

Cervical Cancer Prevention Issues in Depth 3

The Case for **Investing in Cervical Cancer Prevention**

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Cervical Cancer Prevention Issues in Depth #3

Alliance for Cervical Cancer Prevention (ACCP)

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About the Alliance for Cervical Cancer Prevention

The Alliance for Cervical Cancer Prevention (ACCP) consists of five international health organizations—EngenderHealth, the International Agency for Research on Cancer (IARC), JHPIEGO, the Pan American Health Organization (PAHO), and PATH—with the shared goal of preventing cervical cancer in developing countries. Alliance partners work to identify, promote, and implement cervical cancer prevention strategies in low-resource settings, where cervical cancer prevalence and mortality are highest. For more information on ACCP's work and publications, please visit www.alliance-cxca.org.

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The Case for Investing in Cervical Cancer Prevention

Introduction

Data from around the world clearly demonstrate that cervical cancer has a disproportionate impact on the health of women in developing countries. According to the most recent information, women in developing countries account for about 85 percent of both the yearly cases of cervical cancer (estimated at 493,000 cases worldwide) and the yearly deaths from cervical cancer (estimated at 273,500 deaths worldwide).¹ Cervical cancer also disproportionately affects the lowest-income women within most developing countries. In the majority of developing countries, cervical cancer remains the number-one cause of cancer-related deaths among women.¹

Cervical cancer represents a unique public health opportunity. Unlike most other cancers, cervical cancer is preventable when precursor lesions are detected and treated before they develop into cancer. The highest-risk lesions—high-grade squamous intraepithelial lesions (HSIL)—are most common among women in their thirties and forties. The cancer that develops when lesions are left untreated is most common among women in their forties and fifties. This distribution reflects the time it takes for HSIL to progress to cancer.² If cervical cancer itself is diagnosed in an early stage, it can be cured with the appropriate resources (surgical and radiotherapy services). In many developed countries, the introduction of cytologic screening for early detection of precancerous lesions into stable public health infrastructures and the frequent screening of sexually active women has led to a remarkable reduction in cervical cancer incidence and mortality. Yet, in most developing countries, cervical cancer continues to cause high rates of morbidity and mortality.

This inequity between developed and developing countries has three primary sources:

1. The burden of disease from cervical cancer in many developing countries is misunderstood and is often overshadowed by other health priorities, such as AIDS, tuberculosis, and malaria. As a result, health policies to implement effective prevention programs are not in place.
2. Women's health and the important role developing-country women play in many sectors are often undervalued.
3. Effective new technologies and approaches for screening and treating precancerous lesions in low-resource settings are not well understood, and the costs of launching an effective cervical cancer prevention program are assumed to be out of reach.

This document provides evidence on the burden of disease and the importance of women's roles in family and community life to refute the assumptions that underlie the lack of access to cervical cancer prevention services in many developing countries. It also reviews new approaches to cervical cancer prevention in low-resource settings, provides data on cost-effectiveness, and makes the case that, regardless of where they live, women should have access to effective public health programs, which can prevent a significant proportion of cervical cancer deaths.

Many of the data on new approaches to cervical cancer prevention in this paper draw on the work of the Alliance for Cervical Cancer Prevention (ACCP). The ACCP has worked to assess innovative approaches to screening and treatment of precancerous lesions in regions where the incidence and mortality are highest.

Disease and program patterns in developed and developing countries

Disease burden

Cervical cancer disproportionately affects women in developing countries. The hardest-hit regions include Central and South America, the Caribbean, sub-Saharan Africa, Melanesia, India, and other parts of Asia, where age-standardized incidence rates (ASRs) range between about 25 and 43 cases per 100,000 women.¹ Rates in Central and Eastern Europe and the Newly Independent States are also high in comparison to rates in other European countries and the United States. India, with an ASR of 30.7 cases per 100,000 women, accounts for over one-quarter of the yearly cases and deaths from cervical cancer worldwide. In some countries, the incidence rates for cervical cancer are significantly higher; in Tanzania, for example, the ASR for cervical cancer incidence is 68.6 cases per 100,000 women. In Haiti, the ASR is 87.3 per 100,000 women.¹ In contrast, the cervical cancer ASR for North America is 7.7 cases per 100,000 women (see Figure 1).

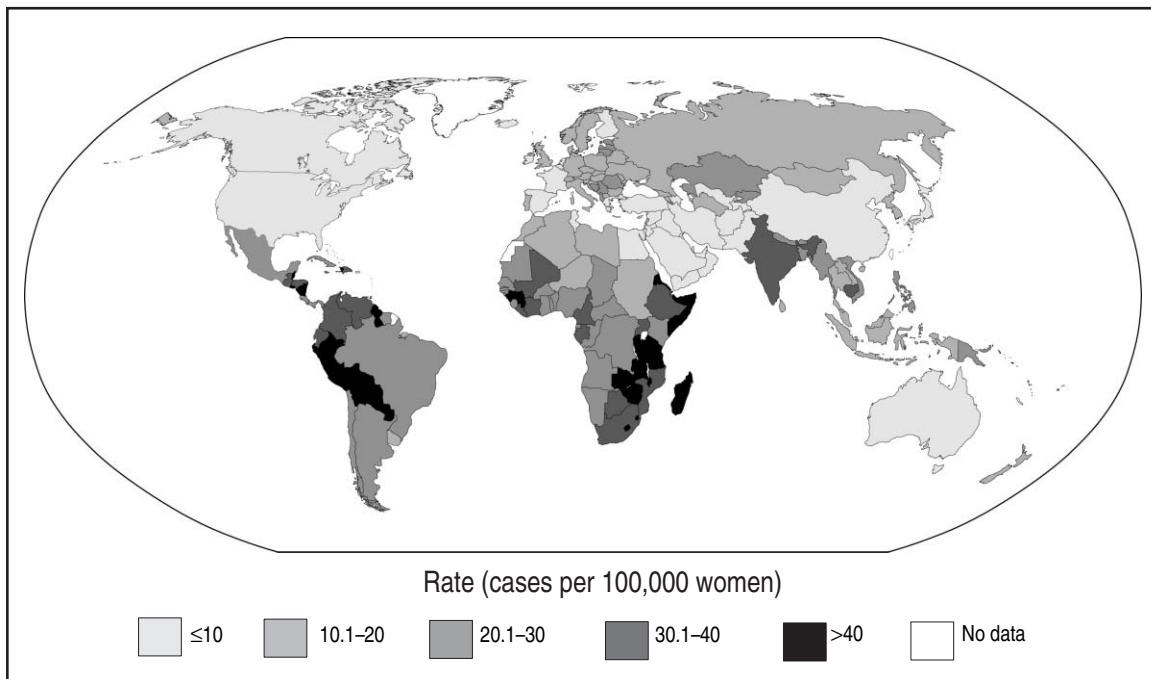


Figure 1. Estimated age-standardized incidence rates of new cases of cervical cancer, 2000.¹

Estimating the burden of cervical cancer

Accurately estimating the burden of disease from cervical cancer in developing countries can be challenging. The majority of available women's health data focuses on maternal health indicators.³ Other quantitative health data often are not disaggregated by sex and age, and deaths from cervical cancer may be misclassified or generically reported as "cancer" or "uterine cancer."⁴ Data collection challenges such as these likely lead to a gross underestimation of the burden of cervical cancer in many settings.

