

# Cervical Cancer Screening in Low- and Middle-Income Countries

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## OUTLINE

### METHODS

CYTOLOGY, VISUAL INSPECTION WITH ACETIC ACID, AND HUMAN PAPILLOMAVIRUS DNA: TEST CHARACTERISTICS IN LOW-RESOURCE SETTINGS

### PAP SMEAR SCREENING

### SCREENING BY

VISUAL INSPECTION WITH ACETIC ACID

### HUMAN PAPILLOMAVIRUS DNA TESTING

### HUMAN PAPILLOMAVIRUS VACCINE

### CONCLUSION

## ABSTRACT

Cervical cancer is a leading cause of death among women in the developing world. Conventional cytology-based cervical cancer screening programs have been largely ineffectual at reducing the cervical cancer burden in low-resource settings. In response, alternative strategies have been tested, such as visual inspection with acetic acid (VIA) screening and human papillomavirus (HPV) DNA-based testing. This manuscript reviews literature addressing the programmatic approaches to implementing cervical cancer screening programs in low-resource settings, highlighting the

challenges, barriers, and successes related to the use of cytology, VIA, and HPV-DNA based screening programs. *Mt Sinai J Med* 78:319–326, 2011. © 2011 Mount Sinai School of Medicine

**Key Words:** cervical cancer screening, cytology, HPV testing, low-resource settings, Pap test, visual inspection with acetic acid.

Cervical cancer incidence and mortality has been reduced by as much as 80% in the developed world through the widespread use of well-organized cytology programs.<sup>1</sup> For example, cervical cancer incidence has declined from 14.2 per 100,000 to 2.4 per 100,000 in the United States since 1974.<sup>2</sup> A similar decline has not occurred in low- and middle-income countries (LMICs). In fact, >80% of the estimated 500,000 new cases and 275,000 deaths due to cervical cancer each year occur in the developing world (Figure 1), of which roughly 31,400 occur in Latin America, 53,000 in Africa, and 159,800 in Asia (Figure 2).<sup>2</sup>

Over the past decade, nonprofit organizations and ministries of health have made cervical cancer prevention a public health priority. Such efforts have led to the implementation of cytology (Pap smear) and visual inspection with acetic acid (VIA) programs. Recently, some countries have started utilizing human papillomavirus (HPV) testing on a national level.<sup>3</sup> This review explores cervical cancer screening in LMICs, highlighting programmatic successes, limitations, and future advances toward the decline in incidence and mortality of cervical cancer across the globe.

## METHODS

A review of the literature on the screening modalities for cervical cancer in low-resource settings was conducted. Inclusion criteria included manuscripts that

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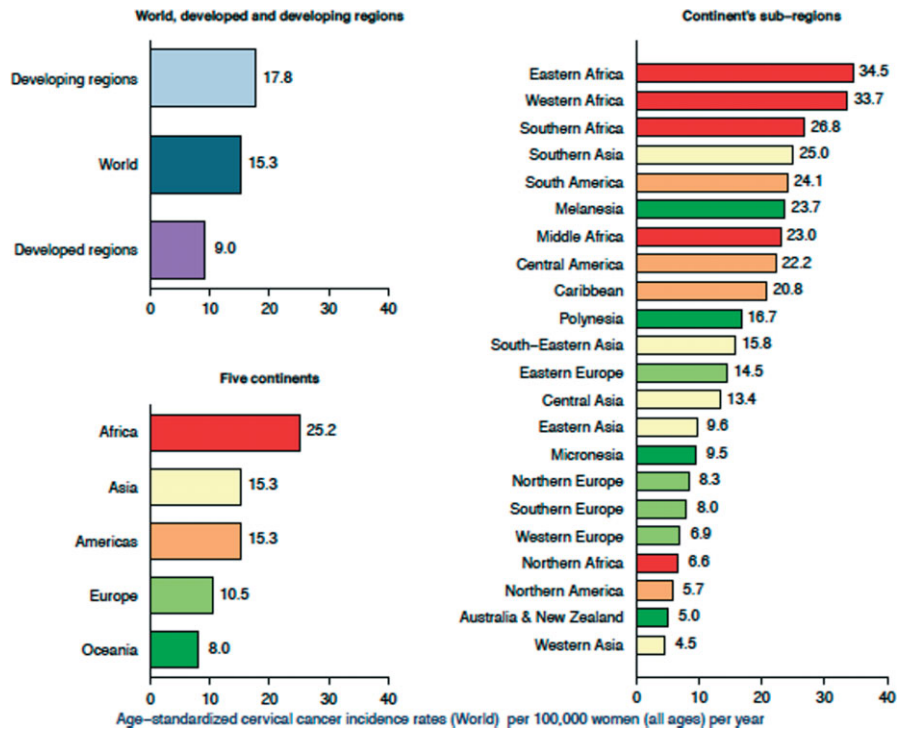


