

HPV Vaccination in Latin America: Global Challenges and Feasible Solutions

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OVERVIEW

HPV vaccine programs in Latin America run the risk of repeating the problems associated with Papanicolaou (Pap) test programs, an efficient, life-saving tool that is unfortunately underutilized for cancer prevention, in low- and middle-income countries. There is a great need for vigilance in the ongoing implementation of the HPV vaccine in Latin America.

INTRODUCTION

Although Latin America has a long-standing history of high vaccination coverage with robust national immunization programs, the HPV vaccine has unique challenges and countries in the region must adjust their existing vaccination platforms to accommodate HPV vaccination. Here we discuss the current status of HPV vaccine coverage in Latin America and the main barriers that must be overcome to achieve adequate coverage.

HPV continues to be a leading cause of cancer in Latin America, mainly owing to cervical cancer (CC) burden. The prevalence of HPV infection is twice as high in Latin America compared with the worldwide average^{1,2} and is associated with 68,220 new cases of CC per year. Incidence rates range from 20 to 80 per 100,000 women and 31,712 CC-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 CC in Latin America will increase to more than 110,000 cases annually by 2030. Because CC affects predominantly young women, it represents the single biggest cause of years of life lost as a result of cancer in the developing world. Furthermore, without effective screening strategies, the annual numbers of other HPV-related cancers (e.g., oropharyngeal and anal cancers) are also increasing.⁴⁻⁷

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 to alter the incidence of HPV-associated cancers in countries throughout Latin America and all other low- and middle-income countries. Large-scale HPV immunization can reduce lives lost as a result of 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, HPV vaccine uptake by populations has been lower than expected for several reasons, including the high cost of the vaccine, the requirement for subsequent doses, limited knowledge of HPV vaccine efficacy and safety, cultural barriers, insufficient provider recommendations, and inadequate implementation strategies.

HPV VACCINATION IN LATIN AMERICA: GLOBAL CHALLENGES

HPV vaccines result in an immune response that is 10 times more effective than the virus itself and are available against the following strains: a bivalent vaccine against HPV 16 and 18; a quadrivalent vaccine against HPV 6, 11, 16, and 18; and a nine-valent vaccine against five additional oncogenic genotypes, including strains 31, 33, 45, 52, and 58.⁸ The total duration of protection is still unknown (but is thought to be around 9 years); however, mathematical studies⁹ indicated high rates of antibody concentration for at least 20 years. The first HPV vaccine to be approved was the quadrivalent in Mexico in 2006, followed by the bivalent in Australia in 2007. In April 2009, the World Health Organization (WHO) issued a position statement recommending that routine HPV vaccination of female individuals should be included in national immunization programs, provided that (1) CC 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 WHO¹⁰ states that “HPV vaccines should be introduced as part of a coordinated strategy to prevent CC” and, importantly, “should not undermine or divert funding from other effective CC screening programs,” such as Pap test programs.

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PRACTICAL APPLICATIONS

- HPV vaccination programs run the risk of being an efficient but underutilized tool in Latin America.
- The main multifactorial barriers to HPV vaccination are limited knowledge of HPV, misguided safety concerns, cost to constrained health systems, and cultural barriers.
- Widespread adoption of the HPV vaccine has unique challenges, and countries in Latin America will need to adjust their existing vaccination platforms to accommodate HPV vaccination. Better adherence may be achieved through school-based vaccine delivery programs.
- Proper strategies for vaccine implementation, integrated monitoring, and a strong and timely response to barriers are needed to ensure successful uptake throughout the region.

According to the WHO, as of March 2017, 71 countries (37%) had vaccines implemented in their national immunization programs for 11-year-old girls and 11 countries (6%) also had them available for 11-year-old boys; after 13 years, more than 200 million doses have been administered worldwide thus far. In Latin America, Panama and Mexico were the first two countries 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, one-dose coverage among 10-year-old girls in Panama was 89%, whereas three-dose coverage was only 46%.⁸ 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 CC.⁸ The quadrivalent HPV vaccine was delivered via mobile health clinics to girls aged 12 to 16 years in these municipalities using a 0-, 2-, and 6-month dosing schedule.⁸ In 2008, one-dose coverage among girls in the target age range within these cities was 98%, and three-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 more than 80% of adolescent girls in the Americas. This does not mean that 80% of girls in the region are being vaccinated² 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, Latin American countries Argentina, Bolivia, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Guatemala, Guiana, Honduras, Mexico, Panama, Paraguay, Peru, and Uruguay have included HPV vaccination in their national recommendations. In 2015, Venezuela included HPV vaccination in its national public immunization policy, but it remains unavailable as of March 2019 (Table 1).¹¹

