Have Current Global Methods in Cervical Screening Gone Far Enough?

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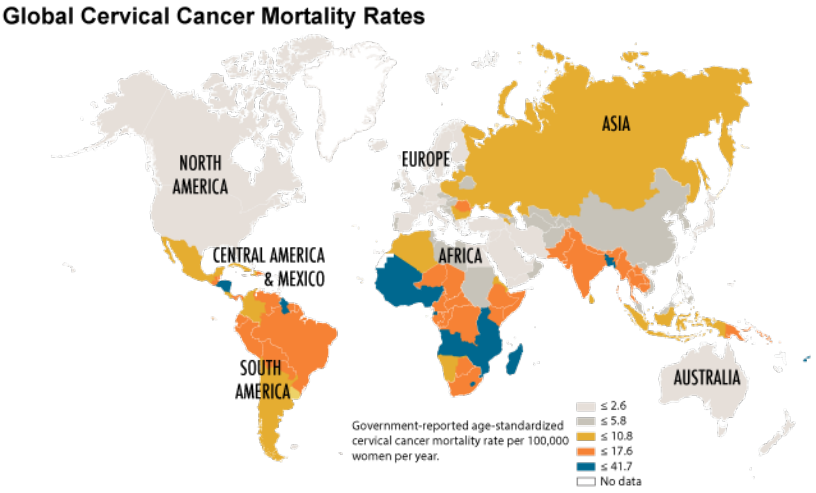
Abstract

Although widespread cervical cancer screening has dramatically reduced the death rates from the disease for women in the developed world, deaths from this scourge remain stubbornly high in developing nations. All too many women still fail to receive screening, primarily due to high costs and lack of access. This paper examines the tests and methods currently used to screen for and prevent cervical disease—the Pap Smear, Liquid-Based Cytology, HPV Screening and the HPV Vaccine. It explores why current screening tests and the HPV vaccine are inadequate for minimizing deaths from cervical cancer in the developing world—and what must be improved to save more lives in developing and developed nations alike.

Too Many Women Continue to Die from Cervical Cancer

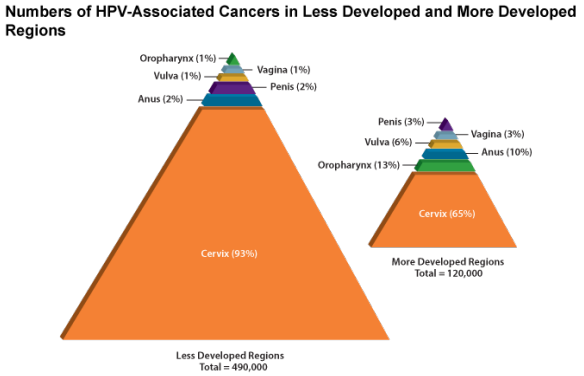
Cervical cancer is a leading cause of death for women in many developing regions of the world. More than 530,000 cases of cervical cancer are diagnosed each year and 311,000 women die. The vast majority (84 percent) of these deaths occur in the developing world[1].



Modified from: Crow, JM. HPV: the global burden. Nature. 2012;488:S2-3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22932437. Data from: World Health Organization, Institut Catala d'Oncologia. Human papillomavirus and related cancers: summary report update. Barcelona (ES): WHO/ICO; 2010 Nov 15.

[1] World Health Organization https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

As with many other cancers, the key to surviving cervical cancer is early detection and appropriate treatment. Widespread screening has reduced death from cervical cancer by 70 percent in the developed world[2], but women in developing nations continue to die in large numbers because they do not get screened. A survey of cervical cancer screening in 57 developing countries found that on average, only 19 percent of women were being screened versus 63 percent in developed countries. As a dramatic example of this dichotomy, the screening rate ranged from one percent in Bangladesh to 73 percent in Brazil[3].



Source: de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22575588

Many factors limit screening rates in the developing world. These include poverty, confidentiality concerns, religious beliefs, an acute shortage of cervical cancer testing and prevention services, inefficient transportation, lack of funds to send slides for interpretation, and limited means of communicating results.

Despite the far greater practice of screening in the developed world, more needs to be done there as well. The United States continues to see 13,000 new cases of cervical cancer with a death rate of 4,250/year[4]. Women still die in the developed countries because of high screening costs, limitations in the tests themselves and unfortunately, inconvenience and anxiety related to the Pap procedure.

New screening strategies are necessary to address the practical and cost issues that impede testing in developing and developed countries alike.

Existing Solutions are Inadequate

Cervical cancer progression takes place slowly. On average, the progression of a premalignant lesion to fully developed cancer takes more than a decade. Cervical cancer screening identifies disease when it is most treatable--before it becomes cancer.