Fig 1. World age-standardized incidence rates of cervical cancer. Numbers indicate cases per 100,000 women. Data are from the International Agency for Research on Cancer, GLOBOCAN 2008.

discussed programmatic approaches to implementing cervical cancer screening in low-resource settings published after 2000 using either cytology, VIA, or HPV testing for cervical cancer screening. General articles on cervical cancer screening that did not include a programmatic implementation component were excluded. We have included meta-analyses, randomized controlled trials, and pilot studies describing regional and country-wide intervention and educational programs. Additional papers have been cited to provide general background information.

### CYTOLOGY, VISUAL INSPECTION WITH ACETIC ACID, AND HUMAN PAPILLOMAVIRUS DNA: TEST CHARACTERISTICS IN LOW-RESOURCE SETTINGS

In 2008, the largest cross-sectional comparison evaluating the screening performance of 5 screening methods (VIA, VILI [visual inspection with Lugol's iodine], VIAM [visual inspection with acetic acid

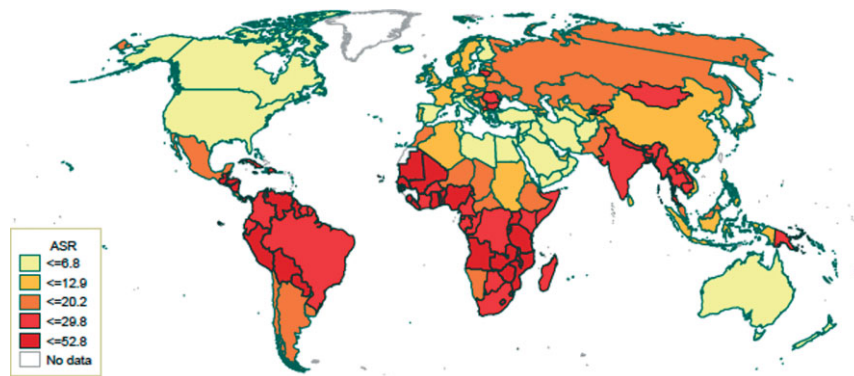


Fig 2. World age-standardized incidence rates of cervical cancer by region. Numbers indicate cases per 100,000 women. Data are from the International Agency for Research on Cancer, GLOBOCAN 2008. **Abbreviations:** ASR, age-standardized rate.

magnified], cytology, and HPV-DNA testing) in low-resource settings was conducted at 11 study sites.<sup>4</sup> In these studies, >58,000 women aged 25–64 years were tested with  $\geq 2$  of the 5 screening tests. All women underwent colposcopy, and the outcome measured was presence or absence of cervical interepithelial neoplasia (CIN). Abnormal colposcopy results received colposcopic biopsies. This large cohort provides the best measure of sensitivity and specificity for the screening tests in low-resource settings.

For the detection of CIN2+, cytology screening exhibited a sensitivity of 57% and a specificity of 93%. Visual inspection with acetic acid had a sensitivity of 79% and a specificity of 85%. Human papillomavirus testing (hybrid capture 2-assay) had a sensitivity of 62% and a specificity of 94%. These numbers likely provide a realistic average of test outcomes for actual use in low-resource settings.

## PAP SMEAR SCREENING

A conventional Pap smear uses a brush and a spatula to remove epithelial cells from the cervix. These cells are then placed on a slide, fixed, and read by a cytotechnologist or pathologist. Women with abnormal results are referred to further testing with colposcopy and directed biopsies, repeat Pap smear, or HPV DNA testing.

Whereas serial cytology screening has significantly reduced cervical cancer incidence and mortality in the developed world, most developing countries do not have adequate infrastructure (national policies, monitoring systems for program performance, national census, quality-assurance structures) to build sustainable programs. Cytology programs require  $\geq 3$  visits before treatment is administered (cytology/colposcopy/treatment), and

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at each step there must be access to supplies, trained providers, reliable transportation of specimens, high-quality laboratories, and a quality-control system.<sup>5</sup> Women must attend each follow-up appointment, which may require extensive travel and time away from their home and family. Due to these requirements, there have been few examples of successful programs in LMICs, and national programs tend to serve only a small portion of the at-risk population.<sup>6</sup>

Chile is one example of a middle-income country that has successfully implemented a cytology-based cervical cancer screening program. Prior to 1987, the program was limited due to lack of supervision and very little evaluation from the health services, resulting in only 10% of women being screened annually.<sup>7</sup> In 1987, the Chilean Ministry of Health and the World Health Organization collaborated to train additional healthcare professionals, establish a system for patient follow-up, improve accuracy of cytologic diagnosis, and improve patient education. As a result, in 1990 Chile increased screening coverage from 44% to 66% among women aged 25–64 years. In addition, follow-up rates increased to 98%, which led to a 39% reduction in mortality between the years 1986 and 2001.

