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Review

Implementation of HPV testing in Latin America

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ABSTRACT

Cervical cancer is one of the leading killers among women in Latin America, a region where most countries have not been successful in implementing population-level cytology-based screening programs. This disease is caused by persistent infection with oncogenic HPV; in recent years, more HPV tests have become available and prices have dropped significantly, making it possible for countries to adopt these technologies. Pilot programs that took place in Nicaragua, Mexico, and Argentina showed a high level of efficacy in detecting precancerous cervical lesions and good feasibility and acceptance of self-sampling. El Salvador, Guatemala, Honduras, and Nicaragua are beginning to institutionalize HPV testing at the population level. The experience from the different countries has created rich information about the barriers and requirements for implementing HPV screening at large scale in these resource-constrained countries. There are several challenges for implementation, including a need to update screening guidelines, strengthen treatment capacity, and develop a comprehensive quality assurance plan for the HPV testing. At the same time, there are several opportunities in Latin America that make the process more feasible and faster than in other regions of the world: most Latin American countries already have screening programs funded by their national governments, several countries in the region are already implementing HPV testing, and there is a regional pooled procurement mechanism that could facilitate the purchase of HPV tests at an accessible price. We envision that most countries in the region will include HPV testing in their national program within the next three to five years.

Contents

1. Background

Cervical cancer is the second most common neoplasia and one of the leading killers among women in Latin America [1]. This neoplasia is related to chronic infection with any of the oncogenic types of human papillomavirus (HPV). There are more than 200 genotypes of HPV, but approximately 14 of them are related to this neoplasia; for this reason, cervical cancer is considered a neoplasia related to a sexually transmitted infection [2]. Screening programs based on cervical cytology (Pap smear) have been successful in reducing the incidence and mortality in developed countries such as the United States and European countries [3]. Unfortunately, most Latin American countries tried unsuccessfully to replicate these results with

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the exception of Chile and Costa Rica; after decades of efforts implementing cytology-based programs, the incidence and mortality of this disease remain very high, with no significant impact on the disease burden [4].

There are several factors contributing to this lack of impact of the prevention programs, one is the suboptimal sensitivity of cervical cytology. Meta-analysis of studies performed in developed countries show that the sensitivity of the test for detecting high-grade intraepithelial lesions (CIN3+) is approximately 50% in well-equipped laboratories with adequate training and quality control [5]. The performance of cervical cytology is even lower in Latin American countries with sensitivity ranging between 22 and 42% [6–8]. This means that even if the countries find resources to invest in high-quality cytology labs, most of the precancerous lesions would be missed by a single round of screening, requiring multiple repetitions of screening to correct the mediocre sensitivity, making the cost prohibitive. Another reason for the low impact of cytology-based screening programs is the need to perform a pelvic evaluation to collect the cervical sample for cytological evaluation, which could be a significant limiting factor in populations that do not accept such pelvic examinations for cultural reasons. Finally, another significant factor, which could be applicable to any screening test, is the weakness of the programs and their inability to perform proper follow-up and treatment of women with a positive screening result.

The limitations inherent in cervical cytology prompted the development of new screening technologies: tests to detect the presence of HPV DNA. The use of HPV tests is based on the fact that all cervical cancers are related to infection with one or more oncogenic types of HPV; a test to detect HPV infection allows for the detection of women who are infected with oncogenic HPV and are therefore at higher risk for harboring precancerous or cancerous lesions. Meanwhile, women without HPV infection are at very low risk for cervical cancer within the next ten years and do not need additional screening tests for 3–5 years [9].

HPV tests have been available in developed countries since the early 2000s, but the initial tests were expensive and unaffordable for Latin American countries. In recent years, more HPV tests became available and the prices dropped significantly, making it possible for some countries to pilot the introduction of these technologies, and more recently, introduce these tests in population-based programs. We intend to provide a brief review of the main experiences in Latin America, with an emphasis on reviewing the challenges and opportunities identified.

