Cervical Cancer Screening and Prevention, and Barriers to Uptake
Introduction

Cervical cancer is the second-most common cancer among women in the developing world.\(^1\) Cervical cancer is caused by the sexually-transmitted human papilloma virus (HPV). Many HPV strains are asymptomatic and clear up quickly, but a few infect the cervix and cause pre-cancerous lesions that can advance to cancer.\(^1\) Roughly 500,000 cases are diagnosed each year, more than half of which result in death. In low-resource contexts, cervical cancer has a greater burden of morbidity and mortality because most cases are detected in the late stages. Screening services that detect pre-cancerous lesions in the cervix may be inaccessible to women due to cost, shortage of equipment and providers, and low knowledge about service options. A 2008 review showed that among women in need of cervical cancer screening, an average of 19% in developing countries had been screened in the last three years, compared to 63% in developed countries.\(^2\) Women who are able to access screening may never receive their results or be lost to follow up for lifesaving treatment.\(^3\)

Screening Methods

Most screening methods test for the presence of pre-cancerous cells in the cervix. In low-resource settings, screening achieves the greatest impact for the lowest cost when it is targeted to women between the ages of 30 and 49.\(^4\) The range of tests available differ in terms of their sensitivity and specificity and the training and resources needed to administer them. A test’s sensitivity indicates its ability to avoid false negatives, and its specificity indicates its ability to avoid false positives. Higher sensitivity and specificity measures highlight the test’s accuracy.

**PAP SMEAR**

The Pap smear has been the trusted screening method in the developed world for more than 60 years. This cytology-based test requires a provider to scrape cells from the cervix and technicians to examine the sample in a lab.

Because Pap smears require equipment and advanced training, and results are not immediately available, they can be difficult to introduce and sustain in low-resource settings.\(^5,6\) Pap smears can be insensitive depending on the conditions in the cervix at the time of the sample, and so need to be done at regular intervals to ensure abnormalities are detected.\(^7,8\) Costs are driven up by multiple rounds of testing.\(^5\)

Evidence shows that other screening tests are more sensitive than Pap smears. The methods described below may be better investments for developing countries due to their relatively greater impact and efficient use of resources.

**VIA/VILI**

Visual inspections with acetic acid or Lugol’s iodine (VIA/VILI) are the predominant screening method in developing most countries due to their low cost and minimal equipment and training requirements.\(^3,6\) During a VIA test, the cervix is washed with acetic acid solution, which turns abnormal cells white and makes them visible to the naked eye. During a VILI test, the cervix is swept with Lugol’s iodine, which stains higher-grade lesions on the cervix. VILI is slightly more sensitive than VIA and can either be performed on its own or after VIA.\(^6,7\)

Visual inspection tests have demonstrated greater accuracy than Pap smears.\(^9\) And because they provide instant results, women who need treatment can immediately receive it at the health facility or be referred to another provider.

**DNA TESTING**

Unlike methods that test for pre-cancerous cells, DNA testing directly identifies HPV DNA in the cervix. Some DNA screening tests can differentiate between the strains of HPV that can and cannot cause cancer.\(^10\) However, HPV-DNA testing does not reliably predict the incidence of cervical cancer,\(^11\) so it is recommended that women with a positive HPV-DNA result also undergo another method of testing, such as VIA, to determine the extent of infection and progression of disease.\(^10,12\)

DNA testing can take several hours and requires laboratory equipment and specialized training; as a result it is typically more costly than other methods of screening.\(^12,13\) Implementation of HPV-DNA screening in low-resource settings can also be challenged by women’s lack of knowledge about the method, and some may perceive the test negatively due to its association with sexually transmitted infections.\(^10\)
The CareHPV test, introduced by PATH in 2012, promises lower costs and shorter turnaround times but is as accurate as more expensive DNA screening. Early evidence shows that CareHPV is more accurate that other cytology-based or visual inspections.12 A 2014 evaluation14 in India, Nicaragua, and Uganda compared cervical careHPV (provider-collected samples) and vaginal careHPV (i.e, self-collected samples) to VIA and Pap smear screening. The evaluation found that cervical and vaginal careHPV were more sensitive for pre-cancerous cells at all sites (more than 80% and 70%, respectively), compared to a 60% sensitivity demonstrated by VIA and Pap smear. The specificity of cervical careHPV and vaginal careHPV was around 90%, while VIA and Pap smear were 84% and 88%, respectively.14

