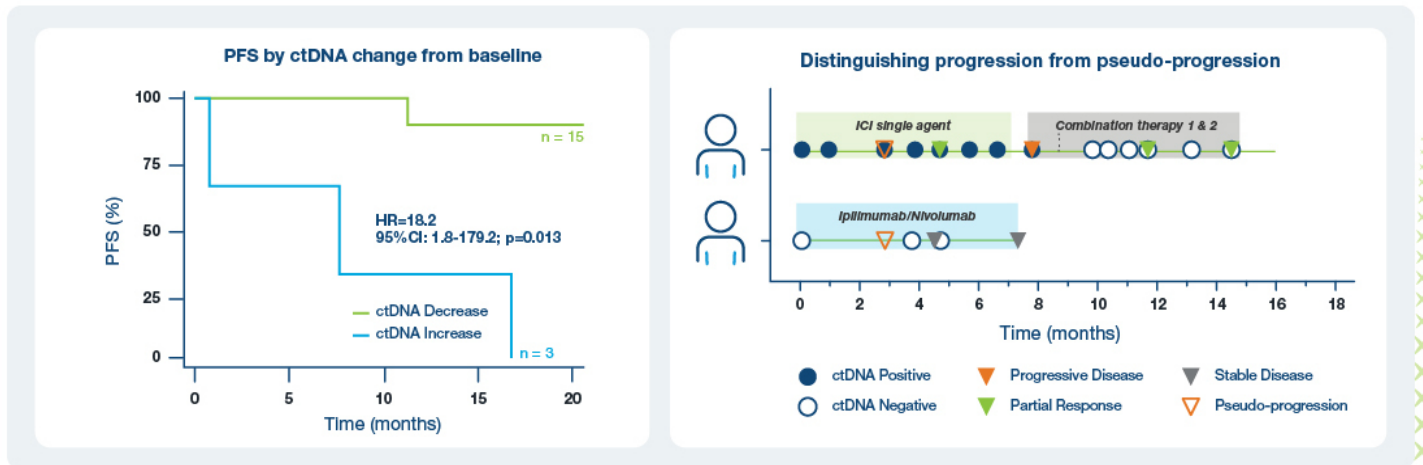


Use Signatera™ ctDNA dynamics to inform earlier treatment decisions in metastatic melanoma patients

Early on-treatment ctDNA dynamics were predictive of PFS in metastatic melanoma patients receiving 1st line ICI treatment¹

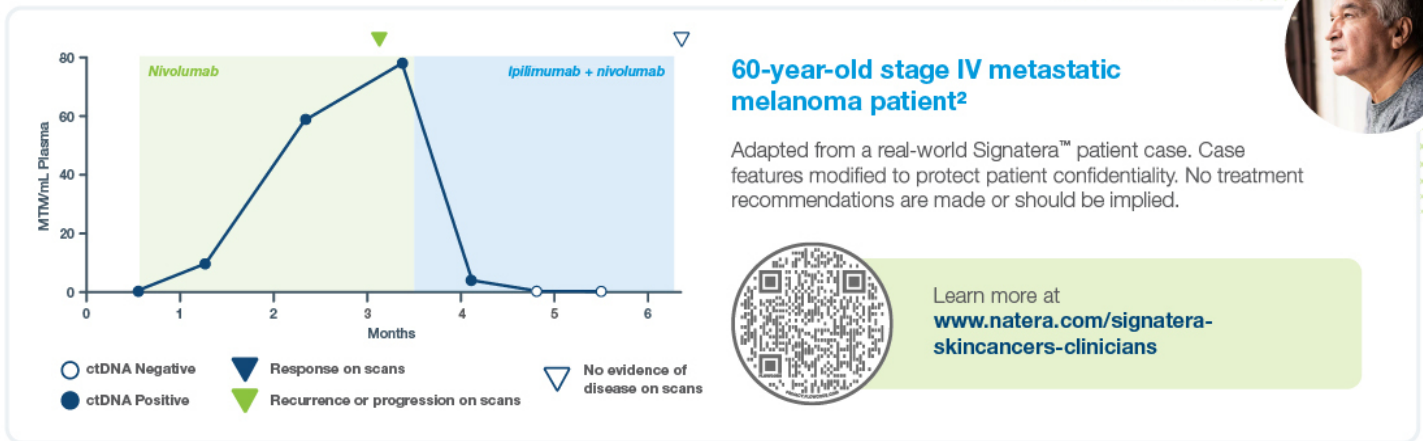
At week 6, Signatera™ identified that patients with increasing ctDNA had a 18x higher risk of progression than ctDNA-negative patients



