. In many countries, treatment options are limited; pre-invasive cervical lesions often are treated with aggressive approaches such as cone biopsy or hysterectomy rather than with more appropriate, outpatient approaches. Although appropriate for certain circumstances, inpatient approaches are expensive and

often result in over-treatment of women. In addition, they can result in serious complications and side effects, and require significant resources for anesthesia, equipment, and inpatient care.

Relatively simple outpatient procedures can be used to destroy or remove precancerous tissue (see Table 2). The specific treatment used depends on the severity, size, and location of the lesion. A common outpatient ablation (destruction) method is cryotherapy, which involves freezing abnormal tissue with a probe cooled by liquid nitrous oxide or carbon dioxide. Cryotherapy has an overall effectiveness rate of 80 to 90 percent; it is most effective with smaller areas of abnormal tissue.²² Another outpatient excisional method is loop electrosurgical excision procedure (LEEP). Although LEEP involves more equipment and supplies, it removes diseased tissue and provides a tissue sample for analysis, reducing the possibility of overlooking invasive cancer. A 1998 study comparing cryotherapy, LEEP, and laser vaporization found the three methods to be equally safe and effective.²³

Some developed-country programs have begun to adopt a "see and treat" approach to treating pre-invasive lesions, in which LEEP is used to remove tissue for diagnosis and treatment immediately following colposcopic diagnosis. This approach reduces the number of visits a woman must make to receive proper care—a clear advantage in many settings. It may result in some over-treatment, however. Also, concern remains that the possible sequelae of treatment—bleeding, discharge, and cervical scarring—need to be better defined. Projects in Thailand and South Africa are evaluating the safety, acceptability, feasibility, and program effectiveness of a see-and-treat approach—VIA followed immediately by cryotherapy as appropriate.²⁴

Client-Provider Issues

In many countries, both women and providers lack information about cervical cancer prevention options. Women may know little about the disease, may not trust

Table 2. Two Treatment Options for Precancerous Cervical Lesions[†]

	Cryotherapy	LEEP
Effectiveness	80%-90%	90%-95%
Side effects	Watery discharge Risk of infection	Bleeding
Anesthesia required	No	Yes
Tissue sample obtained	No	Yes
Power required	No	Yes
Cost	Relatively low	Relatively high

[†]The specific treatment option used depends on the size, severity, and location of the lesion.

Source: Bishop et al., 1995.²²

preventive services, or may not know where services are available. Providers may adopt inappropriate medical protocols and use limited program resources inefficiently. Efforts to improve women's awareness and provider knowledge of prevention options are essential to a successful cervical cancer prevention program.

Increasing women's awareness. A key challenge for programs is encouraging women at highest risk for treatable, precancerous lesions—often women in their thirties and forties—to seek services. Because many women in this age group have completed childbearing and therefore are not likely to access family planning or maternal health services, special approaches are required to inform them of the need for and availability of screening. The best approaches for increasing awareness among women in their post-reproductive years will vary from place to place, and should be developed with input from women themselves (see box below). Possible approaches include reaching women through local women's or community groups; linking screening to an important event in an older woman's life, such as becoming a grandmother; or linking screening to other mid-life health needs, such as contraceptive sterilization. Use of multiple communication strategies to promote screening is likely to be most successful.²⁵

In many regions, the risk of developing cervical cancer is amplified by poverty and isolation. In Colombia, strategies such as special "cytology days" in shanty towns have been initiated using radio, megaphones, and church calls to encourage hard-to-reach women to attend.²

Overall, it is essential to ensure good quality of care at screening sites, treating women with respect and paying attention to their concerns. Program experience

from many countries has demonstrated that women will not attend preventive care services if they believe that they will be treated poorly.²

Increasing provider knowledge and skills. Program success depends upon (1) assisting providers in adopting a public health-oriented approach to screening and treatment, and (2) training them in the skills necessary to counsel clients and provide high-quality services that respect women's concerns and needs. In many settings, it is important to ensure that non-physicians can effectively provide screening services so that screening coverage can be maximized.

Experience from cervical cancer control efforts worldwide suggests that some policies in low-resource settings call for inappropriate service delivery approaches—for instance, screening women as frequently as every six months, focusing screening on younger women, and focusing treatment on advanced cancers. Widespread use of such practices prevents programs from achieving a significant health impact by draining program resources. Both pre-service and in-service provider training can address this issue by presenting clear information about the public health rationale for frequent screening, focusing on broad coverage of older women in their thirties and forties, and emphasizing treatment of precancerous conditions.

Providers also need appropriate training on key clinical and counseling issues related to cervical cancer prevention, along with ongoing supervisory support and assistance in establishing and maintaining referral links. Particularly important is ensuring the quality of screening programs. If Pap smears are used, for example, the smear must be properly collected, stored, and transported to a

Educating Women Is Key to Eliminating Barriers

In many countries, women may not know about cervical cancer or that detecting and treating precancerous lesions can prevent the disease; this lack of awareness is a major barrier to seeking screening services. One Nigerian study of women aged 20 to 65 found that only 15 percent had heard of the disease.²⁶ A smaller study in Kenya found that, when asked to identify the biggest cancer threat in their community, only 10 percent of clients identified cervical cancer, compared to almost 60 percent of providers. When asked what could be done to prevent cervical cancer, 80 percent of the Kenyan women said they did not know; only two percent mentioned Pap smears.²⁷ In a Mexican study, women cited an array of barriers to seeking screening services, including a lack of knowledge about cervical cancer or Pap smears, the perception that cancer is an inevitably fatal disease, problems in client-provider relationships, opposition by male sexual partners, and concern about pelvic exams.²⁵