SELF-SAMPLING
Like other screening methods, DNA testing can be performed on self-collected swabs, potentially reducing women’s need to travel to a health center and the need to train health facility staff to collect samples.5,11 Self-sampling allows women to swab the vagina using a tampon or small brush to collect a cellular specimen to be tested using one of the methods described above. When tested, self-sampled specimens permit sensitivity equal to that of clinician-collected samples, although somewhat lower specificity. A number of studies have indicated that the lower specificity can be attributed to ability of screening tests to detect other vaginal infections that may be collected on the swab.15

Evidence shows that self-sampling is acceptable to women, and may even be more appealing that clinical examinations because of its privacy and convenience and the ability to forego a pelvic exam.5,12,15 Women who do not like self-sampling often report physical discomfort or a lack of knowledge about how to do it; others prefer a clinic setting because they can receive treatment there if needed.5,15 Women in India suggested that self-sampling process would be easier if staff provided more guidance or were available during the procedure, and if women had illustrated instructions and the chance to practice the technique on a doll or model.5

Uptake of Cervical Cancer Screening
To date, there is no systematic review of what works in developing countries to increase women’s uptake of screening services, or the reasons that discourage or motivate them to do so. Results are limited to country contexts; however, a number of studies report similar factors that impede or facilitate women’s interest in and access to screening and treatment, which are outlined below.

COVERAGE OF SCREENING SERVICES
A 2015 analysis of population-based World Health Surveys measured coverage of cervical cancer screening as the proportion of women aged 25-64 who report having had a pelvic exam and Pap smear in the past three years. The analysis indicates that coverage in developing countries is on average 19%, compared to 63% in developed countries, and ranges from 1% in Bangladesh to 73% in Brazil.2 Women aged 45-65 are least likely to be screened despite their increased risk of cervical cancer. The decline in coverage among older women correlates with the increased incidence and mortality of cervical cancer, suggesting that the lack of screening leads pre-cancerous cells to progress undetected.2

There is a stark difference in coverage between income levels (the equity analysis also includes developed countries). Globally, only 31% of women in the poorest wealth quintiles have ever had a pelvic exam compared to 91% of women in the wealthiest quintile. The wealthiest women are seven times more likely to have been screened within the past three years.2

FACTORS ASSOCIATED WITH UPTAKE OF SCREENING
Evidence from a variety of contexts suggests that several factors are associated with a greater likelihood of being screened for cervical cancer. These include:

- Higher education level16-18
- Older age17,19-21
- Higher income level2,18,22
- Greater parity17,21,23
- Knowing someone who has been screened or diagnosed with cervical cancer17,21,22

Some studies have found associations with condom or family planning use, having health insurance, having received other services at health facilities, and marital status.19,21,22
WOMEN’S REASONS FOR SCREENING

Limited evidence suggests that women are often screened on the recommendation of their health provider or because they are experiencing pain or other symptoms. Women who are aware of cervical cancer screening and where to access it may choose to attend services because of their perceived benefit or the perceived consequences of not being screened.

BARRIERS TO SCREENING

The barriers to uptake of screening services in developing countries generally fall into several categories: lack of knowledge about the services available, inconvenience or cost of services, perceived poor quality of services, fears or embarrassment about seeking services, misperceptions about need for and value of screening, and community and interpersonal barriers.

Evidence from Asia, African, and Latin America suggests that many women do not know about cervical cancer screening and are not aware what types of services are available or where and when to seek them.

Women who do want to be screened may be discouraged by the direct cost of services or the costs and inconveniences of needing to miss work or travel far for an appointment. Patients may encounter long wait times because clinics are overcrowded, or because regulations only allow doctors to perform screenings.

Because women have competing priorities for their money and time, their motivation to seek cervical cancer screening may drop if the experience is perceived to be a costly burden.

Conditions at the facility determine women’s satisfaction with the services they receive. Staff overwork and lack of training can result in incompetence and unfriendliness, and some women report that the facilities or equipment appear unclean. In low-resource settings, frequent equipment stockouts or malfunctions mean that women are unable receive their scheduled screening or treatment, and they may be unable or unwilling to return for another visit. A negative experience or long delays in the screening process can make women reluctant to follow-up for treatment, return for future screenings, or recommend the procedure to their friends.

Many women, particularly those with less knowledge about cervical cancer and screening, may not recognize the benefit of screening over its perceived costs. Many do not consider themselves candidates for screening, either because they have no symptoms or because they perceive themselves to be at low risk of HPV infection and cervical cancer.

Others misunderstand the timing of screening and its usefulness for preventing cervical cancer. Women who do understand the value of screening can also hesitate to seek services because they are nervous about pain or side effects or are afraid of receiving a positive result.