- Patients with any increase in ctDNA levels from baseline by week 6 of 1st Line ICI treatment (monotherapy and combination ICIs) had a significantly shorter PFS (HR: 18; p=0.013).
- Signatera™ was able to help distinguish between true vs pseudo-progression

Should treatment be changed or escalated?

Early rise in ctDNA can help inform treatment escalation or change



Covered by Medicare for immunotherapy treatment response monitoring across all stages for solid tumors

PFS = Progression-free survival

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An Alert to Latin America: Current Human Papillomavirus Vaccination Trends Highlight Key Barriers to Successful Implementation

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INTRODUCTION

Human papillomavirus (HPV)-related cancer continues to be a leading cause of cancer in Latin America, mainly due to cervical cancer burden. The prevalence of HPV infection has been found to be twice as high in Latin America compared with the worldwide average,^{1,2} and it is associated with 68,220 new cases of cervical cancer per year. Incidence rates range from 20 to 80 per 100,000 women, and 31,712 cervical cancer-associated deaths occur each year in Latin America.³ According to the Pan American Health Organization (PAHO), if current trends continue, the number of women with cervical cancer in Latin America will reach over 110,000 cases annually by 2030. Because cervical cancer affects predominantly young women, it represents the single biggest cause of years of life lost due to cancer in the developing world.⁴ Furthermore, without effective screening strategies, the annual numbers of other HPV-related cancers (eg, oropharyngeal and anal cancers) also are increasing.⁵

In high-income countries (HICs), due to the invention of the Papanicolaou (Pap) test and after its widespread implementation in the 1960s, the incidence of cervical cancer declined by >60%, thereby confirming this as the most effective cancer screening tool in the history of medicine. However, the Pap test has achieved limited success in low-income and middle-income countries (LMICs) worldwide, including in Latin America. This limited success is attributed to several factors, including a lack of organized screening programs within fragmented health systems, technical limitations, a low population coverage and not sufficiently reaching high-risk subpopulations, poor quality control, and insufficient monitoring. Timely treatment and follow-up for women with abnormal cytology results are among other difficulties encountered. The few, relatively well-organized screening programs that do exist in Latin America are primarily located in major urban centers.⁶

The advent of HPV prophylactic vaccination offers a promising step toward cervical cancer prevention. Based on the high incidence of HPV-related cancers, the strong carcinogenic potential of certain HPV strains, and numerous trials proving the high efficacy of HPV vaccines, prophylactic immunization is considered one of the most important available tools with which to alter the incidence of HPV-associated cancers in countries throughout Latin America and all other LMICs. Large-scale HPV immunization can reduce lives lost due to preventable cancers and relieve health systems strained by the costly treatment of these cancers, which commonly present at later stages. However, despite its proven efficacy and safety, vaccine uptake by populations has been lower than expected for several reasons, including the high cost of the HPV vaccine, the requirement for multiple doses, limited knowledge of HPV vaccine efficacy and safety, cultural barriers, insufficient provider recommendations, and inadequate implementation strategies.