2. Experiences of HPV implementation in Latin America

Over the last decade, there have been multiple experiences with HPV testing in Latin America; some as part of research studies, others to pilot the implementation of HPV tests in the public system, and more recently, actual implementation of HPV testing as part of the regular services provided by the ministry of health facilities.

2.1. Nicaragua

In 2011, the Ministry of Health of Nicaragua led a project to field validate the *care*HPV™ test (QIAGEN, Germantown, MD, USA) in Masaya, a semirural province south of the capital city with a mix of indigenous and non-indigenous populations. Since one of the project's goals was to evaluate women's acceptance of self-collecting a vaginal sample, approximately 5000 women received education and were given the option to self-collect a vaginal sample for HPV testing. As part of the study protocol, all women also underwent a speculum examination by a health care provider during which a cervical sample for HPV testing and a cervical sample for cervical cytology evaluation were also collected [8].

The experience from Nicaragua showed that more than 80% of women agreed to self-collect a vaginal sample [10], and the *care*HPV test with self-collected vaginal samples had better sensitivity (67%) for detecting CIN2+ lesions than cervical cytology (40.7%). The best sensitivity was achieved by *care*HPV testing using the cervical sample collected by a provider (78%). It is important to highlight that all the services—sample collection, sample transportation, and lab testing—were done within the regular public health system and without the intervention of the research team. The samples were tested with *care*HPV in the lab of a small health center in that province, and carried out by the lab technicians who were already working in the facility for more than a decade. Cervical cytology samples were processed by cytotechnologists and pathologists who are part of the regular cervical cancer screening system in the province. The results of this experience prompted the government of Nicaragua—and of other countries in the region such as El Salvador—to start implementation of HPV testing within the cervical cancer screening program already available in their public systems.

2.2. Mexico

Another study in Mexico carried out between 2007 and 2010 had the goal of evaluating the implementation of HPV testing using self-collected vaginal samples [11]. A total of 121,650 women from the State of Morelos were invited to participate in the study, and 82% of them (100,242) accepted self-collection of a vaginal sample. There were three different strategies for the enrollment of women: one strategy used health worker brigades visiting communities to offer self-collection of vaginal samples to women in their own homes; the second strategy offered self-sampling to women attending health facilities for other health related issues; and the third strategy used campaigns scheduled specially and organized for cervical cancer screening.

One of the main findings from the experience in Mexico was the very high acceptance for self-collecting a vaginal sample for HPV testing. The study also found that women were more comfortable self-collecting samples at home [12]; more than 95,000 women were offered the option to collect a vaginal sample during a home visit and 95% of them accepted. Meanwhile, a lower acceptance rate was observed when women were offered the opportunity to self-collect a vaginal sample during a visit to a health center (82%) or during a community outreach campaign (72%). Approximately 11% of women tested positive for the presence of high-risk HPV DNA using the Hybrid Capture 2 (HC2) test (QIAGEN, Germantown, MD, USA), and the adjusted sensitivity for detecting CIN3+ was 81.5%, with a specificity of 89.3%.

The researchers concluded that self-sampling for HPV testing is a very good approach for increasing coverage of cervical cancer screening; but they also highlighted that there could be several challenges for securing proper evaluation of women with a positive HPV result. The suboptimal follow-up rates in this study (74%) could have been associated with the algorithm for management of women with positive results since all of them were required to have colposcopic evaluation; women faced the challenge of limited availability of that service in the clinics, the cost of services, as well as other conflicting obligations at home. Finally, the researchers concluded that there was a need to add triage procedures for HPV-positive women, to avoid overwhelming the services in the colposcopy clinics.

In recent years, Mexico has expanded the implementation of HPV DNA testing to 17 sites across the country, mainly targeting

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low-income women. In the last two years the program has screened over 6 million women.

