Cervical Cancer Control in Latin America: A Call to Action

Brittany L. Bychkovsky, MD, MSc1,2; Mayra E. Ferreyra, MD3; Kathrin Strasser-Weippl, MD4; Christina I. Herold, MD1,2; Gilberto de Lima Lopes Jr, MD5,6; Don S. Dizon, MD7; Kathleen M. Schmeler, MD8; Marcela Del Carmen, MD9; Tom C. Randall, MD10,11; Angelica Nogueira-Rodrigues, MD, PhD12; Aknar Freire de Carvalho Calabrich, MD13; Jessica St. Louis, BA14,15; Caroline M. Vail, BS14,15,16; and Paul E. Goss, MD, PhD2,14,15

Cervical cancer (CC) is second most common cause of cancer in Latin America and is a leading cause of cancer mortality among women. In 2015, an estimated 74,488 women will be diagnosed with CC in Latin America and 31,303 will die of the disease. CC mortality is projected to increase by 45% by 2030 despite human papillomavirus (HPV) vaccination and screening efforts. In this setting, the goal was of the current study was to examine CC control efforts in Latin America and identify deficiencies in these efforts that could be addressed to reduce CC incidence and mortality. The authors found that HPV vaccination has been introduced in the majority of Latin American countries, and there is now a need to monitor the success (or shortcomings) of these programs and to ensure that these programs are sustainable. This topic was also reviewed in light of emerging data demonstrating that visual inspection with acetic acid and HPV DNA testing without Papanicolaou tests have efficacy from a screening perspective and are good alternatives to cytology-based screening programs. Overall, there is a need to build capacity for CC control in Latin America and the best strategy will depend on the country/region and must be tailored to meet the needs of the population as well as available resources. Cancer 2016;122:502-14. © 2015 American Cancer Society.

KEYWORDS: cervical cancer, human papillomavirus (HPV), Latin America, screening, vaccination.

INTRODUCTION

The human papillomavirus (HPV) is the most common sexually transmitted infection worldwide and is associated with the vast majority of cervical cancers (CCs).1 Greater than 500,000 women are diagnosed with CC each year, and CC accounts for >275,000 deaths globally, 88% of which occur in low-income and middle-income countries (LMICs).2,3 In Latin America (LA), CC is the second most common cause of cancer-related deaths among women, with an annual reported incidence of 21.2 per 100,000 women (74,488 cases in 2015) and a mortality rate approaching 8.7 deaths per 100,000 women (31,303 CC deaths in 2015).2 Mortality continues to rise in LA, with current projections estimating an increase of 45% by 2030.4 Despite this, combating CC is not a United Nations’ 2015 Millennium Development Goal.5

Because deaths from CC are preventable by vaccination and screening, we reviewed the tools available to prevent the disease or its progression at relevant time points within its natural history (Fig. 1).1,6 Herein, we highlight the need for a resource-stratified and mixed programmatic approach to reduce CC mortality and found that a comprehensive cost-effective strategy is necessary and could be adopted successfully in LA.

Corresponding author: Paul E. Goss, MD, PhD, Avon Breast Cancer Center of Excellence, Massachusetts General Hospital Cancer Center, 55 Fruit St, Lawrence House, LRH-302, Boston, MA 02114; Fax: (617) 643-0589; pgoss@partners.org

1Department of Breast Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; 2Harvard Medical School, Boston, Massachusetts; 3Oncology Department, Maria Curie Hospital, Buenos Aires, Argentina; 4Center for Oncology and Hematology, Wilhelminen Hospital, Vienna, Austria; 5Clinical Oncology, Cancer Institute of Sao Paulo State, Sao Paulo, Brazil; 6Johns Hopkins University School of Medicine, Baltimore, Maryland; 7Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts; 8The University of Texas MD Anderson Cancer Center, Houston, Texas; 9Division of Gynecologic Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; 10Global Oncology Initiative, Dana-Farber Harvard Cancer Center, Boston, Massachusetts; 11Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; 12Brazillian Gynecologic Oncology Group, Federal University, Minas Gerais, Brazil; 13Clinica AMO, Salvador, Bahia, Brazil; 14The Global Cancer Institute, Boston, Massachusetts; 15Avon International Breast Cancer Research Program, Massachusetts General Hospital, Boston, Massachusetts; 16University of New England, Biddeford, Maine

Brittany L. Bychkovsky was the lead author for the article and contributed to the literature search, study design, data collection, data analysis, data interpretation, and writing. All other authors contributed to the writing and editing of the article. All authors approved the final version of the article.

DOI: 10.1002/cncr.29813, Received: October 5, 2015; Revised: November 3, 2015; Accepted: November 9, 2015, Published online December 15, 2015 in Wiley Online Library (wileyonlinelibrary.com)
HPV, CC PREVENTION, AND SCREENING

**HPV and Cervical Cancer Pathogenesis**

Greater than 100 types of HPV have been identified to date and approximately 40% can infect the genitalia. HPV can be detected by HPV DNA testing. Persistent infection with “high-risk” HPV types (which include HPV-16, -18, -31, -45, -33, -35, -51, -52, -58, and -59) can cause CC. In LA, HPV-16/18 reportedly cause approximately 70% of all CC cases, HPV-45 is reported to cause 6% of cases, and HPV-31 and HPV-33 each cause approximately 4% of invasive CC cases. In the United States, 80% to 90% of sexually active adults will acquire a genital tract HPV infection by age 45 years. To our knowledge, the true prevalence of HPV infection is unknown in LA. Data have consistently demonstrated that immunocompetent women generally clear the virus within 2 years, although many are reinfected or coinfected with another subtype.

If HPV is not cleared by the immune system, cellular changes can occur in the cervix and result in dysplasia, which over time can develop into invasive CC. There is a well-described latency period between initial HPV infection and invasive CC that varies from 5 to 30 years depending on both patient and viral factors. The chronic and stepwise pathogenesis of CC and the long duration between infection and the development of invasive disease allows for multiple opportunities to intervene and prevent cancer.

Based on the pathogenesis (Fig. 1), there are 2 major interventions that can prevent CC: 1) HPV vaccination in HPV-naive subjects, which results in primary prevention; and 2) screening and detection of cervical dysplasia (a precancerous lesion) and early-stage CC, which is secondary prevention.

Public awareness and patient education complement HPV vaccination and screening and male circumcision.
can also decrease rates of HPV infection. In the current study, we focused on prevention using HPV vaccination and CC screening.

**HPV Vaccination**

Two HPV vaccines, the bivalent Cervarix (GlaxoSmithKline, Research Triangle Park, NC), which covers HPV-16 and -18, and the quadrivalent Gardasil (Merck and Company, Kenilworth, NJ), which covers HPV-6, -11, -16, and -18, have been available in the United States since 2009 and 2006, respectively. The quadrivalent vaccine is approved by the US Food and Drug Administration (FDA) for females and males aged 9 to 26 years and the bivalent vaccine is FDA-approved for females aged 9 to 25 years. A 9-valent vaccine (Gardasil-9) recently became available and offers protection against 7 HPV types that cause CC (types 16, 18, 31, 33, 45, 52, and 58) and 2 types that cause nonmalignant genital warts (types 6 and 11). It is important that the vaccine be administered before the first sexual encounter because it has no effect on existing HPV infections or cervical dysplasia. In HPV-naive populations, 3 large randomized trials have demonstrated that both vaccines are highly effective, preventing 93% to 100% of cervical neoplasias due to the specific HPV types in the vaccine.

