

A photograph of a woman with dark hair, wearing a patterned top, holding a baby. The image is overlaid with a blue gradient. The word "Background" is written in white text over the lower left portion of the image.

Background

Part One of this manual provides background information upon which cervical cancer prevention programs can be based.

Chapter 1 includes information on the magnitude of the problem, the natural history of the disease, screening and treatment methods, and the rationale for implementing a prevention program.

Chapter 2 offers an overview of policy issues that most directly affect service delivery and program management. Though all individuals responsible for planning and implementing a program may not be involved in making policy-level decisions, they must be aware of and understand the policies that will impact program effectiveness.

Rationale for Cervical Cancer Prevention

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Key Messages

- Cervical cancer screening and treatment are justified, based on the general principles of public health screening.
- Unlike many other cancers, cervical cancer is mostly preventable. Because of the slow progression of cervical precancer to cervical cancer, there is a window of up to ten years or more to detect and treat precancerous lesions and prevent their progression to invasive cancer.
- Various screening tests are available. All options for screening and for treatment of cervical precancer have strengths and limitations that need to be considered during policymaking, planning, and implementation phases of cervical cancer screening programs.
- Regardless of the screening test used, the focus should be to maximize coverage and link screening and treatment services. The feasibility of the different approaches for linking screening and treatment depends upon available resources in the given setting.
- Cryotherapy can be performed by physicians and non-physicians, at all levels of health care facilities. It has been shown to be safe and acceptable to women, their partners, and providers.

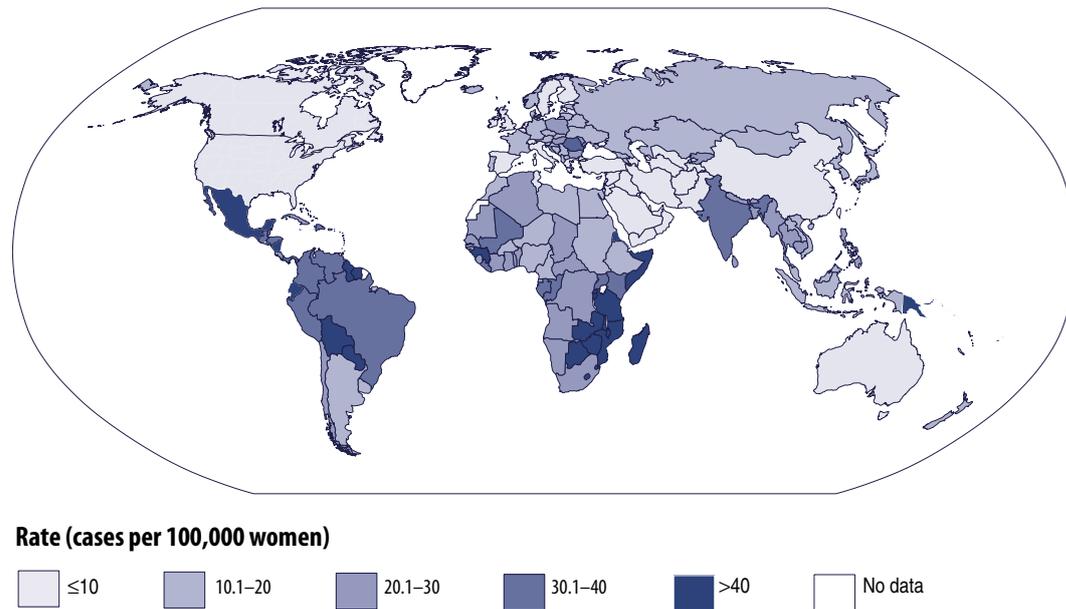
Introduction

To assist the management team in building support for prevention efforts, this chapter presents basic information about the burden of disease from cervical cancer and its natural history. It also discusses available methods for the prevention of cervical cancer—screening tests, outpatient methods for treatment of precancer, and management approaches for women with abnormal tests. It is beyond the scope of this document to provide detailed technical information on different screening tests and treatment options or to provide specific guidance on how to decide which would be best suited to any given setting. Additional information can be found in the Further Reading section of each chapter of this manual.

Burden of Disease

Cervical cancer is the most common cause of cancer deaths among women in developing countries (Ferlay et al. 2004), despite the fact that cervical cancer is preventable. The incidence of cervical cancer by country is shown in Figure 1.1. It should be noted that data on cervical cancer incidence and mortality are more accurate in countries that have cancer registries. Accurate data are not available from most developing countries, and underreporting is high.

FIGURE 1.1. Estimated age-standardized incidence of new cervical cancer cases per 100,000 women in 2002



Source: Adapted from Ferlay 2004.

In South Asia and Latin America the rate of cervical cancer has declined slightly over the last two decades or has remained stable, but incidence rates are increasing in sub-Saharan African countries such as Uganda, Mali, and Zimbabwe (Parkin et al. 2001, Parkin et al. 2002, Wabinga et al. 2000). As shown in Table 1.1, in some developing countries such as Argentina, Chile, China, Peru, South Africa, and Thailand, cervical cancer kills more women than maternal mortality (Parkin et al. 2002, WHO 2001a).

TABLE 1.1. A comparison of deaths from cervical cancer and maternal mortality in selected developing countries in 2000

Country	Cervical cancer deaths	Maternal deaths
Argentina	1,679	590
Brazil	8,286	8,700
Chile	931	90
Peru	2,663	2,500
South Africa	3,681	2,600
China	25,561	11,000
India	74,118	136,000
Thailand	2,620	520

Sources: Ferlay et al. 2004, AbouZahr and Wardlaw 2004.

Natural History of Cervical Cancer

Understanding how cervical cancer develops is essential to designing effective interventions to prevent deaths from this disease. More than 99% of cervical cancer cases and its precursors are related to infection with HPV, a sexually transmitted infection (STI) that is mostly asymptomatic (Walboomers et al. 1999). HPV is the most common STI worldwide, affecting an estimated 50 to 80% of sexually active women at least once in their lifetime (Koutsky 1997, Crum et al. 2003). Women are mostly infected with HPV in their teens, 20s, or early 30s. Cervical cancer is essentially a rare complication of a common STI.

Currently more than one hundred types of HPV have been identified, of which more than 30 types are known to cause genital infection. These are broadly classified as high-risk and low-risk for cervical cancer, with approximately a dozen types considered high-risk (some of the low-risk types are associated with genital warts). Infection of the cervix with high-risk types of HPV can lead to cervical abnormalities which, left untreated, progress to cervical cancer in some women (see Figure 1.2). Most HPV infections are transient, however, meaning that the body's defense mechanisms eradicate them, without posing any risk of progressing to cancer (Elfgren et al. 2000, Ho et al. 1998, Nobbenhuis et al. 1999).