Finally, social and interpersonal factors can discourage women from seeking treatment. Because HPV is a sexually transmitted infection, some communities stigmatize screening, causing embarrassment for women who present for services. In many cultures, the embarrassment is especially salient if only male providers are available.

Women may also face objection from their husbands or family members who are not knowledgeable about the procedure.

FACILITATING FACTORS FOR SCREENING

In contrast, studies indicate that offering convenient, low-cost, and quality services can increase women’s uptake of cervical cancer screening. Complementary interventions that create awareness and social support for screening will allow women to make informed decisions about their options.

The presence of friendly and competent staff is important to screening patients, and women from Asia and Africa reported that a having a private screening room and a female provider would also make them more comfortable with the service.

Convenience, speed, and low cost are critical factors in the decision to seek services. Women value guidance from their providers about when and how to get screened, and are more likely to go if they have a provider’s referral. Counseling prior to screening is appreciated: during the demonstration project, almost all women who had been walked through the process had better expectations and were more tolerant of discomfort.

Information and communications about the value of cervical cancer screening can help generate community support and reduce stigma, making the service easier to access and more appealing to women. Studies from all regions found husband’s support to also be a key motivating factor. In some contexts, like those in Malaysia and rural Zimbabwe, spousal support is especially helpful if it gives women the financial independence to pay for services.
Integration with Other SRH Services

There is a growing movement to integrate health services in LMICs, both to increase access and achieve greater cost-efficiencies. The range of screening options are making cervical cancer prevention increasingly affordable, but there is more to do to make services accessible to women. Cervical cancer is usually classified as a non-communicable disease, but because it is caused by the sexually-transmitted HPV, it fits neatly alongside reproductive health and HIV services. There are few specialized cervical cancer programs in developing countries, so integrating screening into existing programs is a more feasible approach.33

HIV INTEGRATION

HIV infection makes women five times as susceptible to cervical cancer, and antiretroviral therapy has not yet shown to improve chances of survival – in fact, the effectiveness of ART can actually put women at increased risk by extending life expectancy and therefore increases the risk of developing cancer.33-35 Screening programs are necessary to detect pre-cancerous cells as early as possible and also provide women with information about how to avoid HPV infection in the first place.

There have been few studies on the effectiveness of integration for increasing uptake of screening. A qualitative study in Uganda found that many HIV-positive women seek services because they desire to maintain overall good health. Like other women, however, many are discouraged by misperceptions about pain and concerns about privacy, and most face logistical barriers like competing needs for money and time, long waits at the clinics, or forgetting to schedule a visit.36 Designing integrated interventions to inform women living with HIV about the value and realities of screening and overcome their practical barriers may increase their uptake.

A looming challenge for HIV and cervical cancer service integration is the availability of human resources. Providers must have expertise in both health areas and be able to effectively respond to complications that often arise in immunocompromised patients. Providers with these qualifications are scarce in low-resource settings, particularly in rural areas.35

FAMILY PLANNING INTEGRATION

The introduction of cervical cancer screening into family planning clinics may be relatively easy, as family planning providers are familiar with conducting pelvic exams and are generally comfortable talking to women about sexual health.33 This setting may also be appropriate for the delivery of the HPV vaccine to adolescent girls who are not yet sexually active. During the same visit, they can receive information on the various risks of sex and learn how the HPV vaccine and family planning methods can reduce their risk.37

Treatment for cervical cancer can make it more difficult for a woman to conceive and carry a child, so it is important that providers inform women of this risk when discussing family planning options. In cultures where the pressure to bear children is high, this information may be especially salient.37

While this type of integration can drastically improve access for women using contraception, it will miss women who do not use family planning but are still sexually active and at risk, especially those who have reached menopause. In some contexts, the clientele at family planning clinics underrepresents the poor – there is a need to ensure that service delivery remains equitable.38
Barriers and Facilitating Factors to Treatment

THE “SEE-AND-TREAT” APPROACH

The WHO recommends a “see-and-treat” approach for developing countries, through which women with a positive screening result for pre-cancerous lesions are immediately treated, without receiving a diagnostic confirmation. Diagnosis through colposcopy is not a required step after screening, and in resource-limited settings, it is usually abandoned because it is expensive, requires expensive specialized equipment, and many providers are not trained in the procedure. As a result, colposcopy may only be available at certain facilities, and it can be inconvenient and costly for patients to travel to another location.

Diagnostic confirmation can take several weeks, creating a delay from when women receive their results and to when they are referred to treatment. A quick turnaround of test results is valuable to women who have limited time or access to health facilities, since they can promptly be referred to treatment during the same visit. If the time between screening and treatment grows, so does the risk of patients’ loss to follow-up.