In order for women to seek cervical cancer screening services, they must be informed about the disease and have access to services that are sensitive and responsive to their needs. Involving women at risk of cervical cancer (particularly women in their thirties and forties) in the development of educational messages and program interventions is key. Participatory qualitative research methods—such as focus group discussions, in-depth interviews, or community mapping with women of various ages and their partners—can provide insights into their needs and concerns. Program managers seeking ongoing input may consider establishing an advisory team comprising women at risk. These activities can help ensure that women receive persuasive information from their preferred sources and at their preferred delivery sites. They also can help ensure that services are provided in an acceptable manner, thereby increasing women's willingness to seek screening and necessary follow-up care.

cytology laboratory, and results must be accurately interpreted and provided to clients within a reasonable time frame. If visual screening approaches are used, providers must be trained to properly identify abnormal tissue and know what action to take; sufficient practice with a trainer present is crucial to this process.

Appropriate counseling also is critical. Providers must be trained to establish a respectful rapport with women and address their fears and concerns; only then will women get the information they need and feel comfortable returning for required follow-up visits.

Monitoring and Evaluation

Monitoring and evaluation of a prevention program's operations and impact help determine whether the program is meeting its objectives effectively and efficiently. Results of program monitoring and evaluation can be used to help ensure appropriate delivery of services, assess coverage, and correct problems in program operations. Positive evaluation results also can be used to mobilize continued financial and political support for the program.

Client records are key to effective program monitoring. Records should allow programs to follow individual women over time, and they should include the clients' screening results, diagnostic referrals, and treatment outcomes. For example, a basic health card system could include a woman's identifying information, date of each screening test, the results, and any diagnostic or treatment details. Ideally, information from client records should be linked to regional or national databases to allow aggregation of key health data.

Program and Policy Implications

The demand for programs to combat cervical cancer is strong. All over the developing world, women's health providers regularly see women with advanced, incurable cervical cancer. While many countries have expended their scarce resources on providing surgical and radiotherapy services to a very small proportion of these women, there is little they can do for most cancer patients but provide palliative care.

At a minimum, programs must plan to achieve the goals listed below to reduce cervical cancer incidence and mortality:

- increase awareness of cervical cancer and preventive health-seeking behavior among women in their thirties and forties;
- screen all women aged 35 to 50 at least once before expanding services to other age groups or decreasing the interval between screening;
- treat women with high-grade lesions, refer those with invasive disease where possible, and provide palliative care for women with advanced cancer;

- collect service delivery statistics that will facilitate ongoing monitoring and evaluation of program activities and outputs.

At the same time, of course, support for general STI control efforts will contribute to preventing a portion of cervical cancer cases in the long term.

Key activities for achieving these minimum program goals in many low-resource settings include:

- coordinating cervical cancer prevention services with health programs that offer related services and/or reach women in their thirties and forties;
- identifying and addressing bottlenecks to effective service delivery (for example, inadequate cytology services or inadequate information systems) before initiating a new program;
- removing regulatory barriers to broadening access to services, such as regulations that do not allow nurses, midwives, or other paramedical workers to provide screening services;
- ensuring that providers at all levels are trained in all aspects of cervical cancer prevention, including counseling skills;
- using innovative, culturally appropriate, field-tested strategies to reach underserved older women; and
- supporting targeted research on new screening and treatment approaches that may increase access to services and cut program costs.

Through creative service delivery strategies and well-trained, dedicated staff, cervical cancer prevention programs can address the challenges of providing appropriate screening and treatment and ultimately have a lasting effect on women's health.



In 1999, with support from the Bill and Melinda Gates Foundation, five international agencies launched a major new effort to prevent cervical cancer worldwide. This group of organizations, the Alliance for Cervical Cancer Prevention, is working to clarify, promote, and implement strategies for preventing cervical cancer in developing countries.

The Alliance consists of five partner organizations, brought together by their capabilities and experience in global cervical cancer prevention: AVSC International, the International Agency for Research on Cancer (IARC), the JHPIEGO Corporation, Pan American Health Organization (PAHO), and PATH (Program for Appropriate Technology in Health). For more information about the Alliance, visit their website at <http://www.alliance-cxca.org>, or contact PATH, the coordinating agency.

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Additional Cervical Cancer Resources

Alliance Small Grants Program. Provides grants of up to US\$20,000 to support projects by developing-country organizations working to prevent cervical cancer. For information, see the Alliance website at <http://www.alliance-cxca.org>, or write to the Alliance Small Grants Program care of PATH.

Cervical Cancer List. This electronic mail group allows subscribers to share information on cervical cancer prevention issues, with a primary focus on developing countries. For information see http://www.path.org/resources/cxca_listserv.htm, or write to the list moderator at accp@path.org.

Reproductive Health Outlook (RHO) Website. RHO's Cervical Cancer section (<http://www.rho.org/html/cxca.htm>) provides extensive information about cervical cancer prevention, screening, and treatment in low-resource settings.

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Jacqueline Sherris, Ph.D., Editor
 Michele Burns, M.A., Assistant Editor
 PATH
 4 Nickerson Street
 Seattle, Washington 98109-1699 U.S.A.
 Phone: 206-285-3500 Fax: 206-285-6619
 Email: outlook@path.org URL: www.path.org/outlook/

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