For reasons that are not fully understood, approximately 5% to 10% of women infected with high-risk types of HPV develop persistent infections. Evidence shows that these women have an increased risk of developing high-grade precancerous lesions, and, if the lesions are not treated, cervical cancer (Bosch et al. 2002, Ho et al. 1998, Hopman et al. 2000, Muñoz and Bosch 1996, Nobbenhuis et al. 1999, Schiffman et al. 1993, Walboomers et al. 1999). It is not possible to predict in which women precursor lesions will progress to cancer, because the environmental and host immunological factors associated with progression to cancer are also not fully understood.

FIGURE 1.2. The natural history of cervical cancer

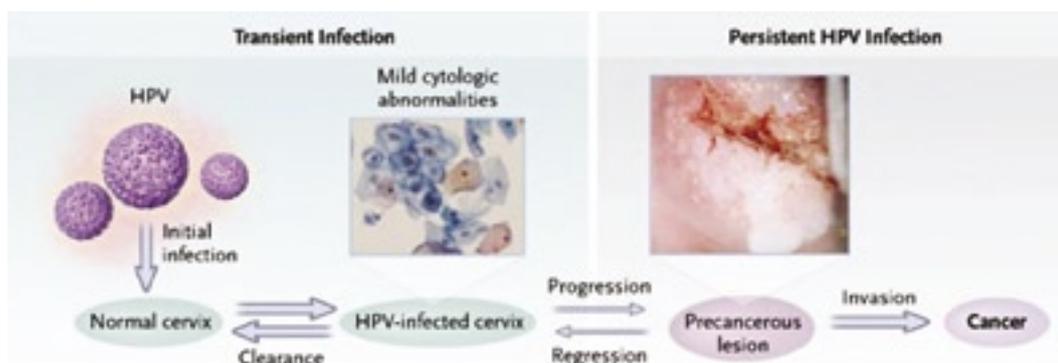


Photo source: Wright TC Jr, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. *New England Journal of Medicine*. 2003;348(6):489–490. ©2003 Massachusetts Medical Society. All rights reserved.

Table 1.2 summarizes information on HPV infection, cervical precancer, and invasive cancer. HPV infection can lead to low-grade lesions. Most of these lesions either regress on their own or do not progress to high-grade lesions or cancer (PATH 2000). High-grade lesions can develop directly from persistent HPV infection or from low-grade lesions (Cox 2001, PATH 2000). Some high-grade lesions will progress to invasive cancer over a period of up to ten years. Therefore, there is ample time to identify and treat infected women before cervical cancer develops (Miller 1992, Jenkins et al. 1996). Most low-grade lesions either regress on their own or do not progress to high-grade lesions or cancer (PATH 2000). Cervical cancer most often develops in women after age 40, and the incidence is highest among women in their 50s and 60s (Miller 1992, Parkin 1997).

TABLE 1.2. HPV infection, cervical precancer, and invasive cervical cancer

HPV infection	Low-grade lesions	High-grade lesions	Invasive cancer
HPV infection is extremely common among women of reproductive age. The infection can persist, lead to cervical abnormalities, or resolve on its own.	Low-grade lesions are usually temporary and disappear over time. Some cases, however, progress to high-grade lesions.	High-grade lesions, the precursor to cervical cancer, are significantly less common than low-grade lesions. High-grade lesions can develop from low-grade ones or directly from persistent HPV infection.	Invasive cancer develops over the course of several years and is most common among women in their 50s and 60s.

Source: Adapted from PATH 2000.

The understanding that HPV is the necessary but not solely sufficient precursor to cervical cancer has focused attention on the potential for primary prevention. Risk factors for HPV—such as early onset of sexual activity, multiple lifetime sexual partners (of a woman or her partners), and history of other STIs—generally reflect sexual activity. Therefore, primary prevention efforts have focused on reducing infection by reducing the number of sexual partners and encouraging the use of barrier contraceptives, especially condoms (Centers for Disease Control and Prevention 2004, Lytle et al. 1997, Weaver et al. forthcoming).

Limited data suggest, however, that these efforts would achieve only minimal effect; in particular, research has demonstrated a weak association between the use of barrier contraceptive methods and a decreased risk of HPV infection (Kjaer et al. 1997, Lytle et al. 1997, Lazcano-Ponce et al. 2001, Molano et al. 2002, Plummer and Franceschi 2002, Shepherd et al. 2000a,b). This is likely because men and women infected with HPV can harbor the virus both on the internal and external genitalia, including areas not protected by condoms. Further, individuals can harbor HPV infection for long durations without knowing they are infected; therefore, even mutually monogamous couples may transmit infections obtained in a previous relationship to a current partner.

The most promising approach to primary prevention of cervical cancer is through development and broad provision of effective HPV vaccines. It is expected that

prophylactic vaccines against HPV 16 and 18 (which account for about 70% of cervical cancer cases) are likely to become commercially marketed in some developing countries before 2010. Early data suggest that these vaccines are likely to be effective in preventing certain types of HPV infection and precancer (cervical intraepithelial neoplasia [CIN]); their long-term impact on cancer rates will not be known for many years after introduction (Koutsky et al. 2002). Even after these prophylactic vaccines become available, it will be important to continue screening and treatment programs for the many women already exposed to HPV as well as for women infected with carcinogenic HPV types other than HPV 16 or 18.

Methods of Cervical Cancer Prevention

Screening tests

Screening involves testing a target group (in this context, women) who are at risk for a given disease (in this context, cervical precancer). The aim of screening is to detect and treat those people identified as having early signs of the disease, usually by means of an inexpensive, accurate, and reliable test that can be applied widely. There are several cervical cancer screening tests in use or being studied around the world. Cervical cytology has been in use for the past 50 years. Newer screening tests are HPV DNA testing and visual screening tests. Each of these tests has potential advantages and disadvantages. The tests are briefly described below, with some additional technical information, plus strengths and limitations, presented in Appendix 1.1. No screening test is perfect, and the advantages and disadvantages need to be carefully weighed in any particular setting when deciding which test or tests to use.