With regard to the vaccination schedule for HPV, both the bivalent and quadrivalent vaccines were designed and studied to be administered in 3 doses over a 6-month period. However, the efficacy of the 2-dose regimen also has been studied in a post hoc analysis by combining data from the Costa Rica HPV vaccine trial and the PATRICIA (Papilloma TRial against Cancer In young Adults) trial and demonstrated that the 2-dose regimen provides similar protection against new infections with HPV-16/18 infections at 4 years compared with the 3-dose regimen. However, data comparing the 2 regimens with respect to definitive endpoints are lacking due to cost reasons. Currently, experts believe that 2 doses are adequate if given over 6 months to adolescent girls aged <15 years, and both the Pan American Health Organization (PAHO) and the World Health Organization (WHO) support this schedule in girls aged <15 years.

In the majority of LMICs, there is significant interest in introducing the 2-dose vaccine rather than the 3-dose schedule because it improves completion rates and is cost-saving. Currently, Chile and Ecuador have introduced the HPV vaccine as a 2-dose series in girls aged <15 years (Table 1) (unpublished data), and other countries are expected to follow soon.

**CC Screening**

**Cytology-based screening (Papanicolaou test)**

Cytology-based smear screening is complex, and requires significant infrastructure: health personnel must be trained to perform pelvic examinations and collect an adequate sample and prepare it for cytolologic interpretation. Cytopathology staff then must interpret the Papanicolaou (Pap) test and results are needed in a timely manner. Because of these requirements, cytology-based screening is best regulated at a national/central level to reduce diagnostic errors. Although most countries in LA have cytology-based screening available (Table 1) (unpublished data), these programs are often underfunded, not comprehensive, and have issues with quality and/or delayed follow-up care.

**Visual Inspection With Acetic Acid (See and Treat)**

When cytology-based screening is not available or feasible, the use of visual inspection with acetic acid (VIA) is recommended. For VIA, acetic acid is applied to the cervix and if whitening of the epithelium indicating dysplasia is observed, immediate treatment with cryotherapy or loop electrosurgical excision procedure is performed (“see and treat”). The method is inexpensive and requires fewer staff and less resources compared with cytology-based screening.

A VIA screening trial in India that relied on community health care workers found that VIA could reduce CC mortality by 31% over a 12-year period. VIA screening is best reserved for women aged >35 years because younger women are more likely to have transient dysplasia from a short-term HPV infection that results in a positive VIA examination but does not require treatment. At the current time, Argentina, Bolivia, Colombia, Costa Rica, El Salvador, Guatemala, Guyana, Haiti, Nicaragua, Suriname, Trinidad, and Tobago, Uruguay, and Venezuela offer VIA screening (Table 1) (unpublished data).

**HPV Screening**

HPV DNA testing is a tool for HPV detection and can be used in combination with cytology-based screening or as a stand-alone method. When used alone without a pelvic examination, a positive HPV test indicates HPV infection and should prompt the performance of colposcopy to determine whether a woman has cervical dysplasia. Historically, HPV testing has been reserved for women aged ≥30 years in conjunction with cytology screening because in younger women, HPV infection often clears without clinical consequences. HPV testing as a stand-alone method is gaining attention based on data from India in...
| Country          | Incidence per 100,000 Women | Mortality per 100,000 Women | Mortality to Incidence Ratio | CC Screening | Presence of National Immunization Program (Year Initiated) | Sex/Age     | Vaccine Type and Dosing Schedule | Estimated Coverage for First Dose (Year)b | Estimated Coverage for Completing the Series (Year)c |
|------------------|-----------------------------|-----------------------------|-------------------------------|--------------|--------------------------------------------------------|-------------|----------------------------------|------------------------------------------|------------------------------------------|
| Argentina        | 20.8                        | 8.3                         | 0.40                          | Both         | Yes (2011)                                             | Girls/11 y  | Bivalent, 0-1-6 mo                | 80% (2011)                              | 50% (2011)                               |
| Belize           | 32.7                        | 14.9                        | 0.46                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Bolivia          | 47.7                        | 21                          | 0.44                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Brazil           | 16.3                        | 7.3                         | 0.45                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Chile            | 12.8                        | 6                           | 0.47                          | Both         | Yes (2014)                                             | Girls/9-10 y| Bivalent, 0-6-60 mo               | 97% of girls aged 11-13 y (2014 overall) | 53% received 2nd dose of girls aged 11-13 y (2014) |
| Colombia         | 18.7                        | 8                           | 0.43                          | Both         | Yes (2012)                                             | Girls/9-10 y| Quadrivalent, 0-12 mo             | NA                                       | NA                                       |
| Costa Rica       | 11.4                        | 4.4                         | 0.39                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Cuba             | 17.1                        | 6.7                         | 0.39                          | Public       | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Dominican Republic | 30.7                        | 12.3                        | 0.40                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Ecuador          | 29.0                        | 14                          | 0.48                          | Both         | Yes (2014)                                             | Girls/9-11 y| Bivalent, 2-dose schedule         | NA                                       | NA                                       |
| El Salvador      | 24.8                        | 11.9                        | 0.48                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Guatemala        | 22.3                        | 12.2                        | 0.55                          | Private       | Public                                                 | No          | NA                               | NA                                       | NA                                       |
| Guyana           | 46.9                        | 21.9                        | 0.47                          | Public       | Public                                                 | Yes (2012)  | Girls/12-13 y                    | NA                                       | NA                                       |
| Haiti            | 24.9                        | 14.8                        | 0.59                          | No           | Public                                                 | No          | NA                               | NA                                       | NA                                       |
| Honduras         | 29.4                        | 14.1                        | 0.48                          | Both         | No                                                     | No          | NA                               | NA                                       | NA                                       |
| Mexico           | 23.3                        | 8                           | 0.34                          | Both         | NA                                                     | Yes (2008)  | Girls/9-12 y                    | 98% (2010)                              | 67% (2010)                               |
| Nicaragua        | 36.2                        | 18.3                        | 0.51                          | Both         | No                                                     | Yes (2008)  | Girls/10 y                      | 95% (2010)                              | 67% (2010)                               |
| Panama           | 18.7                        | 7.1                         | 0.38                          | Both         | No                                                     | Yes (2013)  | Girls/10-11 y                   | NA                                       | NA                                       |
| Paraguay         | 34.2                        | 15.7                        | 0.46                          | Both         | No                                                     | Yes (2013)  | Girls/10 y                      | NA                                       | NA                                       |
| Peru             | 32.7                        | 12                          | 0.37                          | Both         | No                                                     | Yes (2011)  | Girls/10 y                      | NA                                       | NA                                       |
| Suriname         | 38.0                        | 15.7                        | 0.41                          | Both         | No                                                     | Yes (2013)  | Girls/11-12 y                   | NA                                       | NA                                       |
| Trinidad and Tobago | 24.5                        | 12                          | 0.49                          | Both         | No                                                     | Yes (2013)  | Girls/12 y                      | NA                                       | NA                                       |
| Uruguay          | 18.9                        | 7.1                         | 0.38                          | Both         | Private                                                 | Yes (2013)  | Girls/12 y                      | NA                                       | NA                                       |
| Venezuela        | 32.8                        | 12.3                        | 0.38                          | Both         | No                                                     | Yes (2006)  | Girls and boys/11-12 y Girls and women/13-26 y if did not receive it previously. Boys and men/13-21 y if did not receive it previously | Both vaccines, 3-dose schedule            | 57.3% for girls aged 13-17 y (2013), 34.6% for boys aged 13-17 y (2013) | 37.6% for girls aged 13-17 y (2013), 13.9% for boys aged 13-17 y (2013) |
| United States    | 6.6                         | 2.7                         | 0.41                          | Both         | No                                                     | Yes (2008)  | Girls and women/9-26 y Boys and men/9-26 y | Both vaccines for girls and women, 3-dose schedule, Quadrivalent vaccine for boys and men, 3-dose schedule | NA                                       | 85% for girls in grade 6 (2013), 79% for boys in grade 6 (2013) |
| Canada           | 6.3                         | 1.7                         | 0.27                          | Both         | No                                                     | Yes (2008)  | Girls and women/9-26 y Boys and men/9-26 y | NA                                       | NA                                       |