2.3. Argentina

Argentina was the first country in the region to implement HPV DNA testing for primary screening within their public system for all women aged 30 years or older [13]. Implementation started with pilot studies in Jujuy Province in the north of the country, with the goal of screening approximately 19,000 women per year to achieve a coverage of 80% of the target population within a three-year period. The public system in that province already uses community health workers (CHW) who have the responsibility of visiting each household in the province at least two times a year; during those visits the CHW delivers services for children and women. Before the introduction of HPV testing, the home visits included education for women about the importance of cervical cancer prevention and the benefits of screening; after that, women were referred to the nearest health facility for cervical cytology; but only 20% of them ended up completing a cytology screening. When HPV testing was introduced in the home visits and women were offered the option to self-collect a sample during the visit, 86% of them agreed and provided a vaginal sample for cervical cancer screening [14].

Another benefit from the implementation of HPV testing as primary screening in Jujuy Province was the higher number of CIN2+ detected compared to cytology. In 2011, when cytology was the primary screening test, 6.2 women were histologically diagnosed with CIN2+ per 1000 women screened; however, when HPV testing was implemented in 2012, the number doubled to 12.5 CIN2+ cases per 1000 women screened.

2.4. Program implementation in Central American countries

The experiences in Nicaragua, Mexico, and Argentina have prompted several countries in Latin America to make changes in their national cervical cancer prevention programs to incorporate HPV testing for primary screening. The PATH Scale-Up project[1] for cervical cancer prevention in Central America builds on those previous experiences. It aims to institutionalize HPV testing at the population level in four countries: Guatemala, Honduras, and Nicaragua, with direct support from PATH, and El Salvador, with direct support from Basic Health International (BHI) and indirect support from PATH. Even though there are some differences from country to country, the project works in several phases, with each phase addressing a specific, identified need for implementing HPV screening at large scale in these resource-constrained countries.

The implementation in El Salvador is done by the local Ministry of Health with support from BHI. While the work in all four Central American countries includes preparatory phases before starting geographical and population expansion, there are some differences in the magnitude and speed of the implementation. BHI started to work on the implementation of HPV testing in El Salvador in 2013, and the pilot testing expanded progressively reaching 20,000 women in 2015. Meanwhile the other three countries are planning a pilot of 10,000 women before expanding to 100,000 women within a year.

Phase 1 is the preparatory phase, in which partner organizations work with the ministry of health to prepare for implementing HPV DNA screening. It includes developing screening and treatment algorithms that incorporate HPV testing; developing educational materials for women in the community and health workers; implementing training sessions for health workers on offering HPV testing and providing counseling; training lab technicians to run the HPV test; and strengthening the follow-up, referral, and treatment systems, including health information systems and precancer treatment networks.

In Phase 2, the piloting phase, each country begins with an initial batch of 10,000 tests during a 6-month period so that ministries of health can identify and address barriers to enrollment, screening, processing laboratory samples, reporting the test results to the health facilities, and follow-up and treatment of patients. During Phase 2, it is also possible to begin identifying the advantages of the change to HPV testing followed by VIA and cryotherapy for implementing a national cervical cancer prevention program. The algorithms for management of patients with HPV-positive results are based on the different alternatives presented in the new World Health Organization (WHO) guidelines [15]. While patient algorithms vary by country as determined by the ministries of health, VIA is generally used as a triage. All countries started using an algorithm that considers treatment only in women who are VIA positive (Fig. 1), but due to the sub-optimal sensitivity of VIA and the challenge of following women with HPV infection but a VIA-negative result, more countries are now considering using VIA just for determining eligibility for cryotherapy; this means that all HPV-positive women receive cryotherapy (Fig. 2), unless the visual evaluation determines that the patient requires referral due to suspicion of cancer or the presence of a large lesion ineligible for cryotherapy.