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DOI: 10.1002/cncr.30647, **Received:** January 9, 2017; **Revised:** January 30, 2017; **Accepted:** January 31, 2017, **Published online** April 25, 2017 in Wiley Online Library (wileyonlinelibrary.com)

Latin America must remain alert in the ongoing implementation of the HPV vaccine to address these barriers and ensure successful uptake throughout the region. Although Latin America has a long-standing history of high vaccination coverage with robust national immunization programs,⁷ the HPV vaccine has unique challenges, and countries in the region will need to adjust their existing vaccination platforms to accommodate HPV vaccination. Herein, we discuss the current status of HPV vaccine coverage in Latin America and the main barriers that still need to be overcome to achieve adequate coverage.

HPV Vaccine Coverage in Latin America: Where Are We?

Although >140 strains of HPV have been identified to date, only some are associated with cancer. Vaccines are available against the following viral strains: a bivalent vaccine against HPV types 16 and 18; a quadrivalent vaccine against HPV types 6, 11, 16, and 18; and a 9-valent vaccine against 5 additional oncogenic genotypes, including strains 31, 33, 45, 52, and 58.⁸ The specific recommendations for vaccine administration vary by country and vaccine type, but the World Health Organization (WHO) global recommendation includes the primary target group of adolescent girls aged 9 to 13 years, and the so-called “catch-up” vaccination group of women up to age 26 years. It is important to note that there is no current evidence that these vaccines treat preexisting infection or disease, a factor to take into account when considering vaccine efficacy in certain patient subpopulations, as well as the ongoing need for effective secondary screening programs. Because HPV infections are acquired soon after the initiation of sexual activity, the HPV vaccine is most effective when administered before the onset of sexual activity. The majority of programs worldwide do not include a recommendation to vaccinate adolescent boys, mainly due to the cost of the vaccine, the greater cost-effectiveness of high vaccination coverage among girls compared with lower vaccination coverage among both boys and girls, and little recognition of an emerging epidemic of HPV-associated cancers in men. However, many HICs and some middle-income countries have now included boys in their national immunization programs.⁹

The WHO recommends a vaccine schedule of 2 to 3 doses for the primary target population of girls within the age range of 9 to 13 years, completed over a course of 6 months. In April 2009, the WHO issued a position statement recommending that routine HPV vaccination of females should be included in national immunization programs, provided that: 1) cervical cancer and/or HPV-

related diseases constitute a public health priority; 2) vaccine introduction is programmatically feasible; 3) sustainable financing can be secured; and 4) the cost-effectiveness of vaccination strategies in the country or region is considered. The WHO states that “HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer” and, importantly, “should not undermine or divert funding from other effective cervical cancer screening programs,” such as Pap testing programs.⁹

To our knowledge, Panama and Mexico were the first 2 countries in Latin America to include HPV vaccination in their immunization programs. In Panama, the Ministry of Health added a bivalent HPV vaccine to the national immunization program in 2008, aimed at a target population of girls aged 10 years and delivered through adolescent health services in clinics and schools. In 2009, 1-dose coverage among 10-year-old girls in Panama was 89%, with 3-dose coverage reported at only 46%.¹⁰ In Mexico, the HPV vaccine was introduced in 2008 to 125 targeted municipalities with the lowest human development index (comprising approximately 5% of Mexico’s population), which were estimated to have the highest incidences of cervical cancer.¹⁰ Quadrivalent HPV vaccine was delivered via mobile health clinics to girls aged 12 to 16 years in these municipalities using a 0-month, 2-month, and 6-month dosing schedule.¹⁰ In 2008, 1-dose coverage among girls in the target age range within these cities was 98%, and 3-dose coverage was 81%. In 2011, Mexico’s National Immunization Council approved a nationwide expansion of its HPV vaccination program to include school-based vaccination of all girls aged 9 years.