Measures such as years of life lost (YLL) provide an alternate indicator of disease burden and an additional perspective on the impact of cervical cancer in developing countries. According to a recent analysis, cervical cancer caused a loss of 2.4 million weighted YLL* among women aged 25 to 65 years in developing countries, compared with 0.3 million YLL in the developed world.⁵ Although the number of YLL as a result of AIDS and tuberculosis in developing regions is even greater, cervical cancer is the leading cancer-related cause of YLL in South-Central Asia, Latin America and the Caribbean, and sub-Saharan Africa.⁵

Comparing mortality from cervical cancer with maternal mortality—another health concern in the developing world that only occurs among women (see Table 1)—highlights the discrepancy between the impact of cervical cancer and the resources dedicated to its prevention and treatment. Some 9.4 million YLL are attributable to maternal mortality in the developing world (approximately 529,000 deaths yearly), and the highest maternal mortality rates are in Africa and South Asia.⁶ Significant resources and attention are rightly focused on reducing maternal mortality in these regions—and yet cervical cancer kills more women in several parts of the world than maternal causes. For example, more than 32,000 women died from cervical cancer in Latin American and the Caribbean in 2002, compared with 22,000 deaths from pregnancy- and childbirth-related causes in 2000 (see Table 1).

Changes in disease burden with aging population

Although the risk of precursor lesions is highest among women in their thirties and forties, cervical cancer itself occurs most commonly among women in their forties and fifties. The population of older women—women at greatest risk for cervical cancer in the absence of effective screening—is growing rapidly in developing countries (see Figure 2). By the year 2020, three of four women older than 50 years will live in developing countries.³ Latin America will experience the fastest increase in the older population: the population of people older than 60 years is expected to quadruple to 181 million in this region by 2050. In Asia, there currently are approximately 300 million people older than 60; in 2050, there will be 1.2 billion—and approximately 700 million of them will be women.⁷

*Yang and colleagues (2004) calculated weighted YLL for comparability between countries (or regions) or diseases. YLL were weighted on the basis of the age-weights developed by Murray and colleagues (1996).

Table 1. Data on estimated number of deaths due to cervical cancer (2002) and to causes related to pregnancy and childbirth (2000), by geographic area.

Geographic area	No. of deaths	
	Due to cervical cancer ^a	Due to maternal mortality ^b
Africa	61,670	251,000
Asia	142,734	253,000
Europe	29,814 ^c	1,900
Latin American/Caribbean	32,639	22,000
North America	5,796	680
Oceania	844	550
Total	273,505	529,000

^a Data from Ferlay et al.¹

^b Data from WHO.⁶

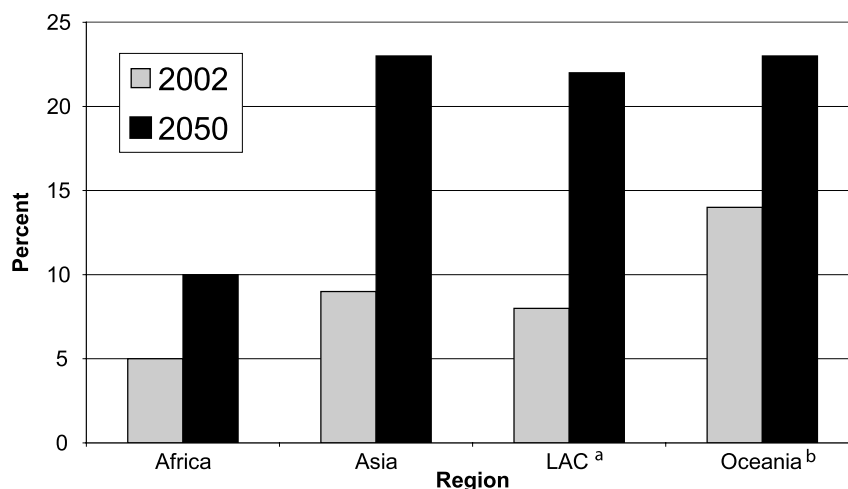
^c 17,198 in Eastern and Central Europe.

Defining “older” populations

Defining the population of “older” women most affected by cervical cancer can be problematic. For the purposes of demographic and population calculations, “older” is typically defined as age 60 or 65 years and above. The United Nations uses the standard of age 60 years and above. For many women in developing countries, however, the changes in health that are associated with old age start in their forties or fifties because of the health consequences of harsh living conditions, poverty, poor nutrition, and frequent childbearing.⁷ The term “older” is used in this document as an indicator for the group of women beyond their childbearing years—primarily in their forties, fifties, and beyond—who are at high risk for cervical cancer.

As populations age across the globe, the need for effective health interventions—including those aimed at preventing cervical cancer—will increase for older age groups. Health care in developing countries has focused on prevention, control, and treatment of infectious disease, particularly among vulnerable populations, such as infants, children younger than five years, and pregnant and lactating women. Disease patterns are changing, among middle-aged and older populations, however, and noncommunicable diseases such as diabetes, cardiovascular disease, and cancer are becoming predominant causes of morbidity and mortality.⁹ Prevention generally is the most cost-effective approach to reducing the burden of diseases that affect older populations.⁹

Figure 2. Percentage of population aged 60 years or more in 2002 and 2050 in developing countries, by region.



^a Latin America and the Caribbean.

^b Oceania includes Australia, New Zealand, Papua New Guinea, as well as islands of the South Pacific Ocean, including the *Micronesia*, *Melanesia* and *Polynesia* groups.

Note. Data from United Nations Population Division (2002).⁸

Access to services

Unavailability or ineffectiveness of programs. Most women in developing countries have little or no access to cervical cancer prevention services, and few countries have organized cervical cancer prevention programs. Furthermore, health resources often are focused on well-established health programs that target, for example, pregnant and lactating women and children younger than five. A 1986 study estimated that only five percent of women in developing countries had been screened for cervical cancer (via a Pap smear) during the previous five-year period.¹⁰ Although nearly two decades have passed since this estimate, there is little indication that the proportion of women screened has changed significantly, except in regions where large studies and demonstration projects have been undertaken.

Most attempts to implement cervical cancer screening programs in the developing world have had little or no impact on cervical cancer mortality rates. Almost all of these programs have been based on cytologic screening, which has presented major logistic, staffing, service delivery, and quality-control challenges. Cytologic screening requires laboratory infrastructure, sufficient consumable supplies, highly trained laboratory technicians, and well-organized follow-up and surveillance systems to effectively screen and treat women for precancerous lesions. Most cytology-based programs have relied on opportunistic screening of relatively young women; few, if any, have targeted both rural and urban women at risk of having precursor cervical lesions (women in their thirties and forties), and few have emphasized high levels of coverage with at least once-in-a-lifetime screening for

at-risk women. As a result, the vast majority of women at highest risk never get screened.¹¹ In parts of Latin America and the Caribbean, for example, cervical cancer incidence and mortality rates have remained largely unchanged, despite the introduction of various cytologic screening efforts in the 1970s. Cervical cancer incidence has been on the rise in other areas, such as regions of sub-Saharan Africa, where there is very limited access to any screening programs.^{11,12}

Another major barrier to effective cytology-based prevention programs in many countries is limited human resources. Trained and experienced providers are in short supply and most available providers reside in major urban areas. Thailand, for example, has too few pathologists to sustain a cytology-based screening program (K. Limpaphayon, unpublished data, 2001). As recently as 2001, countries such as Mali, Burkina Faso, Niger, Chad, Togo, Benin, and Guinea had only one pathologist to analyze or supervise analysis of specimens. Other countries in sub-Saharan Africa have none. These kinds of challenges mean that, in many parts of the world, there is no assurance that traditional cervical cancer prevention programs can be implemented and sustained with appropriate quality and accuracy.⁴

Allocation of funds also can present a barrier to establishing effective, organized screening programs. Resources available for addressing cervical cancer often are allocated to cancer treatment, which is expensive, is often provided too late to save women's lives, and does not reduce overall cervical cancer rates. Furthermore, treatment resources are inadequate in most settings. A situation analysis of facilities in East, Central, and Southern Africa found that only 46 percent of provincial hospitals had the basic equipment necessary to provide surgical treatment to women with cervical cancer, and 79 percent of those did not have a gynecologist on staff to perform curative surgeries. The situation at tertiary-care hospitals often was no better; treatment services frequently were not available to women because of inadequate staffing and a lack of the supplies.¹¹ Radiation therapy often is unavailable as well. Approximately 15 African countries and several countries in Asia have no radiation therapy capability at all.¹³

In addition to the limited availability of effective cervical cancer screening services, women face informational and sociocultural barriers to preventive care. In some communities, many women do not know that—unlike other gynecological cancers—cervical cancer is preventable, and many are unaware of its impact in their communities. Without this knowledge, they have little incentive to seek screening. In addition, in many communities seeking preventive care is not standard practice; people access health care services only when they feel ill. The value of undergoing screening to prevent a cancer that may occur up to 25 years in the future may not be fully understood by women and their partners.¹⁴ Even when women are convinced that screening has value, they may be reluctant to undergo screening because of embarrassment about the pelvic examination, fear of the procedure, stigma associated with sexually transmitted infections, or fear of being told they have cancer. Women also may mistrust health care providers, either because they have been treated badly by health care workers in the past or because they have heard of poor treatment from friends and relatives.¹⁴

The challenge of establishing new, effective programs. Why has it been so difficult to successfully launch, maintain, and evaluate cytology-based programs that reduce women's risk of dying from cervical cancer? The answer to this question can be complex. Global health priority-setting

encompasses influences such as burden of disease, cost-effectiveness of interventions, competing demands for scarce health resources, and images and perceptions of disease.¹⁵ In the case of cervical cancer, the cultural importance placed on older women's health likely also influences health policymakers and decision makers (see p. 11).

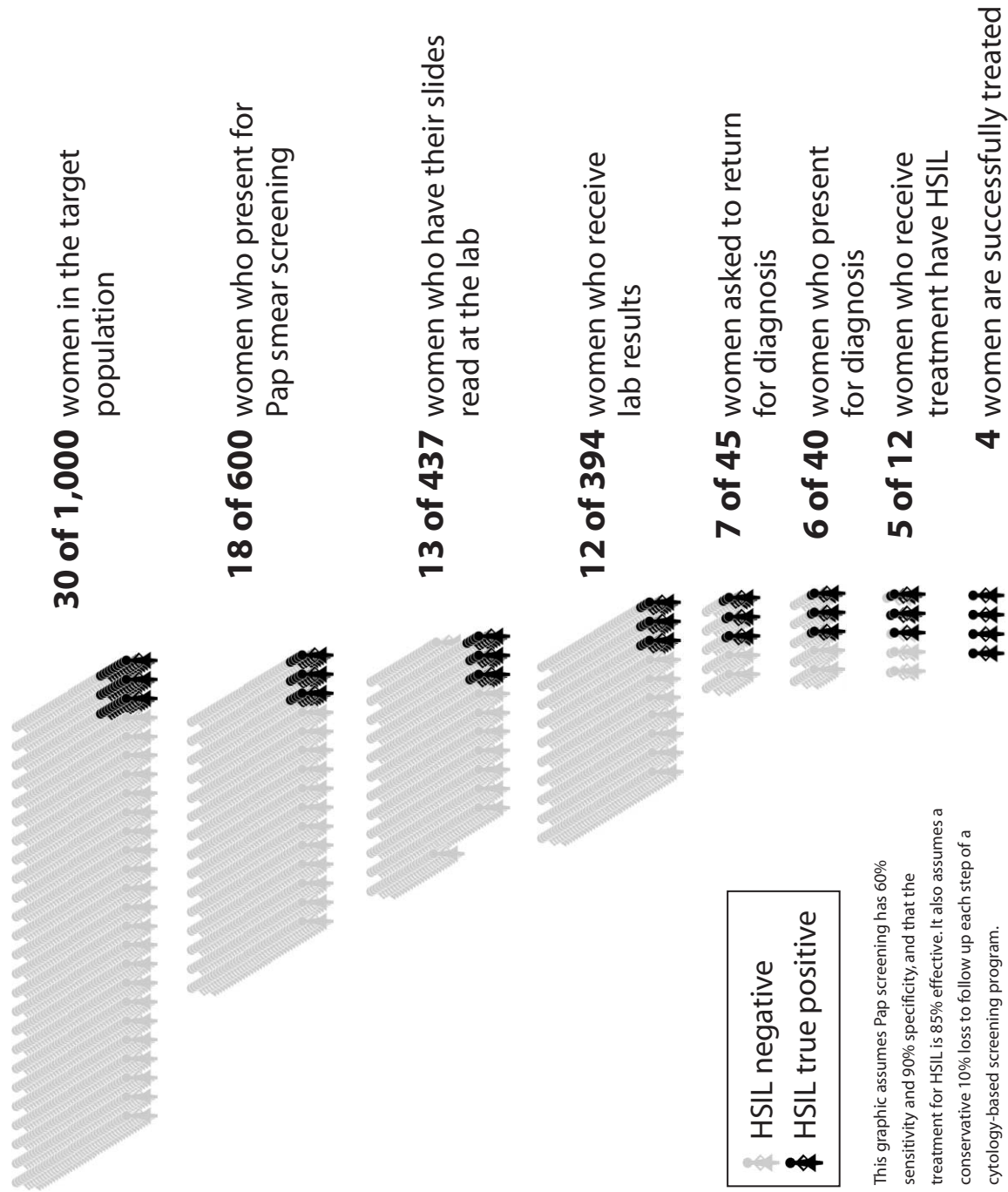
In addition, the multistep nature of standard approaches to cervical cancer control programs creates logistical challenges for many developing-country health systems. To successfully implement a traditional cytology-based program, the following six steps must occur once a woman presents for screening:

1. A cervical cytology sample must be correctly and adequately obtained.
2. Cytology samples must be transported to a laboratory with well-trained and supervised staff and accurately read and recorded.
3. Pap smear results must be communicated back to the screening facility and to the women.
4. Women with abnormal results must be recalled for diagnosis through colposcopic examination and biopsy.
5. Women diagnosed with precancerous or cancerous lesions must be treated appropriately.
6. Treated women should be followed up at, for example, three months and one year after treatment to ensure that treatment was effective.