The experience from Guatemala shows that self-collection of vaginal samples is highly acceptable to women; approximately 90% of women screened self-collected their sample. Phase 3 is when the program scales up in magnitude to a minimum of 100,000 tests annually. The intervention initially remains within the specific geographical areas of the country defined in the pilot phase, with the aim of incorporating more provinces progressively. Since the ultimate goal of all this work is to have a sustainable screening program, it is critical that during this phase, the public system and the country governments assume responsibility for procuring and deploying HPV testing in subsequent years.

By the end of 2015, the preparatory phase was completed in Guatemala, Honduras, and Nicaragua, and they are implementing HPV screening within the pilot phase. The preparatory and pilot phases helped to identify several challenges in the countries. There was a need for updating screening and treatment guidelines for cervical cancer prevention reflecting the latest scientific evidence; without new guidelines it is extremely difficult to achieve consensus on the management of HPV-positive women or to implement new algorithms and protocols. An additional challenge was the requirement for follow-up of HPV-positive women, and strengthening the triage and treatment capacity in these limited-resource contexts. In the project countries, the health information system did not include HPV testing as a screening option, and making the changes to incorporate that indicator took several months of work and included updating the data-collection forms used in the health centers. Once effective tracking is secured, there are several alternatives for the management of screen-positive women, and in the specific case of the work in Central America, VIA and cryotherapy are the most feasible and practical options, with the potential to limit both costs and bottlenecks to treatment access; therefore, before starting the implementation of HPV testing, countries were required to create or improve the capacity to perform VIA and cryotherapy. Where this capacity was present in some countries, it was not sufficient to handle the volume of new HPV-positive women projected to require those services, so additional training and equipment was needed.

An additional critical need identified in the process of implementing HPV testing is the development of a comprehensive

[1] The Scale-Up project seeks to reduce cervical cancer incidence through improved and expanded screening using HPV testing.

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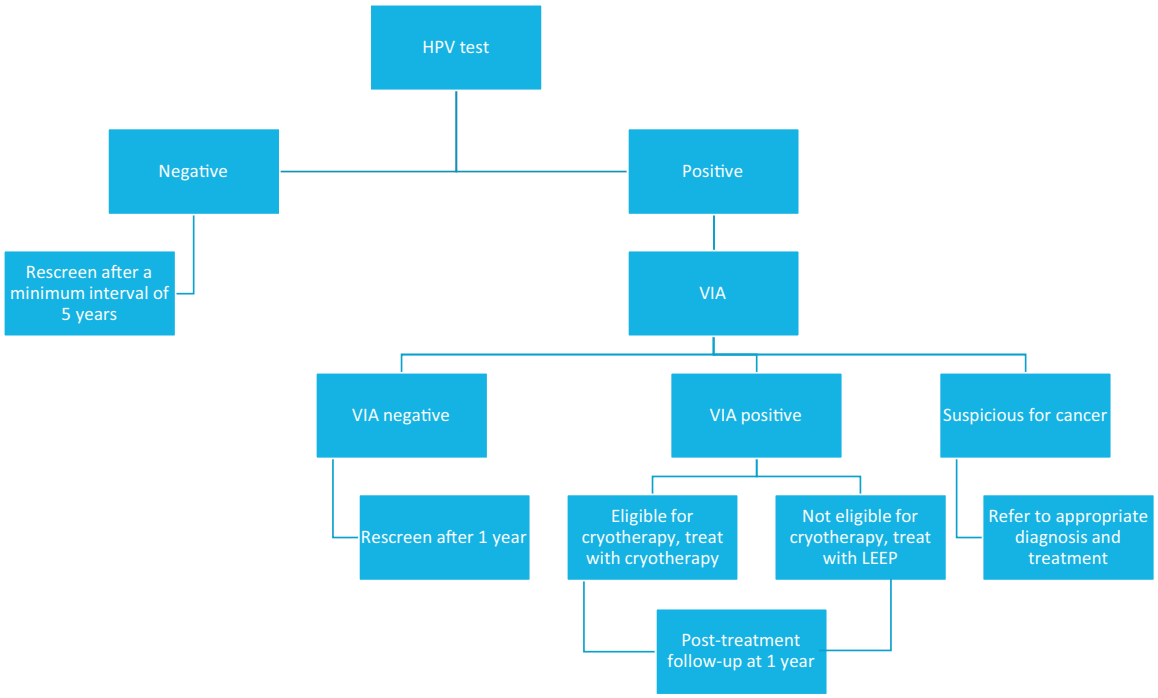