Most programs worldwide do not include a recommendation to vaccinate adolescent boys, mainly owing 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 high-income and some middle-income countries have now included boys in their national immunization programs. Argentina, Brazil, and Panama have already introduced vaccination for boys and Chile has announced it for the second semester of 2019 (Table 1).¹²

An alarming situation in Latin America is the reduction in uptake of even the first vaccine dose in the years following the introduction of HPV vaccination into national immunization calendars. In Brazil, according to the Ministry of Health, vaccination coverage with one or more doses decreased from 92% of the target population (girls aged 11–13) in 2014, when it was implemented, to 69.5% (girls aged 9–11) in 2015, a dramatic reduction of 23% in 1 year.¹³ A similar trend was observed in Guadalajara, Mexico, which saw a 22% reduction in first-dose uptake from 2009 to 2013.¹⁴ Colombia has faced the deepest decrease 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,¹⁵ after the “Carmen de Bolívar episode,” in which families in one 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 seen a similar decline in uptake in the first few years of implementation as the HPV vaccine has in Latin America,¹² alerting 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 (Fig. 1).

Similar to trends observed in the United States and other high-income countries, the rates of second and third doses are far below first-dose rates in Latin America. According to PAHO, in the 2 years following the inclusion of the HPV vaccine in Argentina's national vaccination schedule, more than 80% of girls in the target age group had received the first dose, whereas only 60% and 50% had received the

TABLE 1. Public Policies on HPV Vaccination for Selected Latin American and Caribbean Countries With a Government-Funded HPV Vaccination Program

Country	Target Population (Years)	Year Introduced	Vaccine Delivery
Argentina	Girls age 11	2011	School-based
	Boys age 11	2017	
Bolivia	Girls age 10–12	2017	Started as a campaign
Brazil	Girls age 9–14	2014	Health-center based
	Boys age 11–14	2017	
Chile	Boys	Announced for 2nd semester 2019	School-based
	Girls age 9–14	2014	
Colombia	Girls age 9–17	2012	School-based
Costa Rica	Vaccine not available in the country		
Cuba	Vaccine not available in the country		
Dominican Republic	Campaign announced in March 2019 for girls age 9–10		
Ecuador	Girls age 9–11	2014	School-based/health centers for girls out of school
El Salvador	Vaccine not available in the country		
Guatemala	Girls age 10	2018	School-based
Guiana	Girls	2012	Health centers
Haiti	Vaccine not available in the country		
Honduras	Girls age 11	2016	School-based
Mexico	Girls in fifth grade of primary school; if not in school, age 11	2012 nationwide	School-based/health centers for girls age 11 who are out of school
Nicaragua	Vaccine not available in the country		
Panama	Girls age 10	2008	School-based
	Boys age 10	2016	
Paraguay	Girls age 9–17	2013	School-based
Peru	Girls in fifth grade of primary school	2011	School-based
Uruguay	Girls age 12	2013	Health-center based
		2016	School-based
Venezuela	Vaccine not available in the country		

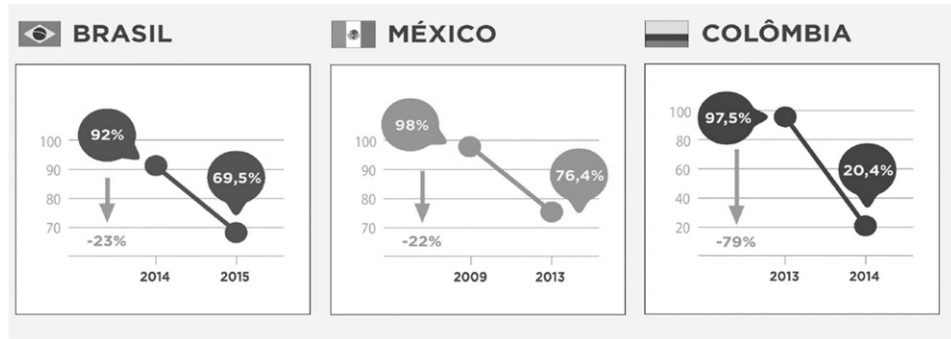
second and third doses, respectively.¹⁶ In Panama, one-dose coverage among girls aged 10 years was 89% and three-dose coverage was 46%.¹⁷ In Mexico, one-dose coverage was 85% and two-dose coverage was 67% (Fig. 2). However, a post hoc statistical analysis of two vaccine trials suggested that a single dose of vaccine may be enough to immunize against HPV 16 and 18¹⁸; as a result, a clinical trial to evaluate the effectiveness of one dose of HPV vaccine is now underway, and future efforts may possibly be focused on high compliance to the first dose only. Despite this potential result, efforts by health systems should continue to focus on adhering to current guidelines. Currently, the WHO recommends a two-dose series (0 and 6–12 months) for most persons who initiate vaccination at ages 9 through 14 years and a three-dose series (0, 1–2, and 6 months) for immunocompromised persons and

individuