Governing Council

ISSUE BRIEF

New Options for Cervical Cancer Screening and Treatment in Low-Resource Settings

Introduction

Cervical cancer kills 270,000 women each year — mainly women in the developing world and in the prime of their productive lives. Yet cervical cancer is preventable by screening asymptomatic women for precancerous cervical lesions and treating the lesions before they progress to invasive disease. In other words, those deaths are largely preventable. Studies suggest that even if a woman were screened for cervical cancer only once in her lifetime between the ages of 30 and 40, her risk of cancer would be reduced by 25-36%.[1]

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In developed countries, screening programs are in place to spot the signs of precancer and treat it early. These programs are generally built on a multi-visit, cytology-based screening approach — Pap smears followed by colposcopy and biopsy where indicated. Such programs require a high degree of organization and management, including actively inviting women who are at risk of the disease to be screened, ensuring the quality of testing and treatment and rigorously monitoring follow-up and care. In developing countries, on the other hand, such screening and treatment services generally are not available or accessible. And where they are available, the programs may be ineffective due to training, quality control or logistical challenges.[2,3]

This brief summarizes the current evidence on various options, namely cervical cytology (Pap test), HPV (human papillomavirus) DNA testing and visual

inspection with acetic acid (VIA) for screening, and cryotherapy for treatment, with a focus on approaches appropriate for low-resource settings.

Cervical screening and treatment: Still a priority in the age of vaccines

New vaccines are available to prevent infection by the HPV types most associated with cervical cancer deaths worldwide. These prophylactic vaccines represent a life-saving development — in particular for girls who have not yet been exposed to the virus through sexual activity.

But screening and treatment of precancer is still the best hope for the millions of women already infected with cancer-causing HPV — the vaccine will not help if infection is present. Research by the Alliance for Cervical Cancer Prevention (ACCP) has shown that in most situations, screening women at least once in their lives, between ages 30 and 40, results in the greatest health impact and cost-effectiveness.[4,5,6] Once high coverage is achieved for these women, and as additional resources become available, programs may consider extending their services to screen women over 40 years as well.

A comprehensive approach to cervical cancer prevention that includes screening, precancer treatment, and HPV vaccination could reduce developing country cervical cancer deaths to the very low levels currently observed in many industrialized countries.[7,8] As Sarah Nyombi, Uganda Member of Parliament, wrote in an article on International Women's Day 2008, "Every woman in the world has the right to prevention. Given the tools that are available, even one cervical cancer death is too many."[9]

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Challenges of using cytology-based screening (Pap) in low-resource settings

Papanicolaou (Pap) testing has resulted in dramatically lowered cervical cancer rates when the test is repeated every few years. But most developing countries lack the resources, infrastructure and trained personnel needed to implement such programs. Effective screening programs require high coverage of women at risk, quality screening tests, and effective follow-up and treatment. These often are challenging to achieve with a cytology-based program because Pap tests require a doctor or nurse to collect a cervical cell sample, a cytotechnician to process and interpret the sample, and a pathologist to confirm positive results. And like other screening strategies, Pap programs also need systems for active recruitment of women, monitoring the quality of test results, and ensuring that all women with abnormal results receive appropriate treatment.

One of the limitations of Pap is the subjective nature of the test — it is dependent on individual interpretation. Additionally, due to the observed low sensitivity (the ability of the test to correctly identify positive cases) of cytology, frequent re-screening every one, three or five years is key to the effectiveness of Pap programs. This further increases the costs and challenges for developing countries.

Cytology can be burdensome for patients. A woman must generally make three or more separate clinic visits, first to be tested; then to learn the results; and where

applicable, to receive further testing, diagnosis, or treatment. Even in countries where such services are available, some women face challenges related to transport, clinic hours, expenses and child care demands. In low-resource settings the time and cost involved with multiple visits, combined with low levels of awareness of the benefits of screening and other cultural issues, can represent major barriers to accessing preventive health services in the post-reproductive years.

New alternatives for screening and treatment of precancer

Fortunately there are alternatives to Pap screening and the evidence base for such strategies has expanded significantly in recent years, thanks to researchers working in Africa, Asia and Latin America. Their studies have assessed visual inspection strategies and HPV DNA testing for screening, along with cryotherapy for treatment of precancerous lesions.

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Visual inspection with acetic acid (VIA)

Visual inspection of the cervix, using acetic acid or Lugol's iodine to highlight precancerous lesions so they can be viewed with the "naked eye", shifts the identification of precancer from the laboratory to the clinic. Such procedures eliminate the need for laboratories and transport of specimens, require very little equipment and provide women with immediate test results. A range of medical professionals — doctors, nurses, or professional midwives — can effectively perform the procedure, provided they receive adequate training and supervision. As a screening test, VIA performs equal to or better than cervical cytology in accurately identifying precancerous lesions. This has been demonstrated in various studies where trained physicians and mid-level providers correctly identified between 45% and 79% of women at high risk of developing cervical cancer.[10,11,12,13,14,15] By comparison, the sensitivity of cytology has been shown to be between 47 and 62%.[16] It should be noted, however, that cytology provides higher specificity (the ability of the test to correctly identify negative cases) than VIA. Like cytology, one of the limitations of VIA is that results are highly dependent on the accuracy of an individual's interpretation. This means that initial training and on-going quality control are of paramount importance.