Fig. 1. Patient algorithm for HPV testing and treatment in VIA-positive women. Source: World Health Organization [15].

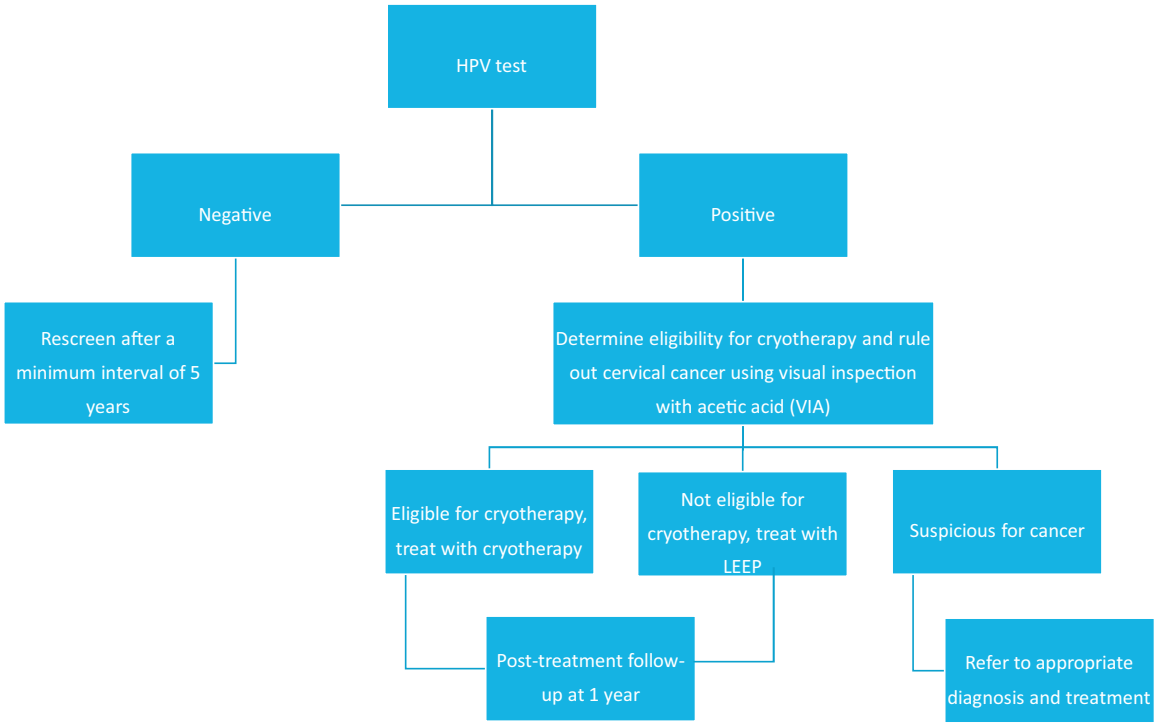

Fig. 2. Patient algorithm for HPV testing and treatment in HPV-positive women. Source: World Health Organization [15].

quality assurance plan associated with the specific HPV test to be implemented, in order to guarantee reliable test results in real-world settings. Even though most HPV tests have their own internal quality control systems, it is necessary to have quality control procedures for ensuring proper storage of the HPV test kits, adequate transportation of test kits and samples, proper labeling and processing of samples, suitable monitoring of the positivity rates and other characteristics of the test to rule out contamination, and monitoring of the community outreach activities and counseling, among other considerations.