Traditional screening methods

Cervical cytology Conventional cervical cytology—also referred to as the Papanicolaou test, Pap test, Pap smear, and cervical smear—detects abnormal cells in a sample taken from the cervix. It involves performing a speculum examination to expose the cervix and the os, and collecting cervical cells using a wooden or plastic spatula, broom, or brush. These cells are then smeared and fixed on a glass microscope slide. The slides are transported to a laboratory where they are usually processed manually. Each slide is then evaluated under the microscope by a trained cytology technician. This multistage process can take several weeks before the results are available to the client, although in well-organized programs results can be available sooner.

Liquid-based cytology (LBC) testing is a new technique that provides a uniform thin layer of cervical cells without debris. It is a more expensive test than conventional cytology and requires additional supplies and sophisticated equipment to process the smear. The impact of LBC on cancer incidence and mortality remains to be established, as does its cost-effectiveness. For further reading on cytology and cytology laboratory services, refer to WHO, *Cytological Screening in the Control of Cervical Cancer: Technical Guidelines* (1988), and to PAHO/WHO, *Pan American Cytology Network. An Operations Manual* (2001).

Existing cervical cancer prevention programs are nearly all cytology-based. Cervical cytology is the screening test that has been most widely used since the middle of

the twentieth century in developed countries and in those developing countries where screening is available. Well-organized and well-implemented cytology-based screening programs that screen women at regular intervals have been associated with measurable reductions in cervical cancer incidence and mortality when screening coverage and the treatment rate of women with abnormal findings are high. However, sensitivity and specificity of cytology have not been consistently high in a range of settings, especially in those with limited resources (see Appendix 1.1). Cytology-based programs can be implemented effectively only if infrastructure and laboratory quality assurance requirements are consistently met.

New screening methods

HPV DNA test The currently available test, Hybrid Capture 2, determines if one or more of the high-risk types of HPV virus (those associated with cervical cancer) are present in a cervical specimen. HPV DNA testing usually involves a speculum exam to obtain a sample of cervical cells using a brush or swab. The sample is transported to a laboratory for processing. Where such laboratory services have been established, an automated system can process 70 to 90 specimens at a time, requiring a total processing time of about seven hours. The results can potentially be returned to the service site in a day. Use of self-collected samples, where no speculum exam is needed, has been explored, and it has been shown that self-collected specimens have adequate sensitivity and are a culturally acceptable method in some settings (Wright et al. 2000, Dzuba et al. 2002).

Although the technical, cost, and infrastructure requirements can make the HPV DNA test difficult to implement, available data suggests that it performs better than cytology and visual tests in detecting precancerous lesions among women in their 30s and 40s (see Appendix 1.1 for general information on test performance). Efforts are ongoing to develop simple, inexpensive HPV DNA tests that can provide quicker results. By 2010, ACCP studies are expected to have evidence on long-term impact of HPV DNA testing on cervical cancer incidence rates.

Visual tests: VIA and VILI There are two kinds of visual tests to identify precancerous cervical lesions. In visual inspection with acetic acid (VIA), sometimes referred to as direct visual inspection (DVI), precancerous lesions temporarily appear white after staining with acetic acid (vinegar). Like cervical cytology and HPV DNA testing, VIA involves a speculum examination and exposing the cervix and the os. After swabbing the cervix with 3%–5% acetic acid using a cotton applicator, abnormal areas have a distinctive white appearance.

VIA can be implemented in a wide range of settings. No laboratory processing is required, the results are immediate, and treatment can be provided in the same visit. Due to the subjective nature of visual assessment, it is important to standardize definitions for positive and negative tests, and to give special attention to regular and consistent quality assurance (Denny et al. 2002). While in most studies to date the sensitivity of VIA has been equivalent to or better than cytology, its specificity has been lower (see Appendix 1.1). By 2010, ongoing ACCP studies will provide evidence of the impact of VIA on cancer incidence rates.

The second test is visual inspection with Lugol's iodine (VILI). Like VIA, VILI involves temporarily staining the cervix—this time with Lugol's iodine. Normal cells take up the iodine stain and appear a mahogany-brown color, whereas precancerous cervical lesions appear yellow. Like VIA, results for VILI are immediate, treatment can be provided in the same visit, and it may be implemented in a wide range of

settings. VILI may perform better than VIA, but further evaluation is needed to demonstrate the effectiveness of VILI in a variety of settings, as well as the impact of VILI as a screening test on the reduction of cervical cancer incidence.

Diagnosis and confirmation

Conventionally, cytology-based screening is linked to treatment through an intermediary diagnostic step using colposcopy, followed by confirmatory biopsy when indicated. Endocervical curettage (ECC) or an endocervical smear can be used to sample the endocervical canal. Laboratory assessment of the tissue samples obtained by biopsy (histology) confirms the presence or absence of CIN in precancer stages and cervical cancer itself.

Colposcopy involves high-powered illuminated magnification of the cervix using a colposcope—a binocular magnifying instrument (see *p. XX*). This enables providers to determine the extent of lesions and is useful in taking biopsies and in providing directed treatment with cryotherapy or loop electrosurgical excision procedure (LEEP). Colposcopy is noninvasive and performed as an outpatient procedure. It does not require anesthesia. Colposcopes are expensive—with cost ranging from US\$800 to \$13,000—and providers require specialized training and experience to use them proficiently. ACCP studies in India and Africa show that including colposcopy as an intermediary step reduces overtreatment; but colposcopy may not be practical in many low-resource settings due to the costs of equipment and training.

Treatment of precancerous lesions

The ability to offer women appropriate and effective treatment for precancerous lesions is a critical component of a successful cervical cancer prevention program. Safe and effective outpatient methods are preferred for management of precancerous lesions. In many limited-resource countries, however, clinicians lack training and experience and often the essential equipment and supplies required for simple outpatient treatment procedures. Hence they rely on more costly and complex inpatient methods such as cold-knife conization or hysterectomy performed under general or regional anesthesia by skilled specialists. Although these invasive procedures might be appropriate in special circumstances, they should be used judiciously since they can be associated with significant complications, including bleeding, pelvic infection, and injury to adjacent pelvic organs.

Cryotherapy and LEEP are two safe, effective, and relatively simple and inexpensive outpatient methods used for the treatment of precancer. The major practical difference between the two methods is that LEEP involves excision of the tissue and hence provides a tissue specimen that allows for histological verification of the diagnosis. On the other hand, cryotherapy is an ablative method that involves destroying the tissue and thereby leaves no sample for histology (see Table 1.3). Regardless of which outpatient method is used, health care providers should be aware of the implications of treating women living in areas where HIV prevalence rates are high (see box on next page). Use of less-invasive methods requires less infrastructural support, can minimize women's health risks, and decreases health care costs. Simpler methods often are more accessible to women because they can be offered at lower levels within the health care system.