Chile's cytology program is a rare example of reallocating resources and infrastructure reformation to combat cervical cancer. Unfortunately other LMICs have not been as successful.<sup>6</sup> The consequence of limited resources was made evident in a community-based study in Honduras where an extremely high false-negative rate of Pap smears was reported.<sup>8</sup> This outcome was attributed to the lack of trained cytopathologists. In addition, this study suggested poor Pap smear quality was due to a lack of supplies such as fixative, spatulas, and cytobrushes. Although >80% of the study population was being screened, poor-quality smears hindered the expected decrease in cervical cancer rates.

Inadequate population coverage and poor patient follow-up are additional factors that contribute to the limited success of cytology programs in LMICs. Throughout Latin America, for example, many countries have made great efforts to sustain cytology-based screening programs, yet they have shown little reduction in cervical cancer incidence and mortality.<sup>6</sup> A clinical record review of 243 women with abnormal cytology results in Peru found that follow-up care after abnormal Pap smears was very poor: 56% of the women lost to follow-up had high-grade precancer, and 3% of the women died of cervical carcinoma at the time of the recruitment for rescreening.<sup>9</sup>

Additional obstacles to cytology programs include poor patient education, lack of organized recall systems, delays in histology results, a lack of skilled professionals, recruitment of women below the target age range, misplacement of cervical specimen, and a poor follow-up referral system.<sup>9,10</sup> Alternatively, small-scale pilot programs have demonstrated that high population coverage (68%–100%) is achievable.<sup>11,12</sup> Unfortunately, scaling up pilot programs to provide country-wide coverage has proven to be difficult.

In low-resource settings, the lessons learned from past mistakes and the few successes are the foundation for developing new interventions. Organizations around the world are working to improve the infrastructure for cytology programs, and are also investigating alternative screening methods for the prevention of cervical cancer, such as VIA and HPV testing, which have the potential to improve both population coverage and follow-up rates, minimize the need for complex technologies, and decrease the monetary burden of staffing laboratories with specialized personnel.

### SCREENING BY VISUAL INSPECTION WITH ACETIC ACID

Visual inspection with acetic acid is a screening method that entails placing diluted acetic acid on the cervix to screen for precancerous lesions. A positive exam is indicated with aceto-white changes on the cervix and can be visualized immediately with the naked eye.

Visual inspection with acetic acid is a speculum exam in which the healthcare provider applies 3%–5% acetic acid directly to the cervix for 1 minute, followed by a naked-eye visual inspection. A VIA exam is considered positive when a well-defined aceto-white lesion is observed in the transformation zone close to the squamocolumnar junction. Visual inspection with acetic acid has a higher reported sensitivity than cytology, but a lower specificity,<sup>4</sup> suggesting that a single VIA test is as good as or better than a single conventional cytology at detecting cervical precancers.

In a large scale, cluster-randomized controlled trial, a single round of VIA screening decreased cervical cancer incidence by 25% and reduced mortality due to cervical cancer by 35% compared with no intervention (the standard of care).<sup>13</sup> It should be

noted, however, that the same author later published findings indicating that neither a single round of VIA or cytology caused a decrease in invasive cervical cancer compared with HPV DNA testing.<sup>14</sup>

Visual inspection with acetic acid is useful in low-resource settings because it may be more cost-effective than cytology programs, as cost estimates for a single VIA exam are <\$1 per test.<sup>8,15</sup> In addition, VIA requires few resources, can be conducted by any level of health provider, and yields immediate results, which can be followed by immediate treatment. Programs that link screening and treatment are referred to as “see-and-treat” programs, or the “single-visit” approach. The single-visit approach is appealing because it eliminates patient loss to follow-up associated with cytology programs and can be conducted with mobile units outside of clinic settings to reach populations in remote areas.<sup>16–19</sup>

Many organizations have developed curricula for VIA training. Member organizations of the Alliance for Cervical Cancer Prevention have developed programmatic materials that include competency-based clinical and didactic components.<sup>20</sup> After a medical professional has received training, it is suggested that quality-assurance measures such as refresher courses and site visits be used to maintain proficiency.