Some practitioners worry that skipping diagnosis may result in overtreatment, but WHO insists that this risk must be weighed against that of failing to treat women who do need it. In some instances, colposcopy has demonstrated a sensitivity as low as 70%. If providers rely on those results, 30% of women who do need treatment may fail to receive a referral. The sensitivity of screening methods is high enough to warrant direct referral to treatment. Because cryotherapy, the prevailing treatment method, causes relatively little harm to healthy women, the benefit of treating all suspected cases outweighs the risks.

The see-and-treat approach is only appropriate for suspected pre-cancer – suspected or confirmed invasive cancer requires specialized surgery. Most facilities lack the equipment and trained surgeons to treat invasive cancer, so women are referred to hospitals or other higher-level facilities. The scarcity and greater cost of treatment for invasive cancer underlines the importance of early screening to detect abnormal cells before they progress.

TREATMENT METHODS

Treatment either destroys the pre-cancerous abnormal tissue by burning or freezing it, or removing it surgically. There are a number of variations on these techniques, but the most widely-available methods are described here.

Cryotherapy freezes abnormal tissues using pressurized nitrous oxide or carbon dioxide. It can be performed by any level of provider (with training), can be completed in 15 minutes, and does not require anesthesia or electricity. Complications from cryotherapy, such as severe bleeding or infection, are unlikely – the most common side effects are cramping, light bleeding, and watery discharge for several days after treatment. Some experts warn that if the temperature of the cryotherapy gases rises too high, the procedure may not effectively destroy abnormal cells. A 2013 meta-analysis of the effectiveness of cryotherapy found that cure rates of 80-90% were achieved through screen-and-treat approaches in low-income countries. The main challenge to cryotherapy is the supply of the consumable gases, which can be expensive and difficult to obtain in low-resource settings.

The loop electrosurgical excision procedure (LEEP) cuts and coagulates the lesion at the same time using a thin wire loop heated with electricity. The procedure takes as little as 30 minutes and requires local anesthesia and a reliable electricity source. Because of the increased risk of heavy bleeding, the provider must have advanced training and the procedure is usually limited to secondary-level facilities with the capacity to respond to complications.

Cold knife conization (CKC) cuts the lesion from the cervix. It takes at least one hour to perform and also carries a high risk of bleeding. Because it requires local or regional anesthesia and advanced surgical training, CKC is usually limited to hospital settings and may be inaccessible to many women in developing countries. In recent years, CKC has reduced in its popularity as compared to LEEP. The advantage of the LEEP and CKC methods is that they preserve a sample of the abnormal tissue, which can be taken for biopsy. During biopsy, the cells are examined under a microscope to diagnose or rule out cancer and determine the degree of abnormality of the lesions.

Cryotherapy and LEEP are recommended by the WHO, but cryotherapy is more commonly often in low-resource settings because of its relatively minimal equipment and training requirements.
Barriers to Treatment

Compared to screening, there are not many studies on the factors related to accessing cervical cancer treatment. The limited evidence suggests that barriers often arise on the supply side, such as equipment malfunction or stockout, unavailability of qualified providers, or unreliable sources of electricity or gas. Implementation of a see-and-treat approach is disrupted if the resources needed to treat are not available at the time of screening.

On the demand side, the same factors that influence a woman to seek screening services can affect her choices about treatment. Costs of the procedure or the need for another family member’s consent can deter her from receiving treatment during the same visit as her screening; on the other hand, the inconvenience of making another visit decreases her likelihood of following up. Negative experiences with the health system, including screening, can discourage women from seeking additional services. Some women may worry about the procedure itself, although cryotherapy is generally acceptable because of its minimal pain and few side effects.

After receiving a positive screening result, women’s fears and uncertainties may intensify. A qualitative study in Uganda found that witnessing cancer morbidity and mortality in the community caused some women to believe that a positive result (mistakenly understood as a cancer diagnosis) was a death sentence and that treatment would be futile. To alleviate fears, providers must counsel patients on what their results mean, clarify that treating abnormal lesions actually prevents cancer, and assure them that treatment is available. Findings from South Africa, Thailand, and India indicate that women also become less anxious about their results when they find out they can be treated immediately.