After the introduction of the vaccine in Brazil in 2014, PAHO stated that HPV immunization is now available to >80% of adolescent girls in the Americas. However, this does not mean that 80% of girls in the region are being vaccinated, but instead indicates that 80% of adolescent girls live in one of the countries of the Americas that offer the HPV vaccine through public immunization programs. To date, Argentina, Antigua, Barbados, Belize, Brazil, Bermuda, Chile, the Cayman Islands, Colombia, Ecuador, Guyana, Honduras, Mexico, Panama, Paraguay, Peru, Puerto Rico, Saba, St. Maarten, Suriname, Trinidad and Tobago, and Uruguay have included HPV vaccination in their national recommendations (Fig. 1). In 2015, Venezuela included HPV vaccination in its national public immunization policy, but it remained unavailable as of December 2016.¹¹ Panama introduced the vaccination of boys in 2016, and Brazil announced the inclusion of the



Figure 1. Latin American countries with national recommendations for the human papillomavirus vaccine. The countries not shown are Saba and St. Maarten.

HPV vaccine for boys in its public national vaccination program, which is planned to start in 2017.¹²

To prevent HPV-related cancers, the Advisory Committee on Immunization Practices, an advisory body of the US Centers for Disease Control and Prevention (CDC), has historically recommended the completion of a 3-dose vaccine series for children aged 11 and 12 years. Although it should be noted that the CDC recently updated its HPV immunization recommendations in December 2016 from 3 to 2 doses for children aged 9 to 14 years, with older adolescents continuing to receive the 3-dose series, adherence to the long-standing 3-dose recommendation is currently low.¹³ For example, in the United States, approximately 60% of female adolescents received at least 1 dose of the vaccine in 2014, but only 39.7% completed the 3-dose series; the same decline in adherence has been observed among boys, with 41.7% completing the first vaccine dose but only 21.6% completing all 3 doses. Therefore, even when the HPV vaccine is considered “available,” adherence to the 2-to-3-dose vaccine schedule is of concern. Despite poor adher-

ence, vaccination coverage with ≥ 1 dose of any HPV vaccine slightly increased in the United States between 2013 and 2014, from 56.7% to 60.0% among adolescent girls and from 33.6% to 41.7% among adolescent boys,¹³ thereby indicating overall positive trends in vaccine uptake.

Conversely, in Latin America, the alarming situation is the reduction in uptake of even the first vaccine dose in the years after the introduction of the HPV vaccination into national immunization calendars. In Brazil, according to the Ministry of Health, vaccination coverage with ≥ 1 dose decreased from 92% of the target population (girls aged 11-13 years) in 2014 to 69.5% (girls aged 9-11 years) in 2015, a dramatic reduction of 23% in 1 year.¹⁴ A similar trend was observed in Guadalajara, Mexico, which reported a 22% reduction in first-dose uptake from 2009 to 2013.¹⁵ Colombia has faced the deepest fall in adherence. In 2013, Colombia had reached a first-dose coverage rate of 97.5%, the second-best rate worldwide after Australia. However, according to the National Vaccine Program Office,¹⁶ after the “Carmen de Bolívar episode,” in which families in a Colombian town claimed the vaccine made girls sick, the coverage decreased to a mere 20.4% by the end of 2014. No other vaccine has experienced a similar decline in uptake within the first few years of implementation as the HPV vaccine has in Latin America,⁷ drawing attention to the fact that, despite Latin America’s history of successful immunization campaigns and strong national programs, the HPV vaccine has distinct characteristics that must be considered when devising optimal implementation strategies.

Similar to trends observed in the United States and other HICs, the rates of second and third doses are far below first dose rates in Latin America. According to PAHO, in the 2 years after the inclusion of the HPV vaccine in Argentina’s national vaccination schedule, $>80\%$ of girls in the target age group had received the first dose, whereas only 60% and 50%, respectively, had received the second and third doses.¹⁷ In Panama, 1-dose coverage among girls aged 10 years was 89%, and 3-dose coverage was 46%.¹⁸ In Mexico, 1-dose coverage was 85%, and 2-dose coverage was 67%. However, a post hoc statistical analysis of 2 vaccine trials suggested that a single dose of the vaccine may be enough to immunize against HPV types 16 and 18¹⁹; this would represent an important step in reducing the cost and resources required to achieve widespread HPV vaccination coverage. As a result, a clinical trial to evaluate the effectiveness of 1 dose of the HPV vaccine currently is underway, and future efforts possibly may be focused on high compliance to the first dose only.