A major limitation of VIA screening is the subjectivity of the test. Test results are based on visual inspection with the naked eye, leading to a high inter-rater variability. A wide range of sensitivities have been reported between pilot programs.<sup>4,21,22</sup> Variability has also been reported between different level of healthcare workers (nurses and physicians), and among highly trained pathologists from the United States.<sup>23,24</sup> A study conducted in Andhra Pradesh, India, reported a sensitivity so low (26.3%) that the authors suggested limiting the introduction and expansion of VIA programs, as they could potentially decrease public confidence in novel screening techniques, making it harder to implement better screening strategies in the future.<sup>25</sup> However, in resource-poor settings, a simple screening program such as VIA may provide screening coverage to a higher percentage of the population than cytology programs. This increase in coverage has the potential to save more lives, even if VIA screening is not as accurate.<sup>26</sup> Visual inspection with acetic acid programs, especially those that advocate for the single-visit approach, not only help increase screening coverage, but also lay down the framework to integrate novel, more sensitive technologies, such as HPV DNA testing.<sup>27</sup>

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## HUMAN PAPILOMAVIRUS DNA TESTING

Human papillomavirus DNA screening identifies the presence of HPV DNA through a sample of vaginal or cervical epithelial cells. The test is highly sensitive and has an extremely high negative predictive value.

The natural history of the HPV has been well-mapped and can be used to develop cost-effective, age-based cervical cancer screening programs. Additionally, HPV DNA testing provides superior sensitivity to cytological methods for detection of cervical precancer.<sup>28,29</sup> Unlike cytology and VIA, HPV-based screening detects the underlying cause of cervical precancers (the HPV), rather than the secondary manifestations of the disease.

In resource-poor settings, it has been suggested that screening women for HPV DNA once, at age 35, or twice, at ages 35 and 40, represent the most cost-effective ways to reduce cervical cancer.<sup>30</sup>

Hybrid Capture II (HC2) is the commercially available HPV DNA test in the United States. A low-cost, low-tech alternative HPV DNA test, careHPV (Qiagen, Inc.), was developed for use in low-resource settings through a grant from the Bill and Melinda Gates Foundation. The test is a single-amplification assay that detects HPV DNA from 14 different carcinogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Based on the detection of CIN2+, the sensitivity of careHPV for cervical specimens is 90.0% and the specificity is 84.2%.<sup>28</sup> Not only is the test reliable and sensitive, but the requirements for running the careHPV assay are minimal. It does not require running water or a laboratory, and the entire assay processing time is about 2.5 hours (compared with about 7 hours for the HC2 system). However, limitations to implementing widespread cervical cancer screening based on the careHPV system include the

*Unlike cytology and visual inspection with acetic acid, human papillomavirus–based screening detects the underlying cause of cervical precancers (the human papillomavirus), rather than the secondary manifestations of the disease. The human papillomavirus DNA test commercially available in the United States is Hybrid Capture II. A low-cost, low-tech alternative, careHPV, was developed for use in low-resource settings through a grant from the Bill and Melinda Gates Foundation.*

small number of tests that can be processed and the difficulty of transporting the testing equipment. Taken together, careHPV and other low-cost HPV-based tests could represent the future of screening in the developing world.

One of the first large-scale HPV testing trials outside of the developed world was the Latin American Screening Study,<sup>26</sup> implemented in Brazilian and Argentine clinics to >4000 women. The prevalence of HPV positivity was high, and HC2 detected the presence of high-grade precancer (CIN3) with a sensitivity of 96.5%. In a pilot program in semirural and rural regions of Mexico, >50,000 previously unscreened women aged 20–70 years received concurrent cytology and HC2 HPV DNA tests and reported a high sensitivity (93.3%) for the detection of CIN2+.<sup>3</sup> The HC2 test exhibited excellent test characteristics, high patient acceptability, and ease of administration by trained nurses.

A cost estimate for the use of HC2 in low-resource settings ranged from \$6.07 to \$6.59 per test (compared with \$1.57 to \$3.37 for cytology screening). Programs that linked screening to treatment in 1 or 2 visits were the most cost-effective.<sup>31</sup> In 2010, the same group published a report on the cost-effectiveness of careHPV testing<sup>32</sup> and found that the most cost-effective service delivery modality was careHPV screening once per lifetime. Screening women aged 33–55 years 3× per lifetime would provide a 34%–50% lifetime reduction in cervical cancer. CareHPV significantly decreases costs of HPV DNA testing and provides an exciting opportunity to use

new technology for the benefit of the most vulnerable populations.