HIV-Specific Treatment Issues

Precancerous cervical lesions tend to be more prevalent, persistent, and likely to recur in HIV-positive women (Ellerbrock et al. 2003, Tate and Anderson 2002). Therefore, these women should receive special counseling prior to treatment. Women should be advised that cryotherapy and LEEP are likely to be less effective in treating lesions in HIV-positive women and that they will need regular follow-up care. There is some evidence that HIV shedding increases substantially—but temporarily—from the treated area of the cervix following treatment (Wright et al. 2001). Currently there is no conclusive evidence linking HIV transmission with cryotherapy or LEEP; this needs further evaluation. For women requiring treatment, it is essential to counsel the client and her partner on the importance of abstaining from sexual intercourse during the healing period (or using a condom if abstinence is not possible) to protect the woman and her partner from possible increased risk of HIV infection.

Cryotherapy

Cryotherapy is a relatively simple procedure that destroys precancerous cells by freezing the cervix, using compressed carbon dioxide (CO₂) or nitrous oxide (N₂O) gas as the coolant. To freeze the lesion, the cryoprobe is placed on the cervix, ensuring that the probe covers the entire lesion. The aim of this procedure is to create an ice ball extending 4–5 mm beyond the lateral margin of the cryoprobe. Cryotherapy is performed using a single-freeze or double-freeze technique. Single freeze involves freezing for three minutes; double freeze involves freezing for three minutes followed by a thaw for five minutes, and then a second freeze for three minutes. The ACCP is conducting a randomized control study comparing single with double freeze to clarify the implications and potential advantages and disadvantages of each; results will be available in early 2005.

Cryotherapy is an outpatient procedure that can be performed easily and quickly (in 15 minutes or less) without anesthesia. It can be safely and effectively performed by general practitioners and non-physicians (Jacobs et al. forthcoming). ACCP studies show that cryotherapy is an acceptable treatment option for women, their partners, and providers (Royal Thai College of Obstetricians and Gynecologists [RTCOCG]/JHPIEGO 2003a).

Women undergoing cryotherapy need clear information and support to alleviate possible anxieties about side effects. Many women experience mild discomfort, such as pain or cramping during or within two to three days after the procedure. They may also experience dizziness, fainting, or flushing during or immediately after treatment. The most frequently experienced side effect of cryotherapy is a profuse, watery vaginal discharge for up to four weeks. Although inconvenient, women can effectively manage it by using a clean cloth or sanitary pads to protect clothing.

Complications associated with cryotherapy are minimal. Available data suggest that cryotherapy is safe, with very little risk of major complications (ACCP 2003a). Severe bleeding and pelvic inflammatory disease, two of the most serious

potential complications, are extremely rare in women treated with cryotherapy. There also is no evidence that cryotherapy is linked to cervical stenosis or has any long-term impact on women's fertility or pregnancy outcomes—important considerations when treating women of reproductive age (ACCP 2003a, RCOG/JHPIEGO 2003b).

Cryotherapy is the most practical treatment approach for most low-resource settings given its simplicity and low cost. In addition, it can be safely performed in primary care settings by non-physicians; so in settings where screening test results are immediately available, women can be treated during the same visit. Other advantages of cryotherapy are that the equipment required is relatively simple, the procedure is easily learned, and it does not require anesthesia or a power supply. One disadvantage of cryotherapy is that because it destroys the tissue, no tissue sample is available to confirm that the entire lesion has been removed. Furthermore, it is not possible to establish whether it is an early invasive lesion requiring further treatment. Cryotherapy is not appropriate for treating large lesions that cannot be covered by the probe or lesions located in the endocervical canal. Also, a regular supply of liquid coolant is necessary.

Loop electrosurgical excision procedure (LEEP)

Sometimes referred to as large-loop excision of the transformation zone (LLETZ), LEEP utilizes a thin electric wire in the form of a loop to remove the abnormal area of the cervix. The procedure is usually done using colposcopic guidance under local anesthesia in a secondary or tertiary care setting and requires local anesthesia, as well as a continuous power supply. Severe bleeding is a possible complication both during and after the procedure, occurring in 1% to 4% of patients (Mitchell 1998, Wright et al. 1992, Sellors and Sankaranarayanan 2002). More sophisticated equipment is required compared with cryotherapy. Table 1.3 compares cryotherapy and LEEP on key criteria.

Two advantages of LEEP are that it is a simple surgical procedure and that the excised tissue can be sent for histopathological confirmation, which allows the exact nature of the lesion to be determined and unsuspected microinvasions to be detected. However, many developing countries lack access to histology services.

TABLE 1.3. Comparison of cryotherapy and LEEP

Indicators	Cryotherapy	LEEP
Effectiveness	86–95%*	91–98%*
Potential side effects	Watery discharge	Bleeding
Anesthesia	None required	Local anesthesia necessary
Tissue sample for histopathology	No	Yes
Power required	No	Yes
Relative cost	Low	High
Level of provider	Physicians and non-physicians	Mostly by physicians

Source: Adapted from Bishop 1995.

*ACCP 2003a, Martin-Hirsch et al. 2004.

Linking screening and treatment

Regardless of the screening test used, screening must be linked to treatment to ensure program effectiveness. This can be done using the traditional approach (screen, diagnose, confirm, and treat), intermediate approach (screen, diagnose, and treat with post-treatment biopsy confirmation), or the screen-and-treat approach (treatment is based on the results of screening test alone). These approaches are described in detail in Chapter 6.

Justification for Cervical Cancer Screening

The purpose of any type of public health screening is to offer a low-cost, accessible means for determining who in a population is likely to have or develop a certain disease, and to then provide diagnostic testing, appropriate treatment, or both. The general principles of public health screening are described in the box opposite.

General Principles of Screening

Criteria for deciding whether or not screening is appropriate include:

- Is the disease a public health problem?
- Is the natural history of the disease understood?
- Is there a recognizable latent or early symptomatic stage?
- Is there an acceptable treatment for the disease?
- Is there consensus on whom to treat?
- Are facilities for screening and treatment available and accessible?
- Is there an economic balance between case finding and subsequent medical care?
- Is the program sustainable?

Source: Adapted from PATH 2000.