Abbreviations: CC, cervical cancer; HPV, human papillomavirus; NA, not available; VIA, visual inspection with acetic acid.

a Cervical cancer incidence and mortality rates are measured as age-standardized rates per 100,000 and were obtained from GLOBOCAN 2012. Not all Latin American countries have comprehensive national cancer registries and data regarding incidence and mortality rates are estimated in countries without comprehensive cancer registries. Available data regarding HPV vaccination were presented.

b Coverage rates were the percentage of individuals who received the HPV vaccine compared with those in the target population.

c Series was defined as 3 doses in designated countries in which 3 doses are recommended and 2 doses in countries in which 2 doses are administered.

d These numbers are from Prince Edward Island, in which a school-based vaccine program was used.

e It is too early to evaluate third dose completion for Brazil.
which screening women aged 30 to 59 years with HPV testing alone reduced CC mortality to a greater effect than VIA or cytology-based screening. Based on these data, the FDA has approved a new HPV DNA test from Roche (Nutley, NJ) as a screening test for CC. Although promising, primary HPV screening is still expensive, requires infrastructure and laboratory expertise, and can miss up to 15% of invasive cancers if used without cytology (vs 3.9% when used with cytology).

**Implications of successful screening**

Screening has been shown to reduce invasive CC incidence, decrease the rate of late-stage disease, and ultimately save lives. Both the Pap test (with or without HPV DNA testing) and VIA have been proven to be effective in detecting dysplasia. Countries with screening coverage of 50% to 69% of women undergoing the Pap test every 3 to 5 years have death rates of 4 per 100,000 women per year whereas in countries with coverage of 50% to 69%, this rate is ≤2 per 100,000 women per year.

By way of example, CC rates have decreased by 70% in the United States over the past 40 years, largely due to the introduction in 1941 of the Pap test and cytology-based screening. Current US guidelines recommend cytology-based testing for women aged 21 to 29 years every 3 years, and in 5-year intervals thereafter using a combination of cytology and HPV DNA testing. CC screening is not advised for women aged <21 years or for women aged >65 years who previously underwent adequate screening and are not at an increased risk of CC.

**LIMITATIONS OF EXISTING CC PREVENTION AND SCREENING EFFORTS IN LA**

**Lack of Primary Prevention (HPV Vaccination)**

Among LA populations, public awareness of HPV vaccination is lacking due to low health literacy. In Honduras, among 632 mothers interviewed in a primary care setting, only 13% had heard of HPV vaccination despite having received information regarding CC awareness. Survey studies from the Bahamas, Guatemala, and Puerto Rico have similarly identified a lack of awareness about HPV infection, its relationship to CC, and the role of the HPV vaccine.

In 2011, only 4 LA countries had included HPV vaccination in their national recommendations, mostly through school-based immunization programs (Argentina, Antigua, Barbados, Brazil, Bermuda, Chile, the Cayman Islands, Colombia, Ecuador, Guyana, Mexico, Panama, Paraguay, Peru, Puerto Rico, Saba, St. Maarten, Suriname, Trinidad and Tobago, and Uruguay). Despite international support for the HPV vaccine in LA, the vaccine is not covered by the public health system in Bolivia, Nicaragua, Venezuela, and Honduras, all of which are countries with high rates of CC (unpublished data). Although the HPV vaccine can be purchased at a discounted price through PAHO, one reason for not introducing a nationwide program is that infrastructure to support wide-scale vaccination is still expensive.

PAHO reports that 80% of adolescent girls in LA now “have access to the HPV vaccine,” which means that based on population data, 80% of girls aged 12 years live in countries with an HPV immunization program. However, this does not mean the girls actually complete the vaccine series or even receive the first dose. Compared with these availability figures, the actual vaccination completion rate is a superior measure of health care delivery outcome, meaning that the vaccine has been procured, delivered, and successfully administered as per the recommended schedule. For example, in Argentina, although 80% of girls aged 12 years received the first dose, only 50% completed the 3-dose series. Similar discrepancies have been reported in Panama (95% of girls receiving the first dose but only 68% completing the series) and Brazil (97% of all girls aged 11-13 years receiving the first dose administered at school but only 53% receiving the second dose, which was administered in health centers) (unpublished data). Alarming, in Brazil, vaccination rates have already declined in the second year of the program: 83% of the target population (girls aged 11-13 years) received the first dose by May 2014 versus only 40% of the target population (girls aged 9-11 years) by May 2015 (unpublished data).

**Challenges of CC Screening**

The majority of women in LA are not receiving screening despite efforts within the past 2 decades to develop cytology-based screening programs. Many women continue to be diagnosed with advanced CC, often at ages <45 years. Among 37,638 cases diagnosed in Brazil between 2000 and 2009, 71% were stage IIB or higher (FIGO staging) and regional studies from urban cities in Brazil, Chile, and Colombia demonstrated that 36% to 56% of all new patients with CC present with stage III
disease at the time of diagnosis (Table 2). In comparison, in the United States, 47% of women diagnosed with CC have localized stage I or II disease, 36% have regional disease (stage III), and 12% have stage IV metastatic disease.

Data from health surveys in countries in LA have demonstrated that <55% of eligible women received a recent Pap test. This is especially true for the urban poor, rural and remote populations, and those with barriers to care. In contrast, women in urban areas and those with private insurance are more likely to undergo CC screening. By way of example, data from Brazil in 2011 indicated that countrywide, 16 Pap tests were performed per 100 women aged 25 to 59 years (or 0.16 Pap tests per woman), which was 79% of the defined target of 0.20 Pap tests per woman. Although the set targets varied from state to state for unknown reasons, the report demonstrated that none of the nation’s 27 regions achieved their targets and 4 regions did not even achieve 60% of their goal. The finding that 80% of all Pap tests were performed on women receiving annual screening indicate very low screening rates outside of these cohorts, and suggest that there is insufficient capacity to expand screening.

Even when available, cytology-based screening is difficult to sustain in resource-limited areas with poor infrastructure and staff. This results in poor-quality tests, and several reports from LA have demonstrated that Pap tests are often suboptimal due to issues with sampling, preparation, or interpretation (Table 3). In Brazil, 10% of all samples taken in the country were not interpretable for quality reasons (poor sample, poor sample preparation, or no timely review and interpretation) and this rate was as high as 60% in the Amazonas state.