New Technologies

THERMAL (COLD) COAGULATION

Thermal coagulation, or cold coagulation, is a relatively new alternative to cryotherapy that uses a probe heated to 100°C to destroy abnormal pre-cancerous cells. Like cryotherapy, thermal coagulation can be performed without anesthesia, has minimal side effects, and it is equally effective. The procedure can be completed within one minute. Although thermal coagulators are initially more expensive than cryotherapy equipment, they become economical over time because they do not use consumable gas. Since they can run on batteries and do not need gas tanks, thermal coagulators are also portable, offering an advantage over cryotherapy for reaching women in remote areas.

CRYOPEN®

The CryoPen® Surgical System is a small, fine-tipped tool that uses an electrical cooling technology to freeze lesions on the cervix. CryoPen® eliminates women’s exposure to cryogenic gases, and like thermal coagulation, it is portable. Its interchangeable tips allow more accurate and efficient targeting of the abnormal tissues.

Research on the effectiveness of the technology and its adaptiveness to low-resource settings has just begun. In 2014, the NIH and National Cancer Institute funded a 5-year, $4 million grant to research the effectiveness of CryoPen® compared to the current standard of care in low- and middle-income countries. Meanwhile, PATH is comparing the performance of CryoPen® against cryotherapy and thermal coagulation, evaluating its feasibility and cost for providers, and analyzing markets for CryoPen® equipment.
HPV Vaccination

While screening and treatment offer secondary and tertiary means of prevention against cervical cancer, effort is mounting behind primary prevention through administration of the HPV vaccine. The vaccine is now recommended for young women, preferably before the onset of sexual activity.

As of August 2015, 84 countries spanning all regions had implemented national vaccination programs, while another 40 had introduced pilot programs. The national programs are concentrated in North and South America and Europe, and most of the pilot programs are taking place in Western Africa, Eastern Africa, and Southeast Asia and the Pacific. Due to the dual need to reach adolescent girls with the HPV vaccine while engaging women older than 35 in screening, it is a challenge to balance costs.

Donor support for vaccination, however, is strong, because many are more willing to invest in primary means of prevention and because the vaccine can, in most settings, be easily delivered through existing programs. The GAVI Alliance, WHO, PATH, and other partners are providing financial and technical assistance to developing countries to scale up campaigns and make the vaccines more accessible and affordable for girls.

Countries eligible for GAVI support must have demonstrated the ability to deliver other multi-dose vaccines to at least half of the target population. As of May 2015, 23 countries were approved for GAVI support, representing about 400,000 girls who would receive the vaccine. Three of those – Bhutan, Lesotho, and Rwanda – had introduced the vaccine on a national scale.

From 2006 to 2011, PATH conducted demonstration projects in four low- to middle-income countries—India, Peru, Uganda, and Vietnam. All four projects used school-based delivery strategies, but India also combined this with a health-center based strategy, and some districts in Vietnam used a health-center strategy alone.

An evaluation of the programs measured the level of HPV vaccination coverage achieved, defined as the percentage of households with eligible girls who had received all three doses of the vaccine. In the first year, coverage through the school programs reached 83% in Peru and Vietnam and 89% in Uganda. In India, coverage through the combination approach ranged from 77.2% to 87.8% depending on the type of geographical area. The highest coverage was achieved through the health center-based program in Vietnam, reaching 94% in the first year and 99% by the second. Preliminary evidence from demonstrations in other countries support the findings of those in Vietnam, Uganda, India, and Peru.

More than two-thirds of parents who participated in the PATH programs said they chose to vaccinate their daughters to protect against cervical cancer, to prevent disease in general, or because they believed that vaccines are beneficial to health. Many indicated that they were motivated by the recommendations of others and the low cost of the vaccine. Parents who did not or only partially vaccinated their children often cited a lack of awareness of the program and their daughter’s eligibility to participate. Some participants had concerns about the safety of the vaccine, but in general were not opposed to the idea of the vaccine.

Similarly, a systematic review of knowledge and acceptability of the HPV vaccine in sub-Saharan Africa indicates that people are willing to receive the vaccine but know little about HPV, cervical cancer, or how the vaccine works. Spreading awareness of HPV, the benefits of the vaccine, and where to access it screening can ensure sustained trust in the vaccine.

Future Directions for Research and Innovation

Presently, most of the evidence on cervical cancer screening and treatment draws from specific country experiences. While implementers should consider the unique service structures, human resource capacities, and barriers to service-seeking in their settings, more cross-cutting evidence is needed on effective ways of on increasing access to and uptake of screening. In the meantime, technological innovations, such as self-sampling swabs and portable equipment, are making screening and treatment procedures faster, cheaper, and farther-reaching, and the scale-up of the HPV vaccine promises to reduce the incidence of cervical cancer. The documentation of best practices for delivering cervical cancer services will inform the design of future programs that will achieve results.


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