Cervical cancer screening is justified according to the listed criteria because:

- Cervical cancer is an important public health problem in many resource-poor settings.
- There is a recognized precursor stage (i.e., precancerous lesions) that can be treated in a safe, effective, and acceptable way.
- The time between the appearance of precancerous lesions and the occurrence of cancer is long (about ten years), leaving ample time for detection and treatment.
- Treatment of early lesions is very inexpensive compared to the management of invasive cancer.

Women who have access to effective prevention programs are less likely to develop cervical cancer than women who do not. It is not surprising then that the incidence of cervical cancer varies dramatically between regions of the world, as well as between different socio-demographic groups within a given region. In the mid-1980s, approximately 40% to 50% of women in developed countries had been screened in the preceding five years, compared to only 5% of women in developing countries (WHO 1986). Although these data are old, there are few indications that the situation has changed significantly since then in most developing countries. For example, more recently, only 8% of more than 20,000 South African women 20 years of age and older reported having had a Pap smear in the preceding five years (Fonn et al. 2002). Likewise, in a rural district in India, where more than 120,000 women were interviewed, less than 1% reported having ever been screened. In developed countries where women regularly receive cytologic screening, programs have led to decreased cervical cancer-related mortality (Mitchell et al. 1996, Eddy 1990, IARC 1986a,b). In most developing regions, however, cervical cancer mortality rates have not declined substantially despite attempts to establish screening programs (Beral et al. 1994).

Conclusion

Cervical cancer is preventable through screening to detect precancerous lesions and appropriate treatment before the lesions develop into cancer. The nature of the disease and the treatment options available justify cervical cancer screening programs, according to general principles of public health screening. Various cervical cancer screening, diagnostic, and treatment methods are currently being used in developed and developing countries. Each method has strengths and limitations that need to be considered in the policy-level decisions about which methods to use. It is important to remember that regardless of the screening and treatment methods chosen, the two must be strongly linked so that women who are identified as having precancerous lesions are able to get the treatment they need to prevent the development of cancer.

Further Reading

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Appendix 1.1. Characteristics of Screening Tests

Characteristics	Cervical cytology	Newer screening tests		
		HPV DNA test	Visual inspection tests	
			Visual inspection with acetic acid (VIA)*	Visual inspection with Lugol's iodine (VILI)
Sensitivity and specificity for high-grade lesions and invasive cancers	Sensitivity = 47–62%** Specificity = 60–95%** Cytology has been assessed over the last 50 years in a wide range of settings in both developed and developing countries.	Sensitivity = 66–100%** Specificity = 62–96%** HPV DNA testing has been assessed over the last decade in many settings in developed countries and relatively few settings in developing countries.	Sensitivity = 67–79%** Specificity = 49–86%** VIA testing has been assessed over the last decade in many settings in developing countries.	Sensitivity = 78–98%** Specificity = 73–91%** VILI testing has been assessed by IARC over the past 3 years in India and 3 countries in Africa. It needs to be evaluated by others in additional settings to confirm the reproducibility of the above results.
Number of visits required for screening and treatment	Requires 2 or more visits.	Requires 2 or more visits.	Can be used in a single-visit approach in setting where outpatient treatment is available.	Can be used in a single-visit approach in setting where outpatient treatment is available.

*VIA is also referred to as direct visual inspection (DVI).

** Source: Sankaranarayanan et al. forthcoming. *Sensitivity* is the proportion of individuals correctly identified by the test as having disease. Higher sensitivity means that fewer lesions will be missed (i.e., there will be fewer false negatives). *Specificity* is the proportion of individuals correctly identified by the test as NOT having disease. Higher specificity means that there will be fewer false positives.

		Newer screening tests	
Characteristics	Cervical cytology	HPV DNA test	Visual inspection tests
			Visual inspection with acetic acid (VIA)* Visual inspection with Lugol's iodine (VILI)
Type of provider	Competently trained nurse, nurse midwife, clinical assistant, physician's assistant, general physician, or gynecologist to obtain and fix the specimen. Competently trained lab technician to process and evaluate the specimen.	Competently trained nurse, nurse midwife, clinical assistant, physician's assistant, general physician, or gynecologist to collect the sample. Competently trained lab technician to process the specimen.	Competently trained nurse, nurse midwife, clinical assistant, physician's assistant, general physician, or gynecologist to perform and interpret the test. Competently trained nurse, nurse midwife, clinical assistant, physician's assistant, general physician, or gynecologist to perform and interpret the test.
Strengths	Widely accepted and used for over 50 years, with evidence that reduction in cervical cancer incidence and mortality can be achieved in high-quality programs. In settings with adequate resources, meets most of the criteria for a good screening test. Permanent record of the test in the form of a slide. High specificity.	Test detects 13 oncogenic HPV types (without distinguishing which type[s] are present). Objective test. Identifies both women with precursor lesions and women who are at a greater risk for developing cervical disease in the future. A negative test result virtually guarantees that there is no HPV infection or related lesions. Not affected by presence of cervical or vaginal infections. High specificity in women over age 35.	Simple procedure needing minimal resources. Immediate results, so immediate treatment is possible. Simple equipment and supplies needed. Easier to detect color changes produced by iodine staining than by acetic acid.

*VIA is also referred to as direct visual inspection (DVI).

Characteristics	Cervical cytology	Newer screening tests	
		HPV DNA test	Visual inspection tests
			Visual inspection with acetic acid (VIA)*
<p>Limitations</p> <p>Subjective test because outcome depends on the technician's interpretation of the results.</p> <p>Systems are needed to ensure that lab results are returned to the clinic and that women with abnormal findings receive appropriate treatment.</p> <p>Significant infrastructure requirements and costs, including trained lab technicians.</p> <p>Potential for mislabeling of samples and damage or loss during transport.</p> <p>Sampling and lab errors can occur.</p> <p>Requires a lab quality assurance system.</p>	<p>Systems are needed to ensure that lab results are returned to the clinic and that women with positive test results receive appropriate treatment.</p> <p>Significant infrastructure requirements and costs, including trained lab technicians.</p> <p>Potential for mislabeling of samples, lab errors, damage or loss during transport, and breakdown of processing equipment.</p> <p>Only moderately specific in women younger than age 35.</p> <p>If treatment is provided based on test results alone, many women are treated unnecessarily because they test positive but do not actually have precancer. This can overload the service site where treatment is being offered.</p>	<p>Subjective test because the outcome depends on the clinician's interpretation of what is seen on the cervix.</p> <p>Limited data on validity of VILI as a primary screening test. Needs further evaluation.</p> <p>Staining can persist for 30 to 45 minutes. Therefore, further clinical evaluation, if needed, is delayed.</p> <p>VILI-positive lesions are not unique to precancer.</p> <p>Not appropriate for screening post-menopausal women.</p> <p>If treatment is provided based on test results alone, many women are treated unnecessarily because they test positive but do not actually have precancer. This can overload the service site where treatment is being offered.</p>	<p>Subjective test because the outcome depends on the clinician's interpretation of what is seen on the cervix.</p> <p>Not appropriate for screening post-menopausal women.</p> <p>VIA-positive lesions are not unique to precancer.</p> <p>If treatment is provided based on test results alone, many women are treated unnecessarily because they test positive but do not actually have precancer. This can overload the service site where treatment is being offered.</p>

*VIA is also referred to as direct visual inspection (DVI).