In many developing countries, ensuring that women participate in all the steps of a multistep medical intervention can be challenging. Losses of 10 to 25 percent at each return visit are not uncommon.^{16,17}

It also is well-documented that the logistic capacity of health systems in developing countries to ensure that Pap smears reach laboratories and that results reach women who need them is mixed at best.¹⁸ This, combined with the inconsistency and quality-assurance challenges that plague many cytology laboratories in developing countries,^{19,20} means that many women who have had Pap smears never get their results, or that the results they do receive are inaccurate. Figure 3 illustrates the dilution of program impact that occurs at each of the steps necessary for implementing traditional cytology-based cervical cancer prevention program, assuming 60 percent of eligible women present for screening and a modest ten percent loss to follow-up at each of the steps identified above.

Figure 3. Tracking women with HSIL through a typical cytologic screening program in a developing-country setting.



Women’s role in the social and economic fabric of developing countries

Preventing cervical cancer has enormous benefits not only for women’s health, but also for the well-being of families and communities. Very often, cervical cancer is not considered a priority because it is perceived as a disease of middle-aged and older women, who may be considered unproductive members of households and communities. This misperception, combined with serious competing demands for health resources, often means that the health needs of middle-aged and older women are overlooked.^{21,22}

Yet, women have a significant influence on family welfare throughout their lives. Middle-aged and older women play central roles as managers of food security, wage earners, caretakers of grandchildren, community leaders in social and political life, and family advisors. In settings where HIV infection and AIDS are affecting a significant proportion of younger people, older women are taking on an even greater role in maintaining community structure. Investing in prevention programs aimed at women in their thirties and forties is an effective way to help ensure the health of individual women and the well-being and stability of families and communities.

Women’s role in the household economy

In most developing countries, women play an important and visible role in maintaining food production and food security for their households and communities. According to the World Bank, almost 75 percent of food production each year is a direct result of women’s labor. Women in sub-Saharan Africa produce and market 80 to 90 percent of local food. Women contribute to 50 to 60 percent of food production in Asia and more than 30 percent in Latin America.²³

Overall, women in developing countries contribute substantially more to the household economy than their male counterparts. Women are often responsible for nonincome-generating work, such as gathering water and firewood, preparing food, tending to livestock, and caring for children and grandchildren.^{23,24,25} The International Labor Organization estimates that if all of women’s household and community work contributions were translated into a monetary value, more than US\$4 trillion a year would be added to the world economy.²³

The welfare of children depends on the health of their mothers and grandmothers. Women’s incomes are more strongly associated with improvements in children’s health and nutritional status than are men’s incomes.^{23,24,25} Although men typically earn more, women spend a larger share of their income on basic household necessities to meet the physical, mental, and social needs of growing children and other household members. Evidence from a study in Tanzania²⁶ suggests that in households where an adult woman had died within the past 12 months, children spent half as much time in school as did children from households where such a death had not occurred. Researchers did not find a statistically significant effect when an adult male died. In many families, older women also have the role of looking after their grandchildren while mothers go to work.²⁷ In those cases, when a grandmother falls ill or dies, women may have to stop working to care for children or may have to pay for childcare, with the consequent reduction in available household resources.

In both urban and rural areas in sub-Saharan Africa, women are the main income earners in approximately one-third of households;^{28,29} this percentage is as high as 47 percent in Botswana.³⁰ In rural areas in developing countries the number of female-headed households is increasing as men migrate because of a lack of employment and other income-generating opportunities.²⁹ In these settings, the effect of a disease like cervical cancer on a woman's children and dependents can be devastating.

Social and economic consequences of cervical cancer

As noted previously, the burden created by cervical cancer is not limited to the suffering of the woman. The family is affected at the psychological level (through anxiety, fear of death, and stress arising from costs of medical bills or drugs) and at the social level (through job and school absences, inadequate child care, and changes in routine life activities).

Families also are strongly affected at an economic level (as a result of medical and nonmedical costs, loss of assets, and debts) and at work (through decreased productivity, job loss, dismissal, and reduction of work-related benefits).^{31,32,33,34} Specific studies of cancer have shown that, even when treatment is provided free of charge or covered by health insurance, the nonmedical costs of cancer can represent up to 50 percent of total family income.^{31,35} In one study carried out in Nigeria,³⁶ 70 percent of women with breast or cervical cancer reported that the family had experienced a major loss of revenue due to the illness. Almost 25 percent of families had taken on moderate or major loans to cover disease-related costs, and for more than 68 percent, disease-related expenditures had made a major impact on the family living conditions. Sixty-two percent of patients reported not being able to attend work, and 33 percent reported that their illness disrupted a relative's work.

Role of older women in communities affected by the HIV/AIDS pandemic

The global AIDS pandemic underscores the importance of older women's contributions and, consequently, the need for cervical cancer prevention services in developing countries. Although older women in developing countries generally are not infected with HIV (see Table 2), the indirect impact of AIDS on women older than 50 years has steadily increased as these women become primary caretakers for their sick children and orphaned grandchildren. Older women can only provide this support for younger generations if they remain healthy.

HIV/AIDS in developing countries. Since the 1980s, AIDS has caused more than 20 million deaths and rendered 14 million children orphans worldwide, mostly in sub-Saharan Africa.³⁸ The number of orphans is expected to continue to increase and to reach approximately 25 million by 2010, unless the epidemic is curbed.³⁹

AIDS is now a leading cause of death in younger men and women. In Africa, for example, most of those who are infected with HIV and live with AIDS are aged 15 to 49 years—the most economically and reproductively active age cohort.⁴⁰ Only 5.6 percent of AIDS cases in Africa in 2000 occurred in people aged 50 or older; among women, only 3.6 percent occurred in those aged 50 or older.

In Asia, only 2.9 percent occurred in women aged 50 or older (see Table 2). As the population of young adults in some countries is decimated, the demographic characteristics of those countries' populations are altered, and traditional family structure and roles are changing.⁴⁰ Older generations are being called on to assume the responsibility for caregiving and financial support for a greater number of dependent household members.

Table 2. Percentage of individuals with AIDS older than 50 years in 2000, by geographic area.

Geographic area	Total number of individuals with AIDS	Percentage of individuals with AIDS who are >50 years old		
		All	Men	Women
Africa	233,336	5.6	7.3	3.6
Asia	119,320	4.5	4.8	2.9
Latin America	198,322	7.4	7.6	7
Australia	8,096	9.3	12.4	17
Canada	16,235	11.2	11	16.3
France	49,421	12.9	13.1	12.4
Germany	18,515	16.4	17.2	10.4
United Kingdom	16,791	11	11.7	5.6
United States	733,371	10.7	11	9.1

Note. Adapted from Knodel.⁴¹

Older women as caregivers. The impact of HIV infection and AIDS extends beyond those with the disease, indirectly affecting surviving family members. In many regions, the parents of people with AIDS—particularly mothers—ultimately serve as primary caregivers to their adult children and grandchildren. This is primarily because of sociocultural traditions underlying the role of extended families worldwide.⁴¹ In addition, poverty and the inadequate health and welfare systems necessitate that much of the care for people with AIDS and their children is home-based and the responsibility of family members (E. Lindsey, unpublished data, 2000).^{40,41}

In the Joint United Nations Programme on HIV/AIDS Thai AIDS Cases Study (TACS), almost 90 percent of participants who had died of AIDS and had living parents had either moved in with or lived adjacent to their parents after becoming sick. This was particularly true during the advanced stages of the disease.⁴¹ In a World Health Organization case study of the impact of AIDS on older people in Zimbabwe, interviewees overwhelmingly stated that no individual or institution is preferable to older family members to take care of orphans after the death of their parents.⁴² Although older persons are not always the only candidates available, they tend to be the most willing or the most geographically convenient sources of care.