For women with abnormal findings on the Pap test, timely colposcopy with biopsies and, if these findings are abnormal, ablative (cryotherapy) or excisional procedures (loop electrosurgical excision procedure) are recommended. For example, a study from Boa Vista, in the Brazilian state of Roraima, reported that although 86% of eligible women participate in screening, the incidence of CC remains high, presumably because screened women with abnormal findings do not receive timely care.

### IMPROVING CC CONTROL IN LA

Multiple and varied strategies exist regarding CC control in LA. Despite promising local initiatives, it is difficult to discern the best strategy given the paucity of...
comparative data and pervasive systemic limitations such as inadequate funding. In this context, we discuss possible strategies for controlling CC in LA.

**Issues to Consider in Primary Prevention (HPV Vaccination) in LA**

When introducing a new vaccine in LA, PAHO recommends attention to several criteria: disease burden, characteristics of the vaccine, adverse events, postmarket surveillance, cost-effectiveness, vaccine supply, and logistical and operational issues such as financing and partnerships to support a program. All these factors, in addition to social criteria and political will, need to be considered when initiating HPV vaccination programs. For HPV vaccination, PAHO recommends that it should be introduced only when there is a clear plan for its implementation, and the vaccine program is both scalable and sustainable: when the immunization program is public, when the program targets one whole birth cohort as a country, and when it is organized to gradually enhance its immunization rate so that high coverage (>95%) can be achieved.

Based on available data, we will address several of these factors that need to be considered when implementing HPV vaccination.

**Effectiveness of the vaccination**

In theory, wide-scale HPV vaccination will substantially reduce the incidence of CC if coverage is high (≥70%). Depending on assumptions related to vaccination and screening, vaccination could theoretically reduce the lifetime risk of CC by 35% to 80%. In the LA region, PAHO supports the purchase of HPV vaccines at a discounted price: as of 2014, the bivalent vaccine was available at a US dollar cost of $13.48 per dose and the quadrivalent vaccine for $14.25 per dose, with a further reduction to $8.50 per dose for the bivalent vaccine in 2015. Through volume discounts, even lower prices can be achieved, which is exemplified by a batch of 15 million doses of the quadrivalent vaccine purchased by Brazil in 2014 for $11.90 per dose. Thereafter, through a technology transfer program with Merck and Company, the Instituto Butantan, a Brazilian biomedical research center affiliated with the Sao Paulo State Secretary of Health, will produce the quadrivalent vaccine locally for <$10 per dose (unpublished data).

For countries with a gross national income of <$1580 per capita, the Global Alliance for Vaccines and Immunization (GAVI) has negotiated an even lower price of $4.50 for the bivalent and $4.60 for the quadrivalent vaccine (in US dollars). However, in LA, only Haiti currently qualifies for the GAVI price, although other countries (eg, Bolivia, Honduras, Guyana, and Nicaragua) were previously eligible when the price negotiations began. Even if the GAVI price appears to be quite affordable, one study found that the HPV vaccination is affordable only in low-income countries such as Haiti if procured at a cost of <$2/dose. To troubleshoot these issues, the Cervical Cancer Action network was founded and is currently working to further reduce the cost of HPV vaccination through programs and grants.

In LA countries with existing national vaccination programs, an HPV vaccine program can simply piggyback onto this system so that a low price might be decisive for making vaccination affordable. However, in countries without established vaccine distribution channels and/or

---

**TABLE 3. Examples of Poor-Quality Pap Test Cytology in Latin America**

| Study      | Location     | No. of Samples | Test     | Comparators                                                                 | Concordancea |
|------------|--------------|----------------|----------|------------------------------------------------------------------------------|--------------|
| Lazcano-Ponce 199768 | Mexico      | 40             | Pap cytology | 30 pathologists compared with a standard cytopathologist certified by the Pathological Anatomy Council of Mexico | κ of 0.04 for moderate dysplasia; κ of 0.29 for invasive cancer |
| Carreon 200769     | Costa Rica  | 357            | Pap cytology | Community pathologist diagnoses to an independent review by 2 pathologists in the United States | US pathologists agreed with 81% to 84% of CIN3 diagnoses and 13% to 31% of CIN2 diagnosis |
| Cendales 201067    | Colombia    | 4863           | Pap cytology | Original reports compared with a second report made by expert pathologists from the National Institute of Colombia | κ of 0.47 for “abnormalities in squamous cells” |

Abbreviation: CIN, cervical intraepithelial neoplasia; Pap, Papanicolaou.

aConcordance is presented as the Cohen kappa coefficient. Kappa (κ) is a statistical measure of the agreement between items in which κ=1 if there is complete agreement and κ=0 when there is no agreement between the 2 comparators or reflects an association that would occur by chance alone.
poor health service infrastructure, HPV vaccination may not be affordable or implementable even if the vaccine is purchased at a low price.

**Cost-effectiveness**

Cost-effectiveness analyses (CEA) consistently demonstrate that HPV vaccination is cost-effective if the vaccine is purchased at a reduced rate.\(^79-82\) Although 2 of these studies were funded by the manufacturer of the bivalent vaccine,\(^80,83\) independent studies specific to Belize, Brazil, and Colombia also have found that HPV vaccination of girls was cost-effective if procured at a reduced price.\(^81,82,84\) The CEA performed for Belize, Brazil, and Colombia considered various vaccination and screening scenarios, the incidence and mortality of CC, and each country’s gross domestic product to determine the cost-effectiveness threshold (determined to be 3 times the gross domestic product). The study from Belize modeled the outcomes of vaccinating a cohort of 4000 girls at age 10 years with the quadrivalent vaccine at a price of $13.79 per dose and found that the cost of vaccination per disability-adjusted life-year (DALY) averted was $429/DALY, which is well below the cost-effectiveness threshold of $14,385/DALY for Belize.\(^82\) The Brazilian CEA found that the most cost-effective strategy was to vaccinate adolescent girls if the vaccine costs <$100 per woman and simultaneously to perform CC screening 3 times over the course of a woman’s lifetime.\(^84\) For Colombia, vaccinating girls aged 12 years is cost-effective with a 3-dose schedule if the vaccines are purchased at ≤$49 per dose for the quadrivalent vaccine and ≤$47 per dose for the bivalent vaccine.\(^81\)

A more recent Brazilian CEA explored expanding HPV vaccination to include boys and found that this was not cost-effective.\(^85\) However, expanding vaccination to include boys may be cost-effective with respect to other preventable HPV-related diseases in males (genital warts, oropharyngeal cancer, anal cancer, and other genital cancers).\(^86\) However, it is impossible to currently perform CEA with this endpoint because we lack comprehensive registry data regarding all HPV-related malignancies in LA.\(^28\)

**Primary target population**

HPV vaccination is most effective in young girls before the onset of sexual activity and exposure to the HPV virus.\(^87\) For this reason, all vaccination plans in LA recommend vaccinating preadolescent girls between the ages of 9 and 12 years.\(^24,87\) Unlike high-income countries, to our knowledge no country in LA to date has included boys and/or men in their HPV vaccination program due to unsubstantiated cost-effectiveness. This strategy is also recommended by experts and international organizations for LMICs.\(^52,87\)