Overview of Policy Considerations

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Key Messages

- Effective cervical cancer prevention programs can be implemented in both developed and developing countries.
- Policymakers must be committed to invest in and devote the necessary resources and dedicated staff to program planning, implementation, and monitoring.
- The policy phase should be as participatory as possible, involving key stakeholders and clearly basing policy decisions on the needs and health priorities of the population.
- Cervical cancer screening policies in limited-resource settings should focus on initially screening a high proportion of women in their 30s and 40s at least once using a screening and treatment approach that involves a minimal number of visits.

Introduction

According to the WHO managerial guidelines for National Cancer Control Programmes, the key phases in developing a cervical cancer prevention program are policymaking, program planning, and implementation. This manual focuses on the program planning and implementation phase at the subnational level (regional/district/state/provincial) and assumes that policy-level decisions are largely determined before the management team is asked to plan and implement services. Although the management team may not be involved in national-level policy decisions, they must be aware of and understand the policies about the screening and treatment methods to be used; target age group, frequency of screening, and desired population coverage level; maximizing access to health care providers; and vertical or integrated services.

The Decision to Develop a Cervical Cancer Prevention Program

The natural history of cervical cancer and the availability of effective screening and treatment methods justify, in principle, investment in cervical cancer prevention programs. ACCP research findings suggest that it is possible in developing countries to implement organized cervical cancer prevention programs that will reduce the burden of disease. However, it is not recommended that screening programs be put into place in any setting unless two conditions are met. First, the incidence of cervical cancer must justify it. Second, the necessary resources must be available and committed for attaining wide screening coverage and ensuring that adequate systems are in place to appropriately manage screen-positive women, in order to achieve program success (WHO 2002a). Therefore, primary policy decisions are whether a cervical cancer prevention program is justified in the given setting and if there is political commitment to dedicate the necessary resources to effectively plan, implement, and monitor such a program.

Selecting appropriate technologies for screening and treating precancer are just the start of a successful program. The resources and requirements for making screening and treatment available and accessible, as well as the willingness and ability of women to use the services, play equally important roles. Implementing an *organized* screening program that addresses these issues is the best way to ensure success. Ideally, an organized screening program should have a population-based cancer registry and a computerized call and recall system, both of which may not be feasible in limited-resource settings. However, a well-managed screening program with coordinated services based on the key characteristics listed in the box below is feasible even in limited-resource settings.

Characteristics of Organized Screening Programs

An organized cervical cancer screening program has:

- A defined target population.
- Effective recruitment strategies to achieve high coverage.
- A health care system with capacity to screen, follow-up on those screened positive, and provide treatment as indicated.
- A quality assurance system.
- A health information system.
- A management team responsible for planning and implementation.

Source: Quality Management Working Group, Cervical Cancer Prevention Network 1998.

Opportunistic, or spontaneous, screening refers to services provided to women who request it or who are already in a health facility for other services, without any effort to reach a particular population. This has less impact on cervical cancer incidence and mortality and reduces cost-effectiveness (Hakama 1997). A major problem with opportunistic screening is that many of the women who are screened are not in the appropriate age group, since most of the screening is limited to women attending primary health care, antenatal, and family planning clinics. Often in these settings many of the women are less than 30 years old and are not likely to show signs of precancer or have low-grade disease which will regress spontaneously. There are few organized efforts in low-resource settings to ensure that women over the age of 30 are screened (Chirenje et al. 2001, Miller 1992). Consequently, women are not identified until they are at an advanced stage of disease, resulting in high morbidity and mortality (Parkin et al. 1993).

Strategic Approach Framework

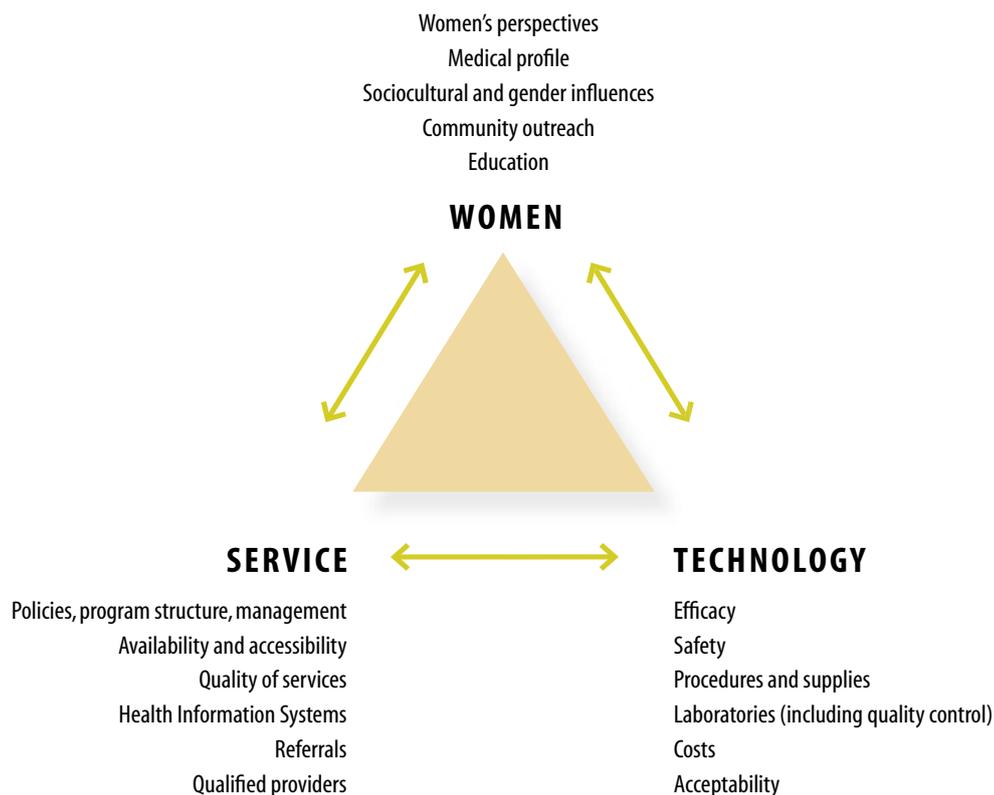
WHO's strategic approach to the introduction of contraceptive technologies (Simmons et al. 1997) can be adapted to the introduction or strengthening of cervical cancer prevention programs. This approach promotes the concept that appropriate decisions concerning policy and program development should be

