HPV Testing in Resource-Limited Settings: How Can We Reach the Next Level of Cervical Cancer Screening in Latin America and the Caribbean?

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Invasive cervical cancer is a disease caused by pathogenic strains of human papillomavirus (HPV) [1]. Screening for preinvasive cervical disease with cytology has been available for more than 50 years, and in developed nations, the rates of invasive cervical cancer have decreased dramatically [2]. In the developing world, however, this program has proven less effective. There are 525,000 cases of invasive cervical cancer worldwide each year and 270,000 deaths [3, 4]. More than 85% of these fatalities occur in low- and middle-income countries (LMICs); most women in these settings present at advanced stage and die of their disease. The more aggressive nature of HPV infection in women living with HIV exacerbates these discrepancies in many parts of the world including sub-Saharan Africa [5] and Amazonia [6]. In the Western Hemisphere, the incidence and mortality of cervical cancer vary dramatically by country; specifically, lower-resource countries in Latin America and the Caribbean (LAC) face a dramatically higher burden of cervical cancer compared with their wealthier neighbors (Fig. 1).

Death from cervical cancer can be eradicated through vaccination, screening, and effective treatment of invasive cancer. Several countries in LAC have initiated vaccination programs, including Brazil and Mexico, which have highly successful nationwide campaigns [7]. The currently used vaccines are expected to prevent 70% of invasive cervical cancer, and the interval from incident HPV infection to the development of invasive cancer is typically 10–30 years, so screening will remain an important component of cervical cancer control.

Although some countries, such as Costa Rica, and regions of others, such as Mexico and Colombia, have had success with Papanicolaou testing, the discrepancy in cervical cancer outcomes between regions reveals a failure of cytology-based screening programs in low-resource settings. The causes of this failure are many and varied, often including a lack of laboratory infrastructure and personnel, poor information systems, limited access of patients to screening and follow-up, and lack of medical and financial resources to manage patients with positive results.

Two major alternatives to the use of cytology-based screening have emerged: visual inspection after application of acetic acid (VIA) and HPV testing. VIA is a low-technology,

low-cost approach that, when combined with immediate treatment of selected test-positive patients (“see and treat”), has been shown in a variety of settings to decrease the incidence and mortality of cervical cancer [8, 9]. Concerns have been raised about the utility of VIA in broader sustained screening programs because of the subjective nature of the procedure, which makes quality control a significant challenge. Under clinical trial or demonstration project conditions, the performance of VIA is similar to that of cytological screening, meaning that VIA must be repeated at regular intervals if significant reduction in invasive cancer is the goal, increasing the costs and challenges of follow-up. HPV testing has been shown in a randomized trial to be superior to VIA or cytology in reducing cervical cancer mortality [10].

HPV testing has several advantages over both cytological screening and VIA that make it particularly suited to resource-limited settings. The test results are objective, so personnel do not need to be trained to interpret the test. The sensitivity and negative predictive value of the HPV test are high, allowing the identification of women who are at very low risk for cervical cancer and who may be screened at more extended intervals. Furthermore, HPV testing will be a more rational way to detect those at risk when women who have been vaccinated become old enough to screen. Different testing platforms are available, supporting a variety of screening strategies; for example, rapid tests allow for results and treatment at the point of care, and high-throughput assays allow for processing at a central laboratory, thus decreasing the infrastructure required at the local level. HPV testing also can be performed on samples that have been self-collected by patients, potentially removing a barrier to screening.

Barriers to the use of HPV testing in LAC include the high cost of the assays, uncertainty about the feasibility and benefits of adding an HPV test to an existing cytology program, confusion about the array of new products that have become available recently, concerns about implementation of the assays, uncertainty about the appropriate management of patients with positive and negative results, and the need to validate and certify each assay within each individual country.

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Figure 1. World age-standardized rates of incidence of and mortality from cervical cancer (per 100,000 woman-years) in the Americas, estimates for 2008, ordered by continent and ranked by increasing mortality from bottom to top (direct standardization using the world reference population).

Despite these barriers, it is clear that HPV testing is a powerful tool in the fight against cervical cancer, and multiple stakeholders have a shared goal of making this technology available to women in LAC. The complexity and magnitude of such work, however, is likely to overwhelm any unilateral effort to implement next-generation cervical cancer screening.