Women are predominant among caregivers in most societies, and the situation is no different in regions heavily affected by AIDS. TACS found that older mothers were five times more likely

than fathers to be the primary caretakers of adult children with AIDS and their orphaned children. Another Thai study corroborated these findings.⁴¹ Almost all older men interviewed in Zimbabwe said that they played a secondary role and that their female partners were the main caregivers, and 91 percent of interviewed caregivers in Botswana were female. Of the female caregivers interviewed in Botswana, 54 percent were older than 55 years; in Zimbabwe, 71 percent were older than 60.

Overview of new approaches to preventing cervical cancer

Researchers have become increasingly interested in alternative approaches to traditional cervical cancer screening that reduce dependence on infrastructure, are programatically more feasible, and perform reliably in low-resource settings. Visual approaches using acetic acid or Lugol's iodine to identify suspicious precancerous lesions and human papillomavirus (HPV) testing have received increasing attention as promising simple, low-cost screening approaches that are appropriate for use in low-resource settings. Since 1999, the ACCP has implemented a number of studies to assess alternative approaches to screening and treatment of precancerous lesions. More than 20 research and demonstration projects have evaluated the effectiveness, safety, accountability, and/or feasibility of different screening and treatment strategies. The following review of results from ACCP projects and related research studies provides an evidence base that supports new approaches to cervical cancer prevention.

Visual inspection with acetic acid

Visual inspection with acetic acid (VIA) involves swabbing the cervix with a three- to five-percent acetic acid (vinegar) solution before visual examination with a strong light source. The application of acetic acid causes precancerous lesions to temporarily turn white, allowing the health care provider to determine whether precancerous lesions are present. Although comparison across studies is difficult because of variations in protocols and study populations, the sensitivity of VIA in detecting HSIL in low-resource settings ranges from approximately 60 to 90 percent. In general, the sensitivity of VIA is equivalent to or better than that of cytologic examination, although the specificity is somewhat lower (see Table 3).⁴³⁻⁵¹

VIA is a simple approach. Health care providers can be trained in a short period (one to two weeks), and in most contexts, the costs associated with launching and sustaining VIA-based programs are lower than for other methods. VIA can be implemented in a range of contexts, but special attention to regular and consistent quality assurance is required because of the test's more subjective nature.^{44,47,52,53,54}

Visual inspection with Lugol's iodine

Visual inspection with Lugol's iodine (VILI), also known as "Schiller's test," uses Lugol's iodine instead of acetic acid to identify potential precancerous lesions. The screening test is similar in approach to the Schiller's iodine test advocated in the 1930s and widely used early in the twentieth century, before the development of cytology. The application of iodine to the cervix results in a brown or black stain on areas that contain glycogen. Because precancerous lesions and invasive cancer do not contain glycogen, they do not take up the iodine, and therefore appear as well-defined, thick, mustard-colored or saffron-yellow areas. VILI may have better test performance characteristics than VIA.^{44,55} A recent study from India found that VILI had a sensitivity of 87.2 percent and a specificity of 84.7 percent (see Table 3).⁴⁴ Data from that study suggest that VILI is at least as sensitive as and more specific than VIA. Additional pooled results from 56,939 women in 11 cross-sectional studies carried out in India and Africa by the International Agency for Research in Cancer suggest similar high sensitivity and moderate specificity for VILI and less variability in results than has been observed for VIA.⁵⁵ VILI's promising performance demands further research.

Table 3. Results of selected studies of visual inspection with acetic acid (VIA).

Reference	Geographic area	No. of women	Age range (years)	End point	Confirmatory test	VIA (%)		Cytology (%)	
						Sensitivity	Specificity	Sensitivity	Specificity
Basu et al. 2003 ^{43,a}	India	5,881	30–64	CIN II and above	Colposcopy and histology (if necessary) for all	55.7	82.1	29.5	92.3
Sankaranarayanan et al. 2003 ^{44,a}	India	4,444	25–65	CIN II and above	Colposcopy and histology (if necessary) for all	82.6	86.5	81.9	87.8
Belinson et al. 2001 ^{45,a}	China	1,997	35–45	CIN II and above	Histology for all	71	74		
U of Zimbabwe et al. 1999 ^{46,a}	Zimbabwe	2,203	25–55	HSIL and above	Colposcopy and histology for all	76.7	64.1	44.3	90.6
Denny et al. 2002 ⁴⁷	South Africa	2,698	35–65	HSIL	Colposcopy and histology (if necessary) for all positive women	69.8	79.3		
Denny et al. 2000 ⁴⁸	South Africa	2,944	35–65	HSIL and above	Colposcopy and histology (if necessary) on all women with positive results	67.4	84.9	78.3	96.8
Sankaranarayanan et al. 1999 ⁴⁹	India	1,351	22–70	Moderate and severe dysplasia and above	Colposcopy and histology (if necessary) on all women with positive results	95.8	68.0	62.0	89.5
Sankaranarayanan et al. 1998 ⁵⁰	India	3,000	20–70+	Moderate and severe dysplasia and above	Colposcopy and histology (if necessary) on all women with positive results	90.1	92.2	86.2	92.7
Megevand et al. 1996 ⁵¹	South Africa	2,426	20–83	HSIL and above	Colposcopy and histology on all women with positive results	64.5	98	35.4	

^a Not subject to verification bias.

CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesions; VILI = visual inspection with Lugol's iodine.

Note. Studies were included because they addressed test performance of VIA as a primary screening method. Their methods were clear, sample sizes were large, and study limitations were addressed; in addition, these studies were carried out in countries where the need for cervical cancer prevention programs is significant.

VILI offers many of the same advantages as VIA. Results of the test are available immediately, and the test does not require laboratory support. The technique is simple and easy to learn, and the test has low start-up and sustaining costs and is only minimally reliant on infrastructure.