based on an understanding of the relationships between the at-risk population, the service delivery system, and the mix of services and interventions being provided. The process also takes into account how these interactions are influenced by the broader sociocultural and political context. This locally led process of program design encourages collaboration and partnership among a broad range of stakeholders concerned about improving the quality of current services or introducing new technologies.

In adapting this strategic approach to the introduction of cervical cancer prevention services, it is recommended that policy-level decisions and planning should address a series of interactions between:

- Women (clients) and the services that are available and accessible to them.
- Women and the screening and treatment technologies, including how acceptable women find the available options.
- Service delivery systems and the screening and treatment technologies, including the ability to successfully introduce new technologies and sustain the services. (See Figure 2.1 below and box on page 22.)

FIGURE 2.1. A strategic approach to cervical cancer prevention



Source: Adapted from Simmons et al. 1997.

Strategic Approach to Assessing Cervical Cancer Prevention Programs in Bolivia

The WHO's three-stage *Strategic Approach for the Introduction of Contraceptive Technology* (Simmons et al. 1997) fosters the participation of local decision-makers, communities, and stakeholders in developing and implementing a strategy for providing and utilizing services. From 2001 to 2002, in an effort to assess the existing cervical cancer prevention and treatment services in Bolivia and to identify appropriate intervention strategies, the Component for the Detection and Control of Women's Cancer of the Bolivian Ministry of Health adapted and initiated the WHO strategic approach. In collaboration with EngenderHealth and PAHO, the ministry instituted the first of the three stages by conducting a situation analysis in four regions of Bolivia. A multidisciplinary team, conducted the situation analysis using semi-structured interviews and observations. A technical workshop was then organized with key stakeholders and together the group developed evidence-based priorities and recommendations to improve services, including future research opportunities, policies, and programmatic interventions. Multidisciplinary involvement enabled the incorporation of many perspectives and encouraged in-country alliances to reinforce and expand ideas for program planning and policy development. This participatory process led to stakeholder ownership of the assessment findings and recommendations in Bolivia.

Source: Bolivia Ministry of Health et al. 2003.



Policy Decisions Concerning Services

As described in the box that starts below, the policy phase of program development consists of the following steps: confirm political commitment, engage high-level stakeholders, conduct a large-scale situation analysis, develop policies based on the assessed situation, and obtain support for the new policies and resources for programming. While the entire management team is not usually involved in the policy development, it is helpful for the team to understand some of the factors that are considered in policymaking, particularly those decisions that most directly affect service delivery and program management.

Steps in the Policy Phase of Program Development

Confirm political commitment

High-level decision-makers must be committed to developing or strengthening a cervical cancer program. This commitment must be reflected in the investment of the necessary resources and designation of a coordinator for cervical cancer prevention with appropriate mandate, authority, and resources to direct the program.

Engage high-level stakeholders

Policymakers need to identify senior individuals representing the key groups that will be involved in or affected by a cervical cancer prevention program to provide guidance and support for program development. Such individuals should be decision-makers within their own organizations, and should include senior Ministry of Health officials, heads of medical organizations, university professors, heads of nongovernmental organizations (NGOs), and high profile community leaders, particularly representing women's groups.

Conduct situation analysis

To make decisions about the feasibility and scope of the program, the burden of disease in the population must be determined and the relative importance of cervical cancer compared to other health priorities must be assessed. Existing services that could be utilized for a screening program must be surveyed, and technical resources that are currently available (or can realistically be developed) need to be identified.

Develop policy

The policies that will govern the services must be determined. These policies should establish the screening and treatment methods to be used, the target age group for screening, the desired population coverage, screening frequency, appropriate provider licensing (e.g., permitting mid-level health providers to perform clinical procedures), and whether the program will be vertical or integrated into other health services. These decisions are made at the national policy level because they require large-scale commitment, support, and allocation of resources. National guidelines and norms should be developed based on these policies.



Obtain support for new policy and solicit resources for the program

Resources must be allocated to ensure the program can be adequately implemented. Support from managerial and medical bodies also must be obtained so that they advocate for the new policies and programming within their own spheres of influence.

Source: Adapted from WHO 2002a.

Screening and treatment methods

Those responsible for making decisions about what screening and treatment options will be implemented in any country, program, or organization should consider the following when deciding which are most suitable:

- Performance of the screening tests.
- Processing requirements of the tests.
- Safety and effectiveness of the treatment.
- Equipment and supplies required.
- Feasibility of using the screening and treatment options in proposed locations.
- Acceptability of screening and treatment options to women, their partners, and providers.
- Likely impact of the screening and treatment options on the burden of disease.
- Costs involved.

Target age group, frequency of screening, and coverage**Target age group**

When determining the target age group for screening—the most appropriate ages to initiate and to stop screening—the following should be taken into consideration:

- The risk of the disease in various age groups.
- The performance characteristics of the screening tests to be used with respect to various age ranges.
- The availability of resources needed to provide screening and treatment.

According to IARC (*IARC Handbooks of Cancer Prevention*, Volume 10, forthcoming) screening should initially focus on women in their 30s and 40s—the ages where women are at the highest risk of precancerous lesions but before the incidence of invasive cancer begins to peak. In most countries, the incidence of invasive cervical cancer is very low among women under age 25. Generally, incidence increases thereafter and reaches a maximum in women in their 50s and 60s. Data from cancer registries in developing countries indicate that approximately 70% of confirmed cases occur among women aged 45 or older. Precancerous lesions, however, are generally detectable for ten years or more before cancer develops, with a peak at about age 35. Women over 50 who have never been screened are at relatively high risk of cervical cancer, though women in this age group who have had one or more negative screens in the last ten years are at low risk.