In fact, despite this potential result, efforts by health systems should continue to focus on adhering to current guidelines, which recommend a 2-to-3-dose schedule.

The paucity of official data regarding HPV vaccine coverage in Latin America limits the current analysis, but these significant reductions in vaccine coverage must be an early warning for countries throughout the Latin American region to collect data and carefully follow their coverage rates. Properly monitoring HPV vaccine uptake and its effects will help countries to better evaluate national trends and implement more efficient strategies according to local situations. Brazil is one country that experiences a significant variance in vaccine adherence, with higher rates of vaccine uptake observed in more developed areas of the country in which cervical cancer is less incident,¹⁴ and lower rates of vaccine uptake noted in areas in which cervical cancer incidence is historically higher. For example, according to the Secretary of Health in the Brazilian state of Alagoas,²⁰ in states in the Northeast region of the country, where cervical cancer continues to be a leading cause of cancer in women, first-dose coverage was only 21.5% of the target population in the second year of public vaccination. In light of trends such as this and the unique nature of the HPV vaccine, countries in Latin America should delineate strategies for measuring and evaluating high vaccine compliance before launching their national programs. This will ensure that public health strategies to support HPV vaccination are effective and efficient, especially within diverse countries and financially constrained health systems.

Overcoming Barriers

According to parents and health care professionals,¹³ barriers to HPV vaccination are multifactorial but tend to fall into 4 main categories: 1) limited knowledge of HPV, HPV-related diseases, and the features of the HPV vaccine; 2) misguided safety concerns by parents and some policy makers; 3) cost to health systems (of both the vaccine and its delivery); and 4) cultural barriers.

In the same way that a lack of knowledge regarding cervical cancer and the importance of cervical cancer screening has hindered the success of Pap testing programs throughout Latin America and in other LMICs, limited knowledge concerning HPV and HPV-related diseases has been a barrier to achieving widespread vaccine uptake.²¹ In a recent Brazilian cross-sectional study, approximately 40.0% of participants reported having heard about HPV, but on closer questioning, only 8.6% had heard of HPV vaccines. Once the participants were informed of the existence of HPV vaccines, approximately 94%

reported that they would get vaccinated and/or vaccinate their teenage children if vaccines were available in the public health system.²² The degree to which health care providers are recommending the vaccine is currently below that which is expected, even in HICs. In a North American survey regarding parental attitudes toward HPV vaccination, approximately 30% of parents cited a lack of knowledge or a belief that the “vaccine was not necessary” as the main reasons for not vaccinating their teens. Among parents of boys, 22.8% reported that the main reason was that HPV vaccination had not been recommended by their physician; among parents of girls, 13.0% reported that HPV vaccination had not been recommended.¹³ Several studies have shown that, once educated that the HPV vaccine prevents cancer, parents and practitioners are more likely to support it.²³⁻²⁵ In addition, the majority of parents in an Australian study agreed that a recommendation from their general practitioner would increase acceptance of the HPV vaccine,²⁶ and the authors of a study from Virginia stated that “provider recommendation remains the strongest modifiable event to promote [HPV] vaccination”.²⁷ Although these data come from HICs, Latin America could learn from the shortcomings of HPV vaccine implementation in these countries and tailor educational interventions for providers and parents to address these concerns. Increasing endorsement from trustworthy references for parents, such as physicians and schools, is an essential step toward leveraging HPV vaccination in Latin America.