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[2] Cancer statistics, 1999.Landis SH, Murray T, Bolden S, Wingo PA, CA Cancer J Clin. 1999 Jan-Feb; 49(1):8-31, 1.

[3] Gakidou, Emmanuela; Nordhagen, Stella, and Obermeyer, Shad Coverage of Cervical Cancer Screening in 57 Countries: Low Average Levels and Large Inequities 2008 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2429949/

[4] American Cancer Society Estimates https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html

Over the last 70 years, several screening methods (Pap Smear, the Liquid-Based Cytology Pap Test, and HPV Screening) have been developed and brought into widespread clinical deployment. All Pap tests identify abnormal cells in the cervical sample but because Pap tests are microscopic exams, they are subjective. Such subjectivity can lead to higher rates of false positive test results and thus, unnecessary colposcopies with their inherent complications. Even worse are false negative test results, which might result in a missed diagnosis of clinically low risk findings such as atypical squamous cells of undetermined significance (ASCUS) or of high grade squamous intraepithelial lesion (HSIL) that are much more likely to progress to cancer. Adopted over the last several years, the HPV screen has proven to be an excellent "negative prognosticator" but has clinical limitations because it only identifies the presence of the HPV virus, not disease.

The HPV vaccine is FDA approved for women up to the age of 45 but is most effective in non-sexually active females from 9 to 26 years of age. Sexually active women must still be screened for the presence of HPV or cervical disease prior to vaccine administration, with all of the attendant screening limitations. Completion rates are also low since the vaccine requires repeat injections and many women fail to show up for later doses.

Overall, as the following discussion will reveal, these existing solutions are impractical in the developing world (and underutilized in developed nations) due to high system costs, skilled operator costs and practical limitations.

Pap Testing

Two methods exist today for performing a Pap Test – A Pap Smear and a Pap Test using Liquid-Based Cytology.

Direct Smear on a Slide

Introduced in the 1940s, the Pap Smear was the first test developed to screen for cervical cancer or pre-cancerous conditions. The microscopic examination of cervical cells has remained the "gold standard" for cervical cancer screening ever since.

With the conventional Pap Smear test, a clinician collects the cervical cell sample by gently scraping the opening of the cervix with a cervical brush, spatula or both with the help of a speculum and then "smears" the sample on a microscope slide, fixes and then stains the sample on the slide. The slide is then sent to the lab where a cytologist reviews and grades the slide, then sends it to the pathologist, an MD, for final review. These visual examinations look for any abnormalities that could signal presence of the disease.

However, direct smear slide preparation is inconsistent, and this method can result in problems related to sample contamination by blood, debris, mucous, or three-dimensional groups of cells that can obstruct the view of hidden, diseased cells. Cervical cytology also requires significant time to prepare and interpret slides by multiple trained professionals adding to the time and expense necessary to complete. All of these factors can prevent accurate determination and result in low sensitivity rates.

Liquid-Based Cytology

Over the last 20 years, roughly 90 percent of laboratories in the United States have adopted the liquid-based cytology (LBC) process[5]. Once the cervical sample has been collected as described above, it is rinsed into a vial of liquid preservative and sent to the lab. In the laboratory, automated equipment processes the liquid sample, eliminating most of the blood and mucous, and prepares a single-cell layer slide. The result is a cleaner slide for the cytologist to read than when the sample is directly smeared on a slide.

However, like the direct "smear" method, interpretation remains subjective, based on the cytotechnologist's or pathologist's assessment of morphologic features to ascertain the presence of disease. Costs are high since LBC systems and slide readers are expensive equipment which must be run and interpreted by highly trained cytologists and pathologists.

Regardless of whether the Pap test is performed by preparing direct smears or using LBC, Pap tests have the following disadvantages:

- **High cost.** Pap tests are expensive.
- **Lack of clinical resources.** The process is time and laboratory intensive. It also requires highly trained personnel, such as pathologists and cytotechnologists, that are not readily available in developing areas.
- **Subjective and inaccurate.** While LBC Pap methods have enhanced visual screening, interpretation relies on microscopic observation of abnormal epithelial cells identified in collected cervical specimens. Because this process is highly subjective, it can be inaccurate. Low test sensitivity and specificity contribute to a high number of false positives that may submit patients to unnecessary treatments that add to costs and false negative test results that fail to identify the presence of cervical lesions.

HPV Screening

Advances in the understanding of how cervical cancer develops have led to additional approaches for cervical cancer screening.

With rare exceptions, most cervical cancers result from persistent HPV infections that progress to premalignant high grade squamous intraepithelial lesions (HSILs) and ultimately, to cervical cancer. Currently, researchers have identified more than 100 HPV virus strains, including approximately 40 that infect the reproductive tract, of which, 14 are high-risk. Persistent infections with high-risk strains of HPV (types 16 and 18) cause 70 percent of all cervical cancers.[6]

First introduced in 1999 and used as a reflex test since 2014, the HPV test was approved as a primary screening tool in 2018. HPV tests typically use nucleic acid-based molecular technology to identify infection with high-risk types of HPV.