To that end, the Pan American Health Organization (PAHO) and the U.S. National Cancer Institute (NCI) Center for Global Health convened a meeting of representatives from industry, international agencies, nongovernmental organizations (NGOs), and ministries of health from several PAHO member states in May 2014. This meeting was planned as a multidisciplinary, collaborative forum in which stakeholders could identify their shared goals and make concrete plans to initiate and improve programs. Each group presented insights and challenges from their viewpoint. All parties share a common interest in improving the health of women in Latin America and the Caribbean through sustained and effective implementation of HPV-based screening for cervical cancer (Fig. 2).

Industry representatives stated that several conditions could improve their ability to provide high-quality HPV

testing at competitive prices, including transparent and consistent regulations and accreditations and longer-term contracts with included commitments for service and support. Specifically, companies aiming for widespread implementation were committed to supporting the technical and human capacity demands of their products. Longer-term contracts make it more worthwhile for industry to make the educational, technical, and financial investments needed to initiate a program in a resource-limited setting.

Representatives from ministries of health expressed interest in HPV screening technology, which is already being implemented in several nations, but expressed several concerns including the costs of the test and of the overall HPV testing program; the challenges of informatics, in particular the issues surrounding reporting of results and ensuring follow-up; confusion about the wide array of new tests; concern about differences in prices offered to different countries in the region; and the need to have doctors and health systems comply with new recommendations for screening and follow-up testing.

NGOs hope to leverage capital and expertise from outside resource-limited settings to assist countries in getting

Figure 2. HPV testing dynamics. Stakeholders in cervical cancer screening have more shared goals than differences.
 Abbreviation: NGO, nongovernmental organization.

screening programs started, and international organizations hope to stimulate human development on many levels, through pooling of financial resources and technical expertise and sharing experiences and lessons learned about how to successfully incorporate HPV testing into organized screening programs.

Our observation is that all parties have many common goals, and our hope is that several notable recent efforts by PAHO and the World Health Organization (WHO) will help catalyze cervical cancer screening throughout the region. The first of these is the PAHO Strategic Fund, which is working toward including HPV tests in future. This is a PAHO program to improve access and availability of strategic public health supplies in member states through pooled procurement and supply management. Such bulk agreements can serve the interest of the countries (by limiting price) and the interest of industry (by maintaining efficiencies of scale.) More information about the Strategic Fund can be found at online (<http://www.paho.org/hq/>).

Whatever approach to negotiation and contracting is taken, all parties must recognize that although each technology has inherent costs, resources are limited and must be divided among multiple pressing health-related and non-health-related priorities. Both novel pricing strategies and frugal innovations are needed to make HPV testing widely available.

The WHO has also added value through rigorously reviewing the literature and updating its publication “Comprehensive Cervical Cancer Control: A Guide to Essential Practice,” which provides a reference for all parties invested in preventing deaths from cervical cancer [11].

Several initiatives are under way that will help optimize delivery of cervical cancer screening in LAC. The ESTAMPA project, sponsored by the International Agency for Research on Cancer with partial support from NCI, the National Institutes of Health (NIH), and PAHO/WHO, has been designed to evaluate the various testing options for triage of women who test positive for HPV on screening [12]. Another uncertainty in implementing large screening programs in LAC is the best approach to the issues of stigma surrounding a positive HPV test result, cancer, and gynecologic exams. The Research to Characterize and Reduce Stigma to Improve Health program supported by NCI and other institutes and centers at NIH could be an important tool to address this problem in LMICs [13]. PAHO will soon publish an online reference of HPV tests to assist stakeholders hoping to understand and track the many products available.

Cervical cancer is a well-understood disease; its prevention is more a matter of logistics and affordable tools than science. We feel that our recent experience shows that stakeholders have much in common, and we exhort all parties to work openly and collaboratively to bring this new

technology to the aid of women in resource-limited settings around the world.

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For Further Reading:

Analia Romina Stormo, Lenildo de Moura, Mona Saraiya. Cervical Cancer-Related Knowledge, Attitudes, and Practices of Health Professionals Working in Brazil's Network of Primary Care Units. *The Oncologist* 2014;19:375–382.

Implications for Practice:

Data on cervical cancer-related knowledge, attitudes, and practices among health professionals in Brazil's network of primary care units are key to developing effective strategies for the promotion of evidence-based practices and inform the incorporation of human papillomavirus (HPV) vaccination on Brazil's National Program of Immunizations in 2014. This study suggests that overscreening may be impeding efforts to increase the screening coverage among the eligible target population of women aged 25–64 years. Furthermore, increasing knowledge about the importance of targeting age-appropriate groups for HPV vaccination will be essential to maximize the benefits of this new strategy for cervical cancer prevention.