The specific characteristics of different screening tests can help determine the target age group. For example, visual screening methods are most suitable for women under the age of 50, because in older women the squamocolumnar junction recedes into the cervical canal and is difficult to see. HPV DNA testing should be restricted to women over 35 years. In younger women HPV DNA testing has low specificity and therefore produces a high rate of false positive test results (Wright and Schiffman 2003). Cytology is appropriate for all ages, although for older women, instruments that allow sampling of endocervical cells are recommended.

Screening frequency

As noted, cervical cancer generally develops slowly from precursor lesions. Therefore, screening can take place relatively infrequently and still have a significant impact on reducing cervical cancer morbidity and mortality. Based on the ACCP's mathematical modeling studies using observed data (prospective cohort studies, databases, and published literature), if resources permit only once-per-lifetime screening, then the focus should be to screen women in the 30s and 40s, especially women between 35 and 40 years. If resources allow screening two or three times per lifetime (rescreening), the optimal interval should be every five years (not every ten years); for example, screening at ages 35, 40, and 45 is better than screening at ages 30, 40, and 50 (Goldhaber-Fiebert et al. 2003, Goldie and ACCP 2004, personal communication with S. Goldie, May 2004). If resources permit more frequent screening, however, then screening can be once every three years from age 25 to 49 and then every five years to the age of 64 (IARC forthcoming).

Screening coverage

Coverage refers to the extent of participation of eligible (i.e., target age) women in the screening program in a given time period and is calculated by dividing the number of eligible women screened during a given time by the total number of eligible women. High coverage of the target population is one of the most important components of a successful cervical cancer prevention program (Pretorius et al. 1991, Sasieni 1991, WHO 1992).

Evidence from some countries where screening programs are in place shows that more than 50% of women diagnosed with cervical cancer have never been screened (Sung et al. 2000). Since most cervical cancer occurs in unscreened women, reaching them with prevention services will have the greatest impact in reducing the incidence of and mortality from cervical cancer. Unnecessarily rescreening women and routinely screening those outside the target age group (e.g., 20-year-old

women attending clinics for prenatal care) can result in substantially higher costs with minimal population benefits. Increasing coverage is generally more important than marginal increases in the frequency of screening (Miller 1992, Sasieni 1991)—or even small increases in the sensitivity of the screening test (Kim et al. 2002a, Kim et al. 2002b)—particularly for countries with low screening coverage (e.g., below 25%). Based on this evidence, the program's coverage objectives should be to focus on screening women in the target age group and to avoid repeatedly screening women who have already been screened in the recent time period.

Once coverage goals are set, the management team must apply them to the population in their own catchment area. This is addressed in Chapter 5. If national coverage goals have not been set, a key step in program planning would be to set such goals for the local area.

Maximizing access to health care providers

The ACCP has found that a wide range of competently trained medical personnel, both physicians and non-physicians, can provide cervical cancer screening and treatment. The decision regarding who can perform specific procedures should be based on national norms and regulations. If norms and guidelines are unnecessarily restrictive, decisions should be made jointly with the relevant in-country professional organizations or licensing bodies to revise the norms and guidelines.

Vertical versus integrated programs

In vertical programs, health care providers and facilities are devoted to only one health care service. A fully integrated program involves integration of all aspects of programming: planning and budgeting, organizational structure, staff roles and responsibilities, training, supervision, logistics, information systems, monitoring, and clients' access to services (Management Sciences for Health 1994). In integrated programs, clients can access more than one health service at the same facility, on the same day, and (sometimes) from the same health care provider. Many factors influence the decision on whether to integrate cervical cancer prevention programs with other health programs. They include political commitment to integration in the existing health structure, competing health priorities, existing national policy on cervical cancer prevention, availability of personnel and material resources, requirements for a shift in resources, and donor preferences and commitment of resources.

Management teams need to consider the strengths and limitations of integrated and vertical programs (see Table 2.1). Ideally, to maximize client access, programs should work toward providing integrated services to the degree that the resources and capacity allow. It is important, however, to ensure that integrated services do not result in an excessive workload for providers, which can adversely affect service delivery and the program's effectiveness. Integrating cervical screening services will work only when services are able to reach a large group of women aged 30 and older. For example, integrating cervical cancer prevention with family planning services makes cervical cancer prevention services less likely to reach older women, because 50% to 60% of women attending family planning clinics are younger than 30 years old (Claeys et al. 2003). Regardless of whether the program is vertical or

integrated, it is important to have a holistic approach to a client's needs and to ensure she receives or is referred for all the services she needs to ensure her good health. Further discussion of vertical and integrated services is found in Chapter 6.

TABLE 2.1. Strengths and limitations of vertical and integrated programs

	Vertical Program	Integrated Program
Strengths	<ul style="list-style-type: none"> • Higher commitment to and focus on the cervical cancer prevention objectives. • Staff roles and responsibilities are clearly defined. 	<ul style="list-style-type: none"> • Health benefits from the opportunity to deal with several health problems during the one visit. • Avoids stigma that a “cervical cancer service” might generate. • Can use an existing referral network, plus benefit from on-site referrals. • Wider range of staff available.
Limitations	<ul style="list-style-type: none"> • Higher cost for the health system (since facilities and equipment are not shared). • Logistical and cost burden to the client (cost of transport, work, and family responsibilities) for referrals or if she needs other health services. 	<ul style="list-style-type: none"> • Competing priorities (prevention seen as less urgent than treatment). • Higher level of planning and organization required. • Has the potential to excessively increase the providers' workload. • Providers' and supervisors' roles and responsibilities are less well defined.

Conclusion

The policy phase of program development is critical because it assesses needs at a population or country level, determines policies that will guide service delivery, and develops political and financial support for programming. The policy phase should be as participatory as possible, involving key national stakeholders and clearly basing policy decisions on the needs and health priorities of the population. Understanding the factors involved in policymaking will help the management team to explain the rationale for program policies and build support at the local level for program planning and implementation.

Given the necessity to commit resources for whatever strategy is chosen, cost-effectiveness becomes a critical consideration for policymaking. Based on the available evidence from cost-effectiveness analysis (Goldie et al. 2001, Mandelblatt et al. 2002), it is recommended that cervical cancer screening policy in limited-resource settings should:

- Focus initially on screening women who are in their 30s and 40s.
- Focus on a screening and treatment approach that involves a reduced number of visits (to minimize the loss to follow-up that occurs with each additional visit).
- Focus on high coverage over increasing screening frequency.

Further Reading

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