HPV DNA testing

There is growing interest among cervical cancer prevention researchers in HPV DNA testing as a primary screening test. HPV DNA testing identifies high-risk HPV DNA subtypes. The presence of high-risk HPV strains indicates that a woman has an increased risk of developing cervical cancer. When used in women in their thirties and forties, HPV DNA testing is objective and generally has a higher sensitivity and specificity for detecting high-grade cervical lesions than does visual screening. Sensitivity levels for HSIL have been found to range from 84 to 97 percent; specificity has been found to be approximately 90 percent (see Table 4). Screening programs based on HPV DNA testing could give women the option of using self-collected sampling techniques, although this approach has not yet been broadly tested. Self-collection of vaginal samples could significantly reduce the number of trained medical personnel needed to implement the screening program, because vaginal examinations only would be required for the fraction of screened women who are HPV positive. In addition, self-sampling has the potential to increase program coverage—studies have shown that women can successfully collect their own vaginal samples for an HPV DNA test and that, for many women, self-collection of vaginal samples is more acceptable than undergoing a pelvic examination by a health care provider.⁵⁹

Although HPV DNA testing is promising as an approach to cervical cancer prevention, the cost and technical and infrastructure requirements can make it difficult to implement in low-resource settings.^{48,60,61} HPV DNA testing relies on technically skilled laboratory specialists, supplies, and computer-based laboratory equipment, and therefore large-scale use in low-resource settings is not feasible at present.⁶² In addition, the commercially available HPV DNA test kits take six to seven hours to process, so that it is difficult to provide women with results and discuss treatment or management decisions in the same visit.⁶² This delay can dilute program impact by increasing the risk that women will be lost to follow-up. Researchers are working to develop biochemical tests that will retain the objectivity and strong test characteristics of the currently available HPV DNA test but will provide results more quickly and be more affordable and feasible for use in developing-country settings.

Single-visit and screen-and-treat approaches

In many developing-country settings, where transportation and time away from home are barriers to follow-up care, a single-visit approach can increase program effectiveness by dramatically increasing the number of women who receive both screening and treatment services (see Figure 4). Because the results of both VIA and VILI testing are available immediately to the provider and the woman, several clinical management options can be made available during the same visit. For example, for women with positive results, providers can perform further investigations, such as colposcopic examination and biopsy, as well as offer outpatient treatments, such as cryotherapy or loop electrosurgical excision procedure (LEEP). Alternatively, immediate treatment with cryotherapy or LEEP can be offered without the use of a further diagnostic step. Programs in some countries are

Table 4. Results of selected studies of human papillomavirus (HPV) DNA testing.

Reference	Geographic area	No. of women	Age range (years)	End point	Confirmatory test	Provider type	HPV DNA test result (%)		Result of cytologic examination (%)	
							Sensitivity	Specificity	Sensitivity	Specificity
Schiffman et al. 2000 ⁵⁶	Costa Rica	8,554	18–90	HSIL or above	Colposcopy for positive cytology (ASCUS or above) or positive cervicography	Physicians	88.4 ^a	89.0 ^a	77.7 ^b	94.2 ^b
Wright et al. 2000 ⁵⁷	South Africa	1,415	35–65	HSIL or above	Colposcopy for all women with positive results	Nurses	83.9 ^d	N/A (15.5 FP)	60.7 ^c	N/A (3.2 FP)
Cuzick et al. 2003 ⁵⁸	United Kingdom	10,358	30–60	CIN II and above	Colposcopy and biopsy as indicated for women with positive results and 5% of women with negative results	Physicians	97.1	93.3	76.6	95.8

^a For women 41 years and older, the sensitivity was 93.2% and the specificity was 94.0%.

^b Using ASCUS as a cutoff.

^c Using low-grade squamous intraepithelial lesions as a cutoff.

^d Clinician-collected samples. For self-collected samples, the sensitivity was 66.1% and the rate of FP results was 17.1%.

ASCUS = atypical squamous cells of undetermined significance; FP = false-positive; HSIL = high-grade squamous intraepithelial lesions.

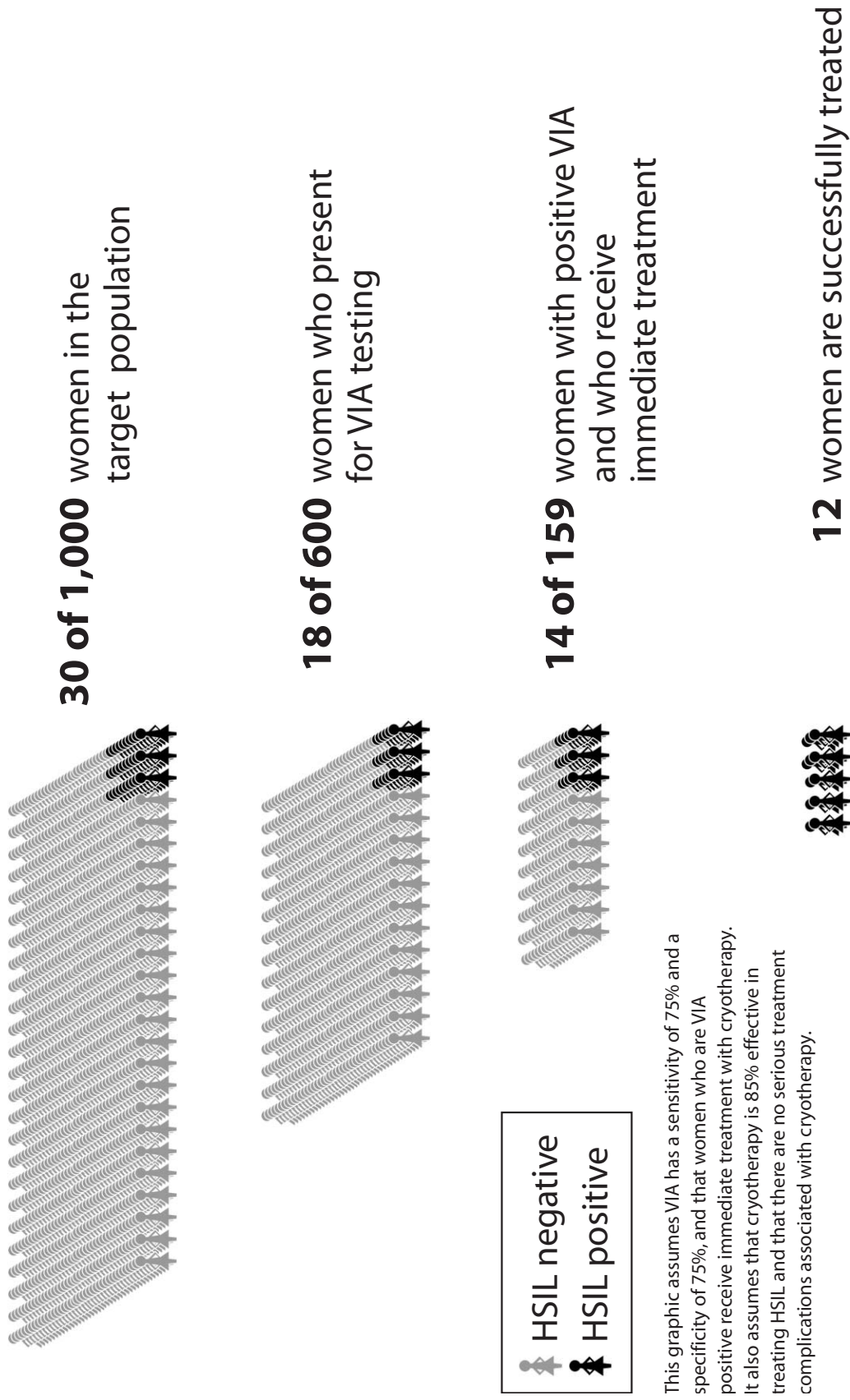
Note. Studies were included because they used HPV DNA testing for primary screening; their methodologies were clear and study limitations were addressed; they provided data that addressed older age groups; they are relatively recent; and they were carried out in developing as well as developed countries.

assessing the effectiveness, safety, acceptability, and/or feasibility of a single-visit, screen-and-treat approach based on visual screening (two-visit screen-and-treat approaches also are being assessed).^{63,64} When available, new generations of biochemical tests that are quicker and easier to process also would allow single-visit, screen-and-treat options.