3. Opportunities for implementation

Approximately 6 countries in Latin America (Argentina, El Salvador, Guatemala, Honduras, Mexico, and Nicaragua) have started to implement HPV DNA testing in their national cervical cancer screening programs, and more countries will follow this path. There are several opportunities in Latin America that are making the process more feasible and faster than in other regions. The first opportunity is that most Latin American countries already have cervical cancer screening programs funded and led by the national

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government; this means that countries already have these activities in their national budget, facilitating the process for reallocating some of that funding for HPV testing activities. A second advantage of having such programs already in place is that there is a culture of screening for cervical cancer among women and providers; women know about the value of prevention and are open to adopt new options such as self-collecting a vaginal sample.

Many Latin American countries also have national or pilot HPV vaccination programs in place. This is key to the success of cervical cancer prevention programs, as both primary prevention (vaccination) and secondary prevention (screening) are needed to resolve the burden of cervical cancer in Latin America. Countries with national HPV vaccination programs include Argentina, Belize, Brazil, Chile, Colombia, the Dominican Republic, Ecuador, Mexico, Panama, Paraguay, Peru, and Uruguay. Countries with pilot HPV vaccination programs include Bolivia and Honduras [16]. Another regional advantage is that, as mentioned before, there are already several countries implementing HPV testing in their national programs. These experiences provide a good example for countries interested in making the change to HPV testing; opinion leaders from El Salvador visited Masaya Province, Nicaragua, to observe the use of *care*HPV in the public facilities. Later, El Salvador started a very successful program implementing HPV testing, and recently that country hosted visitors from Guatemala and Honduras to learn about the operational requirements for implementing the test in their countries.

In addition, there are NGOs, academic institutions, and other regional actors that can play a key role in partnering with ministries of health to overcome challenges in implementation. Several organizations and institutions have experience working in partnership with ministries, and have demonstrated a willingness to share this information with others across the region. As mentioned here, PATH and BHI have experience providing technical assistance to Central American ministries of health making the transition to HPV testing; in Argentina support has been provided by the National Institute for Cancer; and in Mexico the Institute for Social Security and the National Institute for Public Health both have experience working with the government to implement these changes. Efforts are currently underway to document lessons learned from these experiences in a handbook for program managers implementing HPV screening in the Latin American region.

Finally, there is an opportunity that could have a significant impact on making the tests affordable for countries in the region. The Pan America Health Organization (PAHO), the Regional Office of the WHO for Latin America, has several decades of experience in bulk procurement of goods and supplies for its country members. These regional procurement systems at PAHO have been very effective in negotiating reduced prices for vaccines and essential drugs, and now PAHO is evaluating the incorporation of HPV tests into their procurement system. The way the regional procurement system works is that the negotiation with the manufacturers is done by PAHO on behalf of the countries, and a unique reduced price is set, usually more affordable than the price countries could obtain by negotiating individually. The advantage for the manufacturers is to gain access to potentially larger markets.

In conclusion, Latin America is moving toward the change to HPV testing for cervical cancer screening. There are several experiences in the region that show success in increased coverage and better detection of precancer with HPV tests, and there is extensive regional experience being shared among countries and facilitating the transfer of knowledge—even the sharing of training materials. We envision that most countries in the region will have experiences with HPV testing within the next three to five years, and by that time, some countries will have sustainable, population-based programs using HPV testing, funded by their national budgets.

Conflict of interest

Jose Jeronimo was the director of the study in Masaya, Nicaragua, and received all the tests used in the study as donations from the manufacturing company (QIAGEN). Francesca Holme has presented at a meeting of QIAGEN's shipping and logistics department, for which her travel expenses were paid by QIAGEN. Rose Slavkovsky and Claudia Camel have no conflicts of interest to disclose.

Ethical approval

Not required.

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