**Secondary target population**

The WHO states that “vaccination of secondary target populations of older adolescent females or young women is recommended only if this is feasible, affordable, cost-effective, does not divert resources from vaccinating the primary target population or effective cervical cancer screening programs, and if a significant proportion of the secondary target population is likely to be naïve to vaccine-related HPV types.”\(^87\) In LA, where resources are a rate-limiting factor, HPV vaccination strategies that target girls initially are recommended.\(^87\)

To the best of our knowledge, the issue of whether boys should be included in vaccination strategies has not been definitively clarified because none of the prior CEA specific to LA considered the benefit of herd immunity on CC incidence or how vaccination would lower the incidence (and associated costs) of other HPV-related diseases. Herd immunity is the indirect protection that a person who is not immune receives from an infectious disease when a large percentage of the population has become immune to an infection, either by exposure or vaccination. In models of herd immunity, higher vaccination coverage levels among girls alone or strategies that include both girls and boys have been found to reduce the incidence of HPV infections for unvaccinated women. Observational data from Australia have demonstrated that expanding HPV vaccination to boys may benefit a broader population because the prevalence of HPV-16/18 infection also was found to be lowered in unvaccinated women 6 years after introducing HPV vaccination to girls.\(^88\) This has also been shown in models from the Netherlands and Germany, in which vaccinating boys was found to lower HPV infection rates by an additional 13% to 19%.\(^89,90\)

Not only will vaccinating boys reduce the incidence of HPV infection and CC among unvaccinated girls and women, but it will also prevent HPV-related disease in men, which includes genital warts, penile cancer, anal cancer, oral papillomas, and oropharyngeal cancer.

**Vaccination dose**

In 2015, PAHO and WHO recommended introducing the HPV vaccines on either the 3-dose or 2-dose schedule.\(^32,33\) Current dosing schedules in LA countries can be found in Table 1.\(^1,2,3,21-29\) (unpublished data). Given the recent data from the Costa Rica vaccine trial and the
PATRICIA trial, a 2-dose schedule will most likely become the new standard in LA.

Administration of the vaccine
Because the primary target population of HPV vaccination is young girls, programs may be most successful if integrated into schools. School-based HPV vaccination programs have been successful in Australia, the United Kingdom, and Canada, with a 3-dose completion rate exceeding 70%. By contrast, in the United States, where the vaccine is recommended for girls and boys (without school-based programs), recent reports have demonstrated that only 37.6% of girls and 13.9% of boys aged 13 to 17 years have received all 3 doses of the vaccine. School-based vaccination also has been shown to be effective in LA in a study conducted in Barretos, Brazil, in which 85% of a total of 1389 girls participating in a school-based HPV vaccine trial completed the 3-dose vaccine series. This approach would especially benefit indigenous and rural girls who would not otherwise receive HPV vaccination. However, if school-based vaccination programs are introduced in LA, policy makers should recognize that there are large disparities in school enrollment between urban and rural populations, with >6.5 million children not enrolled in school in LA. In contrast, mandating HPV vaccination as a requirement for school enrollment, a strategy that has been suggested for high-income countries, is an inadequate approach to reach disenfranchised LMIC populations.

If school-based programs are not feasible, the HPV vaccine should be administered with another mandatory vaccine at the time of a physician visit. In the United States, where uptake of the HPV vaccination is disappointingly low, the Centers for Disease Control and Prevention predicts that if the HPV vaccine would be administered with another mandatory vaccine, coverage would increase from 54% to 92%. More studies in LA are needed to determine the best strategy to introduce an HPV vaccine program. To highlight this, a pilot project in Peru found that the approach would need to be different depending on whether the population was urban, rural, or marginalized (ie indigenous).

Monitoring the vaccination program
Because many logistical issues can arise that may affect a vaccine’s supply chain, it is important to monitor the performance of a vaccination program to ensure its effectiveness, efficiency, and cost-effectiveness. For example, in Argentina and Panama, approximately 30% of eligible girls who initiated the HPV vaccination did not complete it. Analyzing such data will allow policy makers to work on improving vaccination programs.

Importance of and Issues in Secondary CC Prevention (Screening) in LA
Even under optimal conditions, it will take decades for HPV vaccination to have an effect on CC in LA, and therefore it should be viewed as one tool among many in the armamentarium of CC control. Because the vaccines do not treat preexisting HPV infections and related disease, diligent secondary prevention through CC screening will remain essential for the foreseeable future. However, it must be emphasized again that screening strategies that have been successful and affordable in high-income countries have had poor results in LMICs. Therefore, we have reviewed a few important CC screening studies that have been performed and may be particularly relevant for screening among the LA population.

Cytology-based screening programs are effective only if properly implemented. If the resources and infrastructure to perform high-quality Pap tests do not cover the entire country or reach populations at high risk of developing CC, which is a problem in LA, there is a low probability of achieving a positive impact. To be successful in LA, cytology-based screening programs most likely need to be organized in a nontraditional manner. For example, a mobile HPV screening program in Panama proved to be effective in reducing CC incidence and reached the neediest communities at insignificant cost. This novel approach is worth considering, but it is unclear if this type of program conducted within the confines of a study is scalable.

VIA has proven to be feasible in low-resource settings because of the simplicity and acceptance of this strategy, leading to increased adherence compared with cytology-based screening. A CEA from Honduras found that VIA would cost $3198 per cancer case avoided compared with $36,802 with cytology-based screening. VIA screening is most likely the best approach to reduce CC incidence and mortality in countries in which the gross national income per capita is <$3000, and in remote/rural areas in which there are barriers to cytology-based screening programs.

Based on the ATHENA trial (Addressing the Need for Advanced HPV Diagnostics) demonstrating that HPV screening has a role as a stand-alone test for screening, the incorporation of this approach into clinical practice is expected in LA. With respect to resource-limited settings, a trial performed among 131,746 women aged 30 to 59 years in rural India demonstrated that HPV testing alone was superior in reducing CC mortality compared with VIA or cervical cytology.
The main advantage of HPV testing is that it allows self-sampling, which may be useful in LA populations because CC screening is still stigmatized. The positive impact of self-sampling on adherence was demonstrated in a trial that included >6000 women from Jujuy, Argentina. In this study, 2 approaches were compared: an educational intervention in which women were encouraged to obtain screening at their local community health center versus HPV DNA self-collection screening facilitated by community health workers (intervention arm). In the intervention arm, 86% of women underwent screening compared with only 20% in the control arm. The study is noteworthy because there was a high participation rate and it used community health workers. Screening rates were found to be independent of the sex of the health care worker and the setting (rural vs urban). However, issues regarding health care infrastructure remain even with self-sampling: samples must be promptly delivered and processed in a central laboratory, and patients still need to receive appropriate counseling regarding their results, most likely requiring a clinical consultation at their local health center.

The 2 main disadvantages of HPV testing are its cost and the infrastructure needed for implementation; currently, Mexico is the only country in LA that has included HPV testing in its national cancer plan. Pilot programs from Argentina, Colombia, El Salvador, Nicaragua, Paraguay, and Peru are currently exploring whether HPV testing is feasible for screening on a national level. To overcome infrastructural barriers, new versions of HPV DNA tests that can be performed without the use of water, electricity, or technically trained personnel have been designed. Results are available within 3 hours and self-sampling by the patient is possible. Preliminary studies are promising, but more rigorous test evaluation and validation are needed before adoption by public health systems.