Using a screen-and-treat approach raises questions about overtreatment, however. For example, when treatment with cryotherapy is offered to women in whom lesions are found on visual screening, many more women without HSIL than women with HSIL are treated (see Figure 4). The evidence increasingly suggests that cryotherapy is a relatively safe procedure,⁶⁵ however, and may provide benefits to women with cervical inflammation, as well as to those with low-grade squamous intraepithelial lesions and HSIL.⁶⁶ According to a recent literature review, cryotherapy has an overall cure rate of approximately 90 percent, which is similar to cure rates reported for LEEP and laser ablation. Results indicate a slight trend toward lesser effectiveness of cryotherapy for treatment of severe lesions, lesions that cover 75 percent or more of the cervix, and lesions that extend into the endocervical canal.⁶⁵ Most demonstration projects in which a single-visit screen-and-treat approach is used currently refer women with these findings for alternative treatment methods. Complications associated with cryotherapy—such as severe bleeding or pelvic inflammatory disease—are extremely rare, as are suspected long-term sequelae, such as cervical stenosis, lowered fertility, and poor pregnancy outcomes.⁶⁵ Data from projects in Thailand, South Africa, and India provide additional evidence that cryotherapy is a safe approach.^{61,63,65}

In any cervical cancer prevention program, it is key that women receive complete information about the benefits and risks of treatment to ensure that they can make informed choices. This is a vital component of a high-quality cervical cancer prevention service. In some countries, ministry of health officials and providers have weighed the available evidence and decided that the risks of overtreatment associated with screen-and-treat approaches are balanced by the opportunity to make significant reductions in cervical cancer rates.^{46,63} In these countries, ministry of health officials and program planners are working together to implement programs based on screen-and-treat approaches that provide women with the information and counseling they need to make informed decisions about their options for care when a suspicious lesion is identified.

Figure 4. Tracking women with HSIL through a prototype single-visit cervical cancer prevention program in a developing-country setting.



Cost-effectiveness and acceptability of new approaches

In planning effective cervical cancer prevention programs, it is helpful to compare the cost-effectiveness of alternative screening and treatment programs. In recent years, new mathematical models have been developed to delineate the natural history of cervical cancer and assess the clinical benefits and cost-effectiveness of alternative cancer screening strategies. These models take into account differences in the relative effectiveness and requirements of various recruitment strategies, screening tests, treatment approaches, and follow-up protocols for a given country setting.

This new generation of models has advanced knowledge about the likely cost-effectiveness of cervical cancer screening worldwide in several ways. First, newer models consider new approaches to cervical cancer prevention—visual inspection methods, HPV DNA tests, and combined approaches—and assess the impact of single-visit and once-in-a-lifetime interventions. Second, models are now using data from developing-country populations. Finally, newer models incorporate the effects of HIV infection and AIDS in countries where increased numbers of women at risk of HIV are also at increased risk of HPV infection.

Recent findings from studies using models suggest that the new approaches to cervical cancer prevention provide cost-effective means of reaching women and preventing deaths. Goldie et al. (2001)¹⁶ estimated the clinical benefits and cost-effectiveness of cytologic examination, VIA, and HPV DNA testing in South Africa (see Table 5). The authors defined each strategy by the number of clinical visits, the use of one or two screening tests, the screening frequency, and the target ages for screening. The model suggested that, for South African women, a single lifetime screening with direct visual inspection or HPV DNA testing, combined with immediate treatment for women with positive test results, would reduce the incidence of cervical cancer by 26 to 32 percent and cost less than US\$50 per woman. The authors also compared strategies for different screening frequencies. The model estimated that women who underwent a single screening for HPV DNA at 35 years of age would cost US\$14 per year of life saved (YLS; assuming a cost per test of US\$5) and reduce cervical cancer incidence by 32 percent, compared with no screening. According to the model, using VIA and treating women with positive results of screening during the same visit was almost as effective. This single-visit strategy was estimated to be cost-saving and to reduce cervical cancer incidence by 26 percent. The least effective strategy was cytologic examination, which estimates indicated would reduce cervical cancer incidence by 19 percent, with a cost of US\$81 per YLS.

Table 5. Cost-effectiveness of cervical cancer screening strategies.

Screening strategy	Reduction in cervical cancer incidence (%)	Cost-effectiveness ratio (US\$/YLS)
VIA and treatment	26	Cost saving
HPV DNA testing and treatment	32	14
Two-visit Pap smear	19	81
Three-visit Pap smear	17	147

HPV = human papillomavirus; VIA = visual inspection with acetic acid; YLS = year of life saved. Data from Goldie et al. (2001),¹⁶ with permission.

Other model-based analyses have produced similar rankings of cost-effectiveness approaches. For example, Mandelblatt et al. (2002)¹⁷ estimated the cost-effectiveness of screening programs for women aged 35 to 55 years in Thailand. This model suggested that using VIA to screen women every five years reduced cervical cancer incidence by 31 percent at a cost of US\$263 per YLS. HPV DNA testing every five years reduced cancer rates by 20 percent, at a cost of \$672 to \$3,477 per YLS (cost depended on the cost of the test, which ranged from \$5 to \$30, including personnel and supplies). The model suggested that cytologic screening would be least cost-effective in this setting, reducing cancer rates by 11 percent at a cost of \$1,459 per YLS.

These models consistently show that cervical cancer screening strategies using VIA or HPV DNA testing are cost-effective alternatives to cytology-based screening, even though the absolute values of cost per YLS were different across these two models. Clearly, these results have important policy implications for other low-resource settings where cervical screening has not been introduced or where laboratory-based cytology services are not feasible.

Although the models described above show a clear cost-effectiveness benefit for noncytology-based approaches, one model suggests that cytology-based cervical cancer prevention programs also may be feasible in developing-country settings where consistent, high-quality cytologic services can be maintained and where the infrastructure and resources exist to ensure effective information systems.⁶⁷ Most developing countries, however, have limited resources for establishing cytologic screening services that can effectively reach women in both urban and rural settings.