Many parents also cite safety concerns as a main reason for declining to give their child the HPV vaccine.²⁶ However, data have shown that these concerns are misguided. According to the WHO, >200 million doses of the HPV vaccine have been distributed globally as of January 2016, and the Global Advisory Committee on Vaccine Safety (GACVS) has not found any safety issue that would alter its current recommendations for the use of the HPV vaccine. A French study of >2 million girls demonstrated no difference in the prevalence of diseases potentially associated with the vaccine between vaccinated and unvaccinated cohorts, except for Guillain-Barre syndrome, for which a small increase in risk was identified in the vaccinated group (<1 in 100,000 vaccinated).²⁸ The WHO suggested that additional studies are necessary, but emphasized that if any adverse events are caused by the vaccine, they are infrequent. Several clinical trials of HPV prophylactic vaccines have been conducted in Latin American countries, all of which have confirmed their safety and efficacy.²⁹ Similar to the important role of the health care provider in recommending the HPV vaccine

to parents, providers also should inform parents about its overall safety as part of their recommendation, to dispel these misconceptions and improve acceptance. There are 2 different schools of thought from the medical community regarding how to accomplish this. The first, as recommended by a study from Boston, suggests longer vaccination appointments so that health care providers have adequate time to educate parents regarding vaccine efficacy and safety.³⁰ The second, which was discussed in a study from Washington, DC, proposes presenting the HPV vaccine within the context of other common and historically accepted childhood vaccines; this strategy has been called “bundling,” and it allows practitioners to approach the HPV vaccine in “a confident and presumptive way,” thereby normalizing its administration.³¹

High cost also is an important concern in many LMICs due to the costs associated with both procuring multiple doses of the vaccine and delivering the vaccine to all of the target population. However, the financial burden of procuring the vaccine is improving for many countries in Latin America. PAHO offers HPV vaccines to governments in Latin America and the Caribbean at one low price for all countries, regardless of purchase size or the economic situation of any particular country. Latin American countries can purchase the HPV vaccine for US\$8.50 per dose through the Revolving Fund of PAHO, making it more accessible for more financially constrained health systems. Studies conducted in Latin America have indicated that HPV vaccination alone or vaccination supplemented with screening are cost-effective strategies to reduce cervical cancer mortality.²⁵ For example, in Argentina, use of the quadrivalent vaccine was far below the threshold of 1 gross domestic product per capita (US\$1009) per quality-adjusted life-year gained,³² and 2 Brazilian studies also have shown that the HPV vaccine is cost-effective, especially in a high-coverage area.^{33,34} In light of this, many countries in Latin America have begun to include the HPV vaccine within public health insurance systems, thereby increasing its accessibility and uptake. For example, in Brazil, HPV vaccine uptake had risen from 3.13% of the target population (girls aged 11–13 years) in 2013 to 92% in 2014, when the Public Health System began providing the vaccine.

Despite the improvements in the price per vaccine dose, this is just one key factor to consider when assessing the cost-effectiveness of the HPV vaccine, and national governments also must take into account the additional resources required for vaccine delivery.³⁴ The WHO has stated that secure, sustainable financing is important for successful implementation of the HPV vaccine in Latin

America, due in part to the need to deliver multiple doses to rural and remote populations. For example, in the Peruvian experience, vaccine delivery cost is approximately US\$1.00 to \$1.30 per dose delivered (only around \$3.00 per girl who is fully vaccinated, in addition to the cost of the vaccine itself), but significant incremental costs occurred because some rural schools were so remote and sparsely populated that reaching girls in these areas came at a much higher program cost than in more accessible locations.³⁵ This reflects the overall challenge of increasing access to preventive health care for underserved populations, highlighting the additional costs of vaccine delivery beyond just procuring the vaccine and the fact that successful vaccine implementation should not preclude the continued financing of screening and other secondary prevention programs. Therefore, countries should support the WHO recommendation for sustainable strategies for HPV vaccine implementation, in terms of financing and the efficient allocation of resources within diverse countries.