**CC CONTROL: CALL FOR A COMPREHENSIVE STRATEGY**

Vaccination and screening strategies for CC that are successful in high-income countries cannot simply be extrapolated to LA. Currently, countries in LA appear eager to introduce the HPV vaccine, which is highly worthy but insufficient by itself. LA countries need to invest in both educational and screening initiatives because only in this way will a comprehensive plan against CC lead to reductions in mortality. As Katz and Wright cautioned in 2006, CC screening programs cannot be implemented in isolation because millions of women have already been exposed to HPV before immunization and those who are most vulnerable will not be reached by vaccination programs.

In this review, we endeavored to highlight that despite numerous effective interventions against CC being available in LA, a comprehensive strategy is needed for CC control. This should include education and, most importantly, adequate screening including timely follow-up and treatment of curable lesions. Any approach must

| Rate of stage II or higher CC (per 100,000 person-y) | Standard Care | HPV DNA Testing | VIA | Cytology-Based Screening |
|----------------------------------------------------|---------------|-----------------|-----|-------------------------|
| Rate of CC mortality (per 100,000 person-y)        | 33            | 15              | 32  | 23                      |
|                                                    | 26            | 13              | 21  | 21                      |

**Further Management: Patient Education and the Role of Patient Navigators**

Educational initiatives focused on CC prevention for disenfranchised and rural populations are important for CC control because they increase the level of awareness of HPV infection and CC. Studies from Africa and LA have demonstrated that local educational interventions through media coverage are inexpensive and improve participation and adherence rates to CC prevention efforts.

Loss to follow-up of positively screened patients and the inability of health services to adequately treat patients with preneoplastic lesions in a timely manner are major factors that contribute to the continuously high CC mortality rates reported in LA. Patient navigator programs can significantly improve screening rates and address the known sociocultural barriers of underserved and rural populations and are more affordable compared with new screening technologies (such as HPV DNA testing). These types of programs are important for engaging indigenous women in CC screening and should be organized so that there is both race and language concordance between patients and navigators. This is particularly important for countries with large indigenous populations such as Bolivia, Ecuador, Guatemala, and Peru.
pay special attention to the large cohort of young women who are disenfranchised, live in rural areas, and have not been offered adequate education, because they are the ones most likely to not be effectively vaccinated, to be insufficiently screened, and not able to undergo optimal treatment. Therefore, to reduce CC mortality in LA, a comprehensive strategy that includes underserved and underinsured patients will have the most success.

FUNDING SUPPORT
No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES
Mayra E. Ferreyra, Jessica St. Louis, Caroline M. Vail, and Paul E. Goss are supported by the Avon Foundation. Gilberto de Lima Lopes Jr. has received nonfinancial support and travel fees from the World Health Organization; grants and personal fees from Pfizer, Eli Lilly, Sanofi Aventis, Boehringer Ingelheim, Astra Zeneca, Roche, Merck-Serono, Merck Sharp and Dhome, Fresenius Kabi, and Bristol-Myers Squibb; and grants from the governments of Brazil, Singapore, and the United States for work performed outside of the current study, Tom C. Randall has acted as a consultant for the National Cancer Institute Center for Global Health.

REFERENCES
1. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55:244-265.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2010 v.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10. Lyon, France: IARC; 2014.
3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.
4. Pan American Health Organization. Cervical cancer. http://www.paho.org/whc/spanish/topics/cancer/cancer_cervical.html. Accessed July 21, 2014.
5. United Nations. Millennium Development Goals Report 2015. http://www.un.org/millenniumgoals/2015_MDG_Report/pdf/MDG%202015%20Rev%20(July%202014).pdf. Accessed August 5, 2015.
6. Creative Commons. Syringe images. http://search.creativecommons.org. Accessed March 19, 2015.
7. Hariri S, Dunne E, Saraiva M, Unger E, Markowitz L. Chapter 5: Human Papillomavirus (HPV) Manual for the Surveillance of Vaccine-Preventable Diseases. http://www.cdc.gov/vaccines/pubs/surv-manual/chpt05-hpv.html. Accessed August 12, 2015.
8. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11:1048-1056.
9. Chesson HW, Dunne EF, Hariri S, Markowitz L. The estimated lifetime probability of acquiring human papillomavirus in the United States. Sex Trans Dis. 2014;41:660-664.
10. Schiffman M, Castle PE, Jereonimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007;370:890-907.
11. Julius JM, Ramondeta I, Tipton KA, Lal LS, Schneider K, Smith JA. Clinical perspectives on the role of the human papillomavirus vaccine in the prevention of cancer. Pharmacotherapy. 2011;31:280-297.
12. Albero G, Castelhano X, Giuliano AR, Bosch FX. Male circumcision and genital human papillomavirus: a systematic review and meta-analysis. Sex Transm Dis. 2012;39:104-113.
13. Joula EA, Giuliano AR, Iversen OE, et al; Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372:711-723.
14. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356:1928-1934.
15. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915-1927.
16. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009;374:301-314.
17. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al; Costa Rica Vaccine Trial and PATRICIA study groups. Efficacy of fewer than 3 doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. Lancet Oncol. 2015;16:775-786.
18. Kreimer AR, Sherman ME, Sahasrabuddhe VV, Safaeian M. The case for conducting a randomized clinical trial to assess the efficacy of a single dose of prophylactic HPV vaccines among adolescents. J Natl Cancer Inst. 2015;107(3). pii: dju436.
19. World Health Organization. Summary of the SAGE April 2014 Meeting. http://www.who.int/immunization/ncd/gf/meetings/2014/ april/report_summary_april_2014/en/. Accessed June 18, 2015.
20. Pan American Health Organization. Technical Advisory Group on Vaccine-Preventable Diseases XXI Meeting: Vaccination: A Shared Responsibility; July 3-5, 2013; Quito, Ecuador. http://www.paho.org/immunization/toolkit/resources/tech-recommendations/TAG-2013.pdf. Accessed June 18, 2015.
21. Pan American Health Organization. Cancer in the Americas. Basic Indicators 2013. http://www.paho.org/hq/index.php?option=com_topics&view=article&id=2&Itemid=40735&lang=en. Accessed August 5, 2015.
22. Pan American Health Organization. PAHO Immunization Newsletter December 2014. HPV Vaccine in Chile and Ecuador. http://www.paho.org/hq/index.php?option=com_content&view=article&id=3130:immunization-newsletter&Itemid=3504&lang=en. Accessed April 2, 2015.
23. World Health Organization. HPV Vaccine in Argentina: a leap forward for girls’ and women’s health. http://www.who.int/features/2013/argentina_hpVac_cervin/en/. Accessed March 3, 2015.
24. Munoz N. Progress in HPV vaccine introduction in Latin America. https://www.g-occ.org/uploads/12nov_hpvtoday.pdf. Accessed August 5, 2015.
25. Stokley S, Jeyarajah J, Yankey D, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014—United States. MMWR Morb Mortal Wkly Rep. 2014;63:620-624.
26. McClure CA, MacSwain MA, Morrison H, Sanford CJ. Human papillomavirus vaccine uptake in boys and girls in a school-based vaccine delivery program in Prince Edward Island, Canada. Vaccine. 2015;33:1786-1790.
27. Public Health Agency of Canada. Canada Communicable Disease Report. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php#S. Accessed August 5, 2015.
28. Goss PE, Lee BL, Badovinac-Crncic T, et al. Planning cancer control in Latin America and the Caribbean. Lancet Oncol. 2013;14:391-436.
29. Pan American Health Organization, World Health Organization, Healthy Caribbean Coalition. Situational analysis of cervical cancer prevention and control in the Caribbean: results from a 2013 assessment of country policies and services for HPV vaccination cc, diagnosis and treatment December, 2013. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=23829&Itemid=. Accessed November 2, 2015.
30. Soneji S, Fukui N. Socioeconomic determinants of cervical cancer screening in Latin America. Rev Panam Salud Publica. 2013;33:174-182.
31. Shastri SS, Misra I, Mishra GA, et al. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. J Natl Cancer Inst. 2014;106:dnu009.
32. International Agency for Research on Cancer. Handbooks of Cancer Prevention. Vol 10: Cervix cancer screening. http://www.iarc.fr/en/publications/pdfs-online/prev/handbook10/index.php. Accessed August 5, 2015.

33. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol. 2015;136:189-197.

34. US Preventive Services Task Force. Screening for cervical cancer, clinical considerations. http://www.uspreventiveservicestaskforce.org/3rduspsft/cerv Paperback. Accessed August 5, 2015.

35. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360:1385-1394.

36. US Food and Drug Administration. FDA News Release: FDA approves first human papillomavirus test for primary cervical cancer screening. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm. Accessed September 9, 2014.

37. Tao X, Griffith CC, Zhou X, et al. History of high-risk HPV and Pap test results in a large cohort of patients with invasive cervical carcinoma: experience from the largest women’s hospital in China. Cancer (Cancer Cytopathol). 2015;123:421-427.

38. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. Sys Rev. 2013;2:35.

39. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol. 2012;13:78-88.

40. Arbyn M, Sankaranarayanan R, Muwonge R, et al. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. Int J Cancer, 2008;123:153-160.

41. Arbyn M, Raifu AO, Weiderpass E, Bray F, Anttila A. Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer. 2009;45:2640-2648.

42. Anttila A, von Karsa L, Aasmia A, et al. Cervical screening policies and coverage in Europe. Eur J Cancer. 2009;45:2649-2658.

43. Papanicolaou GN, Traut HE. The diagnostic value of vaginal smears for human papillomavirus vaccination in Honduras. Vaccine. 2011;29:823-831.

44. Arbyn M, Raifu AO, Weiderpass E, Bray F, Anttila A. Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer. 2009;45:2640-2648.

45. Black K, Ottenbacher AJ, Finney Rutten LJ, et al. Predictors of participation in human papillomavirus mass vaccination among adolescents: a concordance study. Biomedica. 2010;30:107-115.

46. Lazzano-Ponce EC, Alonso de Ruiz P, Martinez-Arias C, et al. Reproducibility study of cervical cytopathology in Mexico: a need for regulation and professional accreditation. Diagn Cytopathol. 1997;17:20-24.

47. Carreon JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3; results from a histological review of population-based cervical samples. Int J Gynaecol Obstet. 2007;26:441-446.

48. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007;11:201-222.

49. Carreon JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3; results from a histological review of population-based cervical samples. Int J Gynaecol Obstet. 2007;26:441-446.

50. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007;11:201-222.

51. World Health Organization. WHO Vaccine-Preventable Diseases: monitoring system. 2014 Global Summary. http://apps.who.int/immunization_monitoring/globalsummary. Accessed August 5, 2015.

52. World Health Organization. WHO Vaccine-Preventable Diseases: monitoring system. 2014 Global Summary. http://apps.who.int/immunization_monitoring/globalsummary. Accessed August 5, 2015.

53. de Sanjose S, Serrano B, Castellsague X, 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. Vaccine 2012;30(suppl 4):D1-D83, vi.

54. Pan American Health Organization. Eight in 10 adolescent girls in the Americas have access to HPV vaccine, following its introduction in Brazil. http://www.paho.org/hq/index.php?option=com_content&view=article&id=9394&c. Accessed August 5, 2015.

55. Aday LA, Andersen RA. Framework for the study of access to medical care. Health Serv Res, 1974;9:208-220.

56. Teixeira LA. From gynaecology offices to screening campaigns: a brief history of cervical cancer prevention in Brazil [in English, Portuguese]. Hwa Cienc Saude Manguinhos. 2015;22:221-239.

57. Stormo AR, Espey D, Glenn J, et al. Findings and lessons learned from a multi-partner collaboration to increase cervical prevention efforts in Bolivia. Rural Remote Health. 2013;13:2595.

58. Carmo CG, Luis RR. Survival of a cohort of women with cervical cancer diagnosed in a Brazilian cancer center. Rev Saude Publica. 2011;45:661-667.

59. Mascarello KC, Zandonade E, Amorim MH. Survival analysis of women with cervical cancer treated at a referral hospital for oncology in Espirito Santo State, Brazil, 2000-2005. Cad Saude Publica. 2013;29:823-831.

60. Pardo C, Cendales R. Survival analysis of cervical cancer patients [in Spanish]. Biomedica. 2009;29:437-447.

61. Sepulveda VP, Gonzalez CP, Napolitano RC, et al. Cancer de cuello uterino: sobrevida a 3 y 5 anos en Hospital San Jose. Rev Clin Obstet Ginecol. 2008;7:151-155.

62. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynaecological Cancer. Int J Gynaecol Obstet. 2006;95(suppl 1):S43-S103.

63. Quintero JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3; results from a histological review of population-based cervical samples. Int J Gynaecol Obstet. 2007;26:441-446.

64. Carreon JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3; results from a histological review of population-based cervical samples. Int J Gynaecol Obstet. 2007;26:441-446.

65. Instituto Nacional de Cancer Jose Alencar Gomes da Silva. Controlle del Cancer del Colo di Utero. http://www2.inca.gov.br/wps/wcm/connect/acess_programas/site/home/nobi/brazil/programa_nacional_controle_cancer_colo_uteres/indicadores/. Accessed August 5, 2015.

66. Murillo R, Wisnies C, Cendales R, Pineros M, Tovar S. Comprehensive evaluation of cervical cancer screening programs: the case of Colombia. Salud Publica Mex. 2011;53:469-477.

67. Cendales R, Wisnies C, Murillo RH, et al. Quality of vaginal smear for cervical cancer screening: a concordance study. Biomedica. 2010;30:107-115.

68. Lazzano-Ponce EC, Alonso de Ruiz P, Martinez-Arias C, et al. Reproducibility study of cervical cytopathology in Mexico: a need for regulation and professional accreditation. Diagn Cytopathol. 1997;17:20-24.

69. Carreon JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3; results from a histological review of population-based cervical samples. Int J Gynaecol Obstet. 2007;26:441-446.

70. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007;11:201-222.

71. Navarro C, Fonseca AJ, Sibajev A, et al. Cervical cancer screening: the CCA Report Card. http://cervicalcanceraction.org/pubs/ pubs.php#reportcard. Accessed August 5, 2015.

72. de Sanjose S, Serrano B, Castellsague X, 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. Vaccine 2012;30(suppl 4):D1-D83, vi.

73. Pan American Health Organization. Eight in 10 adolescent girls in the Americas have access to HPV vaccine, following its introduction in Brazil. http://www.paho.org/hq/index.php?option=com_content&view=article&id=9394&c. Accessed August 5, 2015.
76. Pan American Health Organization. Revolving fund prices. [Accessed August 5, 2015.](http://www.paho.org/hq/index.php?option=com_content&view=article&id=9561:healthmid-40714&lang=en)

77. Goldie SJ, O’Shea M, Campos NG, Diaz M, Sweet S, Kim SY. Health and economic outcomes of HPV 16, 18 vaccination in 72 GAVI-eligible countries. *Vaccine*. 2008;26:4080-4093.

78. Gomez JA, Lepetic A, Demarteau N, et al. Cost-effectiveness analysis of a cervical cancer vaccine in five Latin American countries. *Vaccine*. 2009;27:5519-5529.

79. Aponte-Gonzalez I, Fajardo-Bernal L, Diaz J, Eslava-Schmalbach J, Gamboa O, Hay JW. Cost-effectiveness analysis of the bivalent and quadrivalent human papillomavirus vaccines from a societal perspective in Colombia. *PLoS One*. 2013;8:e80639.

80. Talhari SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme: a cost-effectiveness analysis in a low-resource setting. *Br J Cancer*. 2007;97:1532-1538.

81. Olesen J, Jorgensen TR. Revisiting the cost-effectiveness of universal HPV-vaccination in Denmark accounting for all potentially vaccine preventable HPV-related diseases in males and females. *Cost Eff Resour Alloc*. 2015;13:4.

82. Albornoz G, Arrossi A. Improving the Pan American Health Organization’s vaccine supply chain. [Accessed August 5, 2015.](http://www.unesco.org/new/en/education/themes/strengthening-education-systems/inclusive-education/single-view/news/221_million_children_and_adolescents_in_the_region_are_not_in_school_or_at_serious_risk_of_dropping_out/)

83. Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in HPV vaccination coverage among adolescent girls, 2007-2012, and postlicensure vaccine safety monitoring, 2006-2013-United States. *MMWR Morb Mortal Wkly Rep*. 2013;62:591-595.

84. Penny M, Bartolini R, Mosqueda NR, et al. Strategies to vaccinate against cancer of the cervix: feasibility of a school-based HPV vaccination program in Peru. *Vaccine*. 2011;29:5022-5030.

85. Ak A, Heier JL, Wardell CL, et al. Improving the Pan American Health Organization's vaccine supply chain. [http://hscenter.gatech.edu/sites/default/files/ImprovingPAHOsVaccineSupplyChainpaper.pdf. Accessed November 18, 2015.](http://hscenter.gatech.edu/sites/default/files/ImprovingPAHOsVaccineSupplyChainpaper.pdf)

86. Paulino M, Arrossi S. Analysis of the reasons for abandoning the follow-up and treatment process in women with pre-cancerous cervical lesions in the province of Jujuy: implications for health management [in Spanish]. *Salud Colect.* 2012;8:247-261.

87. UNICEF. 22.1 million children and adolescents in Latin America and the Caribbean. *Cancer*. 2013;35:1134-1138.

88. Talhari SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis*. 2014;14:958-966.

89. Matthijssen SM, Hontelez JA, Naber SK, et al. The estimated impact of natural immunity on the effectiveness of human papillomavirus vaccination. *Vaccine*. 2015;33:5537-5564.

90. Horn J Damus O, Kretschmar ME, et al. Estimating the long-term effects of HPV vaccination in Germany. *Vaccine*. 2013;31:2372-2380.

91. Bellard K, Myers P. Evaluation of the National HPV Vaccination Program Campaign. [http://hpv.health.gov.au/wp-content/uploads/2013/01/HPV-Vaccination-Campaign-Evaluation-FINAL-171213-D13-2437752.pdf. Accessed August 6, 2015.](http://hpv.health.gov.au/wp-content/uploads/2013/01/HPV-Vaccination-Campaign-Evaluation-FINAL-171213-D13-2437752.pdf)

92. Bowyer HL, Dodd RH, Harlow LA, Waller J. Association between human papillomavirus vaccine status and other cervical cancer risk factors. *Vaccine*. 2014;32:4310-4316.

93. Fregnan JH, Carvalho AL, Eluf-Neto J, et al. A school-based human papillomavirus vaccination program in Barretos, Brazil: final results of a demonstrative study. *PLoS One*. 2013;8:e62647.

94. UNESCO. 22.1 million children and adolescents in Latin America and the Caribbean are not in school or at serious risk of dropping out. [http://www.unesco.org/new/en/education/themes/strengthening-education-systems/inclusive-education/single-view/news/221_million_children_and_adolescents_in_the_region_are_not_in_school_or_at_serious_risk_of_dropping_out/](http://www.unesco.org/new/en/education/themes/strengthening-education-systems/inclusive-education/single-view/news/221_million_children_and_adolescents_in_the_region_are_not_in_school_or_at_serious_risk_of_dropping_out/)

95. Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination coverage among adolescent girls, 2007-2012, and postlicensure vaccine safety monitoring, 2006-2013-United States. *MMWR Morb Mortal Wkly Rep*. 2013;62:591-595.

96. Penny M, Bartolini R, Mosqueda NR, et al. Strategies to vaccinate against cancer of the cervix: feasibility of a school-based HPV vaccination program in Peru. *Vaccine*. 2011;29:5022-5030.

97. Ak A, Heier JL, Wardell CL, et al. Improving the Pan American Health Organization’s vaccine supply chain. [http://hscenter.gatech.edu/sites/default/files/ImprovingPAHOsVaccineSupplyChainpaper.pdf. Accessed November 18, 2015.](http://hscenter.gatech.edu/sites/default/files/ImprovingPAHOsVaccineSupplyChainpaper.pdf)

98. Coleman MA, Levison J, Sangi-Haghpeykar H. HPV vaccine acceptability in Ghana, West Africa. *Vaccine*. 2011;29:3945-3950.

99. Ruiz de Garcia de Zuniga M, Arocon Fresco CH, Ruiz Cosp, M, et al. Knowledge, attitudes and practices on the Papancinaeus smear test (PAP) in pregnant women attending public hospitals of the Department of Alto Parana, Paraguay, [http://scielo.isc.unlp.edu.ar/scielo.php?script=sci_arttext&pid=S1812-95282008000020008&lng=es&nrm=iso. Accessed August 6, 2015.](http://scielo.isc.unlp.edu.ar/scielo.php?script=sci_arttext&pid=S1812-95282008000020008&lng=es&nrm=iso)

100. Battaglia TA, Bak SM, Heeren T, et al. Boston Patient Navigation Research Program: the impact of navigation on time to diagnostic resolution after abnormal cancer screening. *Cancer Epidemiol Biomarkers Prev*. 2012;21:1645-1654.

101. Charlot M, Santana MC, Chen CA, et al. Impact of patient and navigator race and language concordance on care after cancer screening abnormalities. *Cancer*. 2015;121:1477-1483.

102. Suarez E, Prieto M. Cervical cancer: the Chilean perspective. *FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer*. *Int J Gynaecol Obstet*. 2006;95(suppl 1):5235-5238.

103. Kanz JT, Wright AA. Preventing cervical cancer in the developing world. *N Engl J Med*. 2006;354:1110.