Promoting a public health approach to cervical cancer prevention

As demonstrated, cervical cancer is a significant health problem for women in many developing countries, and new screening and treatment approaches for prevention have the potential to be cost-effective alternatives to traditional cytology-based screening systems in low-resource settings and to reduce mortality associated with cervical cancer. New approaches offer “the possibility of lowering the rates of years of life lost in developing countries down to levels equivalent to those of developed countries, and the opportunity to implement effective prevention—an opportunity that does not necessarily exist to the same extent for other diseases of comparable burden” and “should not be missed.”⁵

Advocacy and policy change

Program planners considering broad-scale introduction of programs based on these new approaches need to proactively address some of the challenges they will face in promoting an unfamiliar strategy for reducing cervical cancer deaths. Advocacy efforts are needed at the international, national, and local levels to increase awareness of and support for programs implementing new approaches to cervical cancer prevention. For example, physicians may approach cervical cancer prevention from a clinical perspective (which focuses on the risks and benefits an individual patient will experience when undergoing a procedure), rather than from a public health perspective (which focuses on the risks and benefits a program confers on an entire population). These providers may be concerned about using an alternative screening strategy that they perceive to be less accurate than Pap screening. They also may be hesitant to use nontraditional methods to manage the cases of women with positive screening results—that is, without a definitive diagnostic step. As ACCP research and demonstration projects in India, Ghana, Kenya, Peru, and Thailand have shown, addressing and overcoming these concerns will require advocacy, education, and training for providers at the local and national levels, as well as supportive leadership by health officials.^{68,69}

Policymakers, health care providers, women, and community leaders need clear, accurate, and compelling information about new approaches and the potential they have for real health impact at the population level. Well-organized and well-documented program monitoring and evaluation also are key to long-term commitment to the program, so that health personnel at all levels can see that programs using new approaches are achieving a positive impact by offering women safe and effective screening and treatment options.

Another potential barrier to launching a new, impact-focused cervical cancer prevention program are regulations that restrict nurses and other mid-level health providers in some countries from screening women, making treatment decisions, and providing treatment (with cryotherapy). As described earlier, many developing countries lack a sufficient number of general physicians, let alone gynecologists or pathologists. To ensure program coverage levels that will result in measurable impact, nurses, midwives, and other mid-level providers can be trained in key screening and treatment services. Although the clinical community may resist involving mid-level providers in program implementation, projects in Thailand, India, Peru, and other countries are demonstrating

that these providers can safely and effectively provide needed services.^{53,55,63} Regular monitoring and evaluation of mid-level providers' work will help ensure ongoing quality assurance.^{44,47,52,53,54}

The impact of changing policies and shifting from a clinical to a public health approach is illustrated by the example of emergency obstetric care in developing countries and authorization to provide anesthesia for a cesarean section. Freedman (2002)⁷⁰ addressed this issue from a public health and human rights perspective that juxtaposed the safety and survival of an individual patient to whom anesthesia is administered by a highly trained specialist against the safety and survival of the population to which anesthesia could be administered if lower-level providers were allowed to perform the procedure. Allowing nurses trained in anesthesiology to administer anesthesia—thus increasing population coverage—increased the hypothetical survival rate in his model from 9.9 to 63 percent.⁷⁰

The programmatic impact of cervical cancer prevention programs can be demonstrated by comparing traditional cytology-based programs to new approaches (see Figures 3 and 4). This exercise—although simplified—illustrates how new approaches that reduce the number of visits can reach significantly more people with appropriate services than can traditional approaches. Model-based analyses of new screening and treatment approaches provide further evidence that increased coverage with reasonably accurate screening strategies and strong program follow-up (e.g., appropriate treatment of all women who are identified with precancerous lesions through single- or two-visit approaches) enhances program impact.^{16,17}

Rights-based arguments

The public health rationale for making simpler, more feasible interventions broadly available via a range of health providers is bolstered by human rights arguments. For example, the United Nations–sponsored International Covenant on Economic, Social, and Cultural Rights,— entered into force in 1976 and ratified by 148 countries, declared that people have the right to the highest attainable standard of physical and mental health and to the benefits of scientific progress. It also declared that governments must take steps within their abilities to achieve full realization of this right.⁷¹ Documents such as this encourage policymakers to consider the access of the overall population to necessary health care. Although these rights can be applied to a large range of health issues, in recent years, health advocates for specific issues (e.g., maternal health care) have tried to hold government signatories accountable for investing in programs that will improve the health of their countries' populations.

For cervical cancer, the public health/human rights perspective can be helpful in selecting specific screening and treatment protocols. In countries with no established cervical cancer prevention program, program planning must focus on and invest in safe and effective strategies that are most likely to maximize high coverage and effectiveness. In many countries, instituting a cytology-based screening program under severe financial constraints and with little infrastructure to sustain it would deny most women their right to health care services and would place undue burden on the countries' economies. On the other hand, relatively simple—and effective—screening and treatment methods can help ensure availability and access for the broad population of women at risk.

Rights arguments also have been helpful to countries considering new approaches to disease prevention that are very promising but have not undergone many years of extensive clinical and epidemiologic testing. As described in Freedman (2002),⁷⁰ a South African court made such an argument for expanding access to Nevirapine to prevent maternal to child transmission of HIV, even before definitive results of pilot projects were available. In the case ruling, the courts drew upon international standards and a decision made in another South African case involving post-apartheid housing stating “those in most desperate need . . . are not to be ignored in the interests of an overall program focused on medium and long-term objectives.”⁷² Applying this type of argument to cervical cancer screening lends support not only to alternative screening protocols, such as a screen-and-treat approach, but also to expansion of services that will increase coverage of the population at risk. Making new approaches broadly available in developing countries and low-resource areas (assuming that appropriate quality control and monitoring mechanisms are in place) is clearly preferable to offering women nothing at all.

Looking to the future

In addition to the approaches to secondary cervical cancer prevention described here, primary prevention through HPV vaccines holds tremendous promise. Within five years, HPV vaccines against two carcinogenic HPV types—types 16 and 18—may be available to developed-country markets. One decision-model analysis suggests that administering an HPV-16/18 vaccine that is 98 percent effective at preventing persistent HPV infection to all adolescent females (before the onset of sexual activity) would reduce the burden of cervical cancer by 51 percent over a 40- to 50-year period.⁷³ Achieving this result in many developing countries will present a number of challenges, however, including reaching significant proportions of young women with a multidose vaccine, monitoring the impact of a vaccine program, and developing financing strategies so that countries can purchase sufficient vaccine to achieve disease reduction goals.

Given these challenges and the long delay between launching an HPV vaccine program and reducing death rates, developing-country programs must continue to build awareness of and attention to secondary prevention of cervical cancer at all levels. This includes strengthening policy support for cervical cancer prevention activities; establishing feasible, acceptable, and effective screening and treatment programs that reduce deaths; and developing accurate and sustainable information systems to monitor progress and impact. These activities will help women who are currently at risk and will form a strong base for launching, sustaining, and monitoring HPV vaccine programs when effective vaccines become affordable and available worldwide.

Conclusion: opportunities and challenges for moving forward

Cervical cancer represents a unique public health opportunity to reduce the burden of disease among women worldwide. Cervical cancer kills a disproportionate number of women in developing countries, despite the fact that evidence-based secondary prevention methods exist, and new, cost-effective approaches—for instance, visual screening, HPV DNA testing, and screen-and-treat approaches using cryotherapy—are being shown to be acceptable, feasible, and effective in many low-resource settings. The middle-aged and older women who are most affected by cervical cancer play key roles in the lives of their families and communities, especially as the impact of the HIV/AIDS pandemic increases in countries around the world. Governments and international organizations should support and implement effective, public health-oriented cervical cancer prevention programs in countries where the need is the greatest. As they address women’s rights to health and the benefits of scientific progress, these programs have the potential to save hundreds of thousands of women’s lives in the coming decades.

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