To further increase the cost-effectiveness and population coverage of HPV-based screening, samples can be self-collected.

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Self-sampling involves a woman taking a sample of vaginal epithelial cells using a tampon, vaginal lavage, brush, or swab to test for the presence of HPV DNA. Self-collected vaginal samples exhibit only slightly inferior sensitivity (about 10%) compared with provider-collected cervical samples<sup>28</sup> and there is good concordance between self-collected and clinically collected vaginal samples.<sup>33,34</sup> Self-sampling is cost-effective and reduces the time it takes to conduct screening.<sup>32,35</sup> Furthermore, self-sampling has been shown to be highly acceptable among women.<sup>11,35</sup> Self-sampling for HPV DNA may also increase population coverage among women who are uncomfortable with provider-conducted screening for fear of speculum exam, loss of privacy, pain, or resistance from spouse.<sup>36,37</sup>

Population coverage can improve dramatically by increasing the screening interval that has been suggested with traditional cytology. A single negative HPV DNA test provides 5–10-year reassurance against high-grade cervical precancer and cancer.<sup>38</sup> However, both sample self-collection and lengthening screening intervals may be difficult to translate

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into practice. In countries with preexisting cytology programs, successful implementation will hinge on shifting the mindset of policymakers, healthcare providers, and women. Clinical guidelines must also be developed and disseminated to healthcare providers, and educational and communication campaigns must be targeted to reproductive-age women.

A landmark study was recently conducted by Denny *et al.* demonstrating that screen-and-treat

programs using HPV testing cause a decrease in cumulative high-grade cervical precancer.<sup>39</sup> The study randomized 6637 women to either see-and-treat with HPV DNA (HC2), see-and-treat with VIA, or no screening. At 6 months, all women were evaluated with colposcopic biopsies (the gold standard). A subset of 3639 women was followed every 12 months up to 36 months to determine long-term disease status. The greatest decrease in cumulative high-grade precancer was detected in the “HPV-and-treat” group, suggesting that countries should advocate for a system in which treatment is provided based on HPV positivity rather than the presence of a cervical lesion. In this study, HPV testing was conducted with the costly HC2 system; for widespread programmatic implementation, careHPV or another low-cost HPV-based screening test could be used. In addition, visual triage (a speculum exam very similar to VIA that is used to rule out invasive cancer and lesions too large to treat with cryotherapy) was conducted on all women positive for HPV. The visual triage exam is an integral part of the see-and-treat method, and demonstrates how an established VIA program can easily integrate HPV-based screening into their services.

## HUMAN PAPILLOMAVIRUS VACCINE

An exciting prospect for primary cervical cancer prevention is the incorporation of the prophylactic HPV vaccine into existing cervical cancer prevention efforts. The vaccine protects against HPV16 and HPV18, the causes of >70% of all cervical cancers.

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However, the vaccine does not protect against the remaining 30% of cervical cancer causes, nor does it treat existing HPV infections.<sup>40</sup> In addition, the cost of the vaccine may make it prohibitive in many low-resource settings. However, one study predicted that if 70% of adolescent girls in the world's poorest countries were vaccinated, the future deaths of >4 million women over the next decade could be prevented.<sup>41</sup> Assuming a 70% coverage rate, average lifetime cancer risk would reduce by nearly half.<sup>42</sup> Although these estimates are hopeful, the high

vaccine cost prohibits its current use in many low-resource settings. Even once the vaccine is available, the benefits of wide-scale population coverage will not be achieved for at least 30 years,<sup>43</sup> reinforcing the need to continue focusing on secondary prevention through screening.

## CONCLUSION

It is an exciting era for cervical cancer prevention. Low- and middle-income countries will soon have access to highly sensitive, cost-effective screening tools that may lead to changes in screening paradigms. However, as we move forward, it is important to remember that increasing screening coverage and adequate follow-up for abnormal tests is the most important aspect to prevention programs, regardless of screening method used. Utilizing HPV DNA screening without providing follow-up will do nothing to reduce the risk of precancer and invasive cancer. We must develop unique prevention programs that focus on screening and treatment, based on each country's healthcare infrastructure, resources, and cultural norms. If we succeed in this, we may finally witness a decrease in cervical cancer incidence and mortality in the developing world.

The authors have extensive experience partnering with low-resource countries investigating screening modalities in low-resource settings. This experience has been used to highlight the advantages and disadvantages of VIA, Pap, and HPV DNA testing.

## DISCLOSURES

*Potential conflict of interest:* Nothing to report.

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