VIA can offer significant advantages over Pap in low-resource settings, particularly in terms of increased screening coverage, improved follow up care and overall program quality. Due to the need for fewer specialized personnel and less infrastructure, training, and equipment, with VIA public health systems can offer cervical cancer screening in more remote (and less equipped) health care settings and can achieve higher coverage. Furthermore, providers can share the results of VIA with patients immediately, making it possible to screen and treat women during the same visit. This helps ensure that follow up care can be provided on the spot and reduces the number of women who may miss out on treatment because they are not able to return to the clinic at another time. In a "screen and treat" project in Peru, for example, only 9% of women who screened positive failed to receive treatment in the single-visit approach, compared with 44% of women who were lost to treatment using a multi-visit model.[3,17]

VIA has successfully been paired with cryotherapy, a relatively simple and inexpensive method of treating cervical lesions that can be performed by primary care physicians and mid-level providers (see below).

HPV DNA testing

Current HPV DNA tests detect the presence of cancer-causing HPV types in cervical or vaginal cells, indicating whether a woman is currently infected. Most HPV infections clear spontaneously and do not lead to cervical cancer — these are most common among women in their teens and 20s. But when cancer-causing HPV is found in women aged 30 or older, there is a good chance that the virus has persisted in their systems; these women are considered to be at high risk of current or future cervical cancer. In order to focus precious health system resources and provider time where it will have the greatest impact, HPV DNA testing often is recommended for use in women aged 30 years and older. Those who test positive subsequently are assessed for precancerous lesions or cancer, and are treated as indicated.

For HPV testing, cervical or vaginal samples are collected by a trained provider. In some cases the woman herself can collect a vaginal sample. Vaginal self-sampling has been proven acceptable to women in many settings, can be performed at home or in a clinic, and does not require use of a speculum.[14,16,18,19,20] Cervical or vaginal samples can be stored in a preservative solution if necessary, then transported to a laboratory for processing by trained personnel.

HPV DNA testing is the most sensitive screening exam — most studies have found that HPV DNA tests are between 66 and 95% sensitive in identifying women who have abnormal precancerous lesions.[10,16,19] Unlike Pap smears and VIA, HPV DNA results are processed by a machine and are not susceptible to differences in human interpretation.

Management options vary for women who test positive for HPV. In low-resource settings where colposcopy and biopsy may not be available, performing VIA after a positive HPV test can help determine if precancerous lesions are present on the cervix and if cryotherapy treatment is appropriate (see below). In some settings, even if the woman does not have a visibly obvious lesion, cryotherapy has been performed on the entire cervical transformation zone (where lesions are most likely to appear), especially if the woman is unlikely to return for follow-up care.[20] If the affected cervical cancer area is too large or inaccessible for cryotherapy or appears to be cancerous, a woman may need to be referred for alternative treatment methods such as the loop electrosurgical excision procedure (LEEP) or cold knife conization.

Large studies have found that HPV testing was more effective than either VIA or Pap at reducing women's long-term risk of cervical cancer and on their overall mortality.[20,21,22] Unfortunately, there are disadvantages to using the current HPV test in low-resource settings — these are addressed in detail below.

Cryotherapy

Cryotherapy, or freezing cervical tissue that is likely to develop into cancer, can be used to treat precancer among women who have been screened using Pap, VIA or HPV DNA testing. The procedure does not require electricity, and is both cheaper and technically simpler than other treatment options.

Cryotherapy has been proven effective and safe in multiple studies and can be done either in a single-visit approach or at a convenient referral site. A systematic literature review, including 32 studies of cryotherapy effectiveness, found an overall cure rate of 89.5% for all grades of cervical intraepithelial neoplasia (CIN) after one cryotherapy treatment at 12 months post-treatment. [23] More recent studies of

cryotherapy following VIA or HPV DNA testing have achieved similar results. A project in Peru reported cure rates over 90% for CIN 1 and 2 and 70% for CIN 3 within three years of cryotherapy treatment[24] and a study in South Africa found cure rates of over 90%. A separate study in India found similar cure rates even when nurses, rather than physicians, provided cryotherapy in field clinics.[25]

Regarding safety, the 2003 systematic review and a 2009 updated review suggest that major complications, such as severe bleeding and Pelvic Inflammatory Disease (PID), are very unlikely events following cryotherapy and occur less often than after LEEP or laser ablation treatment.[23,26] For example among almost 950 women in South Africa who received cryotherapy treatment after a positive HPV DNA or VIA test, only one serious adverse event occurred (a woman who refused hospital treatment for cervical bleeding).[20] Efforts are needed to ensure that adequate numbers of effective, affordable cryotherapy units are accessible to cervical cancer prevention programs worldwide.[27]

Looking ahead: A new, rapid, low-cost HPV DNA test

Although highly effective, the current HPV test was not designed for use in low-resource settings: it requires a laboratory, sophisticated equipment, refrigeration, and trained technicians usually found only in well-resourced, urban settings. In addition, the test takes at least 4.5 hours to run, meaning that a single-visit approach would not be feasible.