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[5] Gibb, Randall K and Martens, Mark G. The Impact of Liquid-Based Cytology in Decreasing the Incidence of Cervical Cancer 2011 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3101960/

[6] World Health Organization https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

These tests improve on the Pap test because they are objective negative indicators. They can tell with a high degree of certainty that a woman does not have particular high-risk types of HPV (16, 18, 45). Since these strains cause cervical cancer, if a woman does not have them, she is highly unlikely to have the disease.

Limitations of the HPV test

The key disadvantage of the HPV test is that when a woman receives a positive result, the HPV test provides no information about the presence of tissue changes or disease state.

Virtually all cervical cancers are caused by HPV infection, but only a very small number of women who have HPV will develop cervical cancer. Women's immune systems clear most HPV infections spontaneously within one or two years.

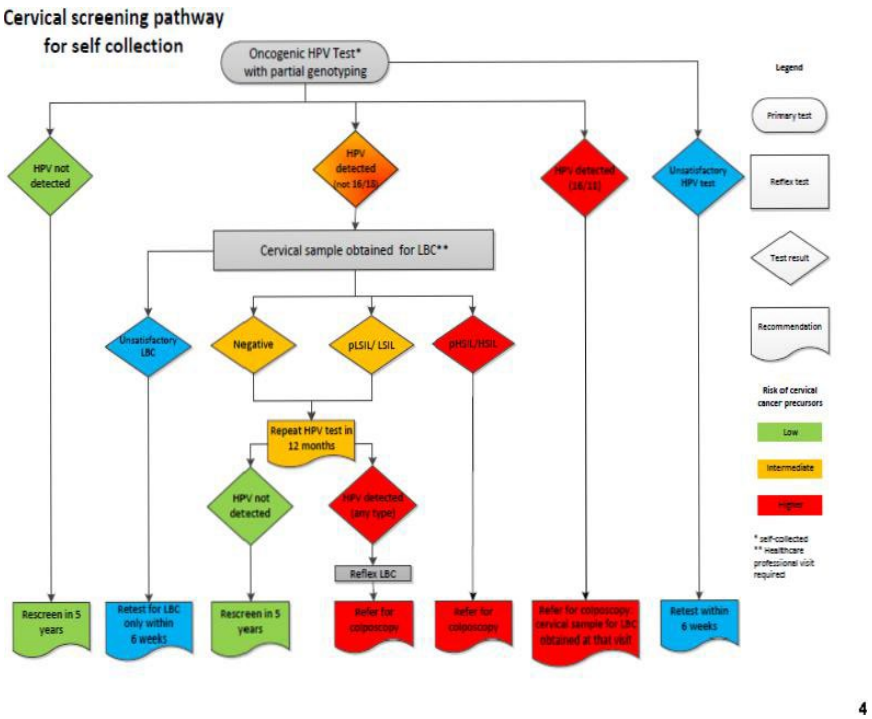
In the U.S., approximately 79 million individuals currently have HPV infections and about 14 million new infections arise each year.[7] Yet, the US has only 13,170[8] cases of cervical cancer each year. Thus, only about 1.6 in 10,000 women with HPV infection actually get cervical cancer. Prevalence of HPV infection varies regionally with a higher prevalence in less developed countries than in developed countries.[9]

While the rate of cervical cancer is much lower than the incidence of HPV infection, in some cases, the virus integrates into the genome of the patient's cervical cells. This leads to significant changes in viral and host cell protein production and ultimately, to the development of premalignant cervical lesions. Such progression is more common in women from developing countries whose immune systems may be compromised by other diseases, such as HIV or tuberculosis, or by specific genomic differences[10].

Therefore, if the patient receives a positive HPV test result, additional testing is indicated to more accurately understand disease status and future risk. The clinician will perform a reflex Pap test and / or an exam such as colposcopy, a visual examination of the cervix under magnification, to determine whether disease exists.

For example, this "triage" flow chart is used in Australia to direct patients receiving an HPV positive finding:

[7] Centers for Disease Control and Prevention https://www.cdc.gov/std/hpv/stdfact-hpv.htm
[8] https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html
[9] Bosch FX, de Sanjose S, Serrano B, et al. Human papillomavirus (HPV) and ´ related cancers in the global alliance for vaccines and immunization (GAVI) countries: a WHO/ICO HPV Information Centre Report Preface. Vaccine. 2012; 30(suppl 4).
[10] World Health Organization https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer



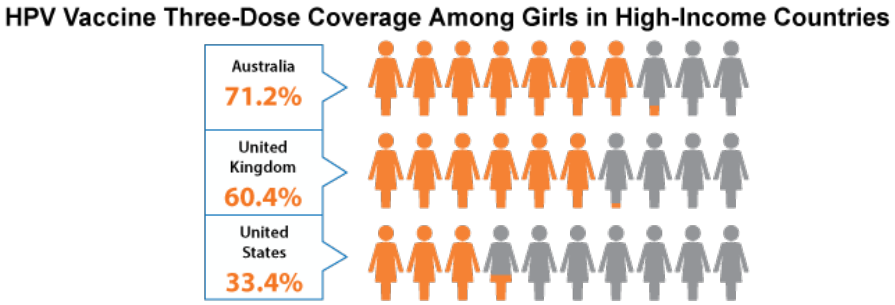
National Cervical Screening Program, Department of Health, Australia, July 2016

This follow up process can cause unnecessary anxiety for the woman. It is also very resource intensive, requiring expensive laboratory equipment, which combined with the demands for HPV screening such as thermocyclers and trained personnel, escalates costs and infrastructure needs. Many regions of the world simply do not have the necessary infrastructure/labs/pathologists to support such practices. Even when the infrastructure is available, as in developed countries, the follow up process adds significant costs that many women can't afford. Follow up exams can also be subjective. The pathologist might find abnormal cells and be unable to rule out HSIL or disease. This means women can be overtreated, further increasing costs.

The upshot: when clinicians use HPV as a frontline screen for women with a high-risk strain of HPV, the incidence of false positives for the presence of clinically significant disease is very high. Clinicians need additional filters that can accurately detect the presence of disease to limit the number of women who must go on to the next step in order to reduce unnecessary treatment and costs.

HPV Vaccine

In the developed world, women are increasingly turning to the HPV vaccine (e.g. Gardasil) to protect against HPV infection. The HPV vaccine prevents not only cervical cancer, but also other types of illnesses that come from HPV exposure, such as penile cancer in men, anal cancer, and throat cancer.



Centers for Disease Control and Prevention. Human papillomavirus vaccination coverage among adolescent girls, 2007-2012, and post licensure vaccine safety monitoring, 2006-2013—United States. MMWR. 2013;62(29):591-5.

However, the developing world faces several roadblocks to adopting the HPV vaccine. For starters, the HPV vaccine can only be given to women who are not already infected with the HPV virus. Unless children are inoculated before they become sexually active, clinicians must first perform HPV screening, with all its attendant downsides. Additionally, the vaccine requires not one, but multiple injections, yet a high percentage of women don't come back for subsequent injections. Most important, the HPV vaccine is generally not available in regions of the world where women are dying. Thus, the HPV vaccine will likely take many years to become widespread around the world.

The Need for a Solution

Available screening methods most certainly save lives. But they do not go far enough, particularly in the developing world.

Because Pap Smears rely on human experts to determine the presence of the disease, interpretation is subjective, resulting in false negatives and false positives. The need for interpretation by highly trained professionals also leads to unaffordable costs for women in the developing world, and even for many in developed nations. Highly skilled clinicians also may be difficult to find in many parts of the world.

Attempts to automate pap-smear characterization have led to the development of computer-assisted diagnosis tools and algorithms; however, they require expensive equipment that is not cost effective for low resource settings and display considerable weakness in cell characterizations resulting in low accuracy.[11]

While HPV tests objectively indicate when a woman does not have cervical disease, they say nothing about whether the women has progressed from the simple presence of the virus to either pre-cancerous lesions or cervical cancer. This means that the many women who test positive for HPV will require costly and subjective follow up.

For women in developed nations, the HPV vaccine still requires screening and all the attendant downsides that come with it. And many women fail to show up for the follow-on required injections, limiting the vaccine's effectiveness.

[11] William W, Ware A, Basaza-Ejiri AH, Obungoloch J. A review of image analysis and machine learning techniques for automated cervical cancer screening from pap-smear images. Comput Methods Programs Biomed. 2018 164: 15-22.

What's needed is a solution that will address the deficiencies of existing methods of cervical cancer screening and prevention. Such a solution should:

- Provide an objective measure that tells clinicians definitively when the disease is present to eliminate the uncertainty of subjective measures, allowing less highly trained personnel to successfully perform tests in areas with limited access to cytologists and pathologists.
- Lower costs by reducing the need for highly trained professionals to read slides and perform follow up examinations, such as colposcopy, and by eliminating unnecessary treatments for false positives.
- Ensure that cervical sampling methods effectively address both developed and emerging world sample collection issues
- Empower women to perform screening tests in a more convenient manner to remove barriers associated with poor transportation and communication infrastructure.

Only when all these conditions are met can screening be successfully brought to underserved women to save countless lives in developing and developed nations alike.

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