Cultural aspects also influence HPV vaccination programs, just as they have influenced Pap test programs throughout Latin America. Although we cannot necessarily compare a screening program, which places a high demand on a health system, with a vaccination program, there are significant similarities between Pap testing and HPV vaccination programs that are important to recognize to avoid repeating Pap implementation failures in Latin America. Religious conservatism and the nature of HPV as a sexually transmitted infection have allowed cultural taboos to hinder communication and education regarding HPV. Specifically, there is a general discomfort among both parents and providers in discussing sex,³⁶ and an unfounded belief that the HPV vaccine would increase adolescent sexual activity, which deters some parents from giving their child the vaccine. These beliefs are not unlike those commonly held regarding Pap tests, such as the misconception among a cohort of Mexican women that a Pap test will take away a woman’s virginity or that an unmarried woman will be judged for being sexually active if she undergoes a Pap test.³⁷ Such attitudes lead to low rates of Pap test screening, and similar misconceptions now threaten HPV vaccine efforts. However, extensive studies have shown that HPV vaccination is not associated with increased sexual activity or earlier sexual activity among adolescents.^{38,39} Such information must be properly promoted by medical societies in Latin America and communicated to parents by primary health care providers in an effort to dispel taboos that prevent the uptake of beneficial health interventions. The focus of the HPV vaccine

narrative must be shifted away from cultural taboos and toward the prevention of life-threatening diseases.

The success of HPV vaccine coverage also will depend on where the vaccination is provided. The majority of other vaccines are required within the first 2 years of life,⁷ when medical appointments are regular, thereby favoring vaccination adherence. However, the HPV vaccine is administered much later in life compared with other common vaccines. Thus, the same vaccination infrastructure and strategies that have been successful in Latin America in the past may not apply to the HPV vaccine, and different strategies must be devised to reach the appropriate target population. In large-scale HPV vaccination programs in the United Kingdom, Australia, and New Zealand, better results were achieved with school-based vaccine delivery programs. Furthermore, higher adherence rates have been achieved with mixed models of vaccine delivery (using both health facility-based and school-based vaccination programs) compared with a school-based model only. Similar studies should be conducted in Latin America to determine the most successful model of HPV vaccine delivery for the unique Latin American context.

Conclusions

Considered to be one of the most important advances in women's health, HPV vaccination has faced more hurdles than initially expected in Latin America, including limited knowledge regarding the vaccine and the diseases it prevents, questions of safety, financial constraints, and cultural barriers.

As of 2016, a total of 22 Latin American countries offer the HPV vaccine in their public health systems, but to our knowledge little information exists regarding adherence in the years after implementation. With support from PAHO, procurement of the vaccine currently is not a major problem, and local factors may be to blame in areas in which uptake is below that expected. These barriers need to be identified and analyzed to be overcome; otherwise, HPV vaccine programs run the risk of repeating the problems associated with Pap testing programs in LMICs: an efficient, life-saving tool that unfortunately is underused for cancer prevention. There is a great need for vigilance in the ongoing implementation of the HPV vaccine in Latin America. Understanding the unique social and structural barriers pertaining to HPV vaccination and mounting a strong and timely response to this public health problem, which should include both improved patient-provider communication and integrated monitor-

ing and evaluation strategies, is needed to attain a significant impact on cervical cancer control.

Given that HPV-associated cancers arise years, if not decades, after an initial infection and that existing vaccines appear to have no therapeutic efficacy on preexisting cervical cancer, countries in Latin America must continue to improve Pap testing programs as a secondary prevention measure. Further delays in implementing high-coverage HPV vaccination programs, coupled with ineffective screening strategies, will only lead to a continued loss of life from a preventable disease and undue financial burden on constrained health systems.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Angelica Nogueira-Rodrigues, Alexandra Bukowski, Eduardo Paulino, Jessica St. Louis, and Paul E. Goss are supported in part by the Avon Breast Cancer Crusade. This funding source had no role in the planning or content of this article. Cinthya Sternberg has received Speakers' fees from AstraZeneca for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

Angelica Nogueira-Rodrigues was the lead author of the article and contributed to the literature search, data collection, data analysis, data interpretation, writing-review, and editing. **Alexandra Bukowski, Eduardo Paulino, Jessica St. Louis, Adriana Barriello,** and **Paul E. Goss** contributed to the literature search, data interpretation, and writing-review, and editing. **Cinthya Sternberg, Markus A. C. Gifoni,** and **Silvana Luciani** contributed to the writing-review and editing. All authors approved the final version of the article.

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