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A simple, accurate, affordable, rapid, and acceptable HPV test would have great potential to reduce cervical cancer in the developing world and could be cost-effective in low-resource settings.[3] PATH launched the START and START-UP projects with the goal of developing two different molecular screening methods appropriate for low-resource settings.

The first test, "*care*HPV," is based on the current HPV test technology. *Care*HPV will be simpler to perform, portable, and will allow for field interpretation of results within 2.5 hours. The test will be available at a preferential price for public sector and non-profit organizations of developing countries. The first field evaluation of *care*HPV, among 2500 rural women aged 30 to 54 years in Shanxi, China, found that the new test's accuracy is much superior to VIA and approaches that of the current, laboratory test.[28] Given these results, new projects in Uganda, India and Nicaragua are assessing use of the test by local health providers. It is expected that *care*HPV will be made commercially available in 2011 or 2012, after it is registered in China, the country of manufacture. In addition, an application has been made to pre-qualify the HPV tests with the World Health Organization (WHO). If approved, *care*HPV could be available for bulk purchasing by WHO and other UN agencies, reducing prices and permitting wider access to the technology.

Another new test manufactured by Arbor Vita Corporation focuses not on HPV DNA but on the E6 biomarker, a viral protein that appears during precancer stages. The advantage of this test is that a provider can differentiate between women who simply have HPV infection (which might spontaneously clear) and those who have begun to develop neoplastic, precancerous cells.[29,30,31,32,33] The E6 technology is still in development.

In the coming years, these and other tests could bring high-sensitivity cervical cancer screening to low-resource settings.

Implications for programs

Each of the available screening methods — cytology, VIA, or HPV testing — has its own strengths and limitations. The critical issue for screening programs is to select the test that is most appropriate for their situation, and which can help their programs achieve high screening coverage, high quality testing and reliable follow-up care for women.

The success of VIA, HPV testing, and cryotherapy in field settings signals new potential for cervical cancer control in places where cytology programs have not been effective. Single-visit approaches using VIA to screen can be offered now, and single-visit approaches using HPV tests for primary screening and VIA for treatment triage may be possible in many low- to medium-resource settings in the near future.

How these new approaches are programmed will depend on a number of factors, including the resources and health care infrastructure in a country. For example, an industrialized nation with sufficient budget and a strong health system could use either cytology or HPV testing to screen adult women, confirm diagnosis with colposcopy and biopsy, and then treat appropriately. A country with fewer resources might consider introducing VIA and same-visit treatment; or, if more resources are available, HPV testing. In the future, a test using new molecular tests such as E6 might become a good choice for a very low-resource country, as it would enable prioritization of women at highest risk of future cancer.

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Once HPV vaccination becomes routine and more sensitive screening tests are in widespread use, it is likely that the screening strategies common today (such as Pap smears repeated every few years) will be revised. One proposed scenario is to vaccinate prior to sexual debut, then screen only a few times when the woman is in her 30s and 40s, using HPV testing (or other future, biomarker tests).[34] Such a strategy would be feasible in low-resource settings and also would save considerable expense in wealthier countries.

A question for the future is what will happen when the current generation of newly vaccinated girls reaches the appropriate age for screening. Epidemiologists have raised concerns that HPV vaccination will negatively impact Pap-based screening programs. According to this theory, as cervical lesions become less prevalent, technicians will become less familiar with interpreting cytology and the ability of Pap to predict future cancer may decrease.[35,36] In this sense, the clear and objective results of the new HPV DNA or biomarker tests will provide an additional advantage. More generally, the principles of public health screening will help to determine how resources should be allocated in future years, taking into consideration factors such as vaccine coverage and cervical cancer prevalence.

Ministries of Health in the developing world have struggled for decades to initiate and maintain cervical screening using cytology, but by and large their efforts have not been sustainable. With the advent of HPV vaccines, it is possible that decision-makers may perceive vaccination to be a simpler, more straightforward focus for their cervical cancer prevention efforts. But only a comprehensive program —

offering both vaccination of young adolescent girls and screening of adult women — can quickly reduce mortality rates to those seen in wealthier countries. To avoid unnecessarily limiting choices, it is crucial that decision-makers learn that new options — including VIA and HPV testing, coupled with cryotherapy for treatment of most precancers — offer hope that the vision of "every woman screened at least once in her lifetime" soon could become reality.

Cervical Cancer Action

Cervical Cancer Action: A Global Coalition to Stop Cervical Cancer (CCA) was founded in 2007 to expedite the global availability, affordability, and accessibility of new and improved cervical cancer prevention technologies to women in developing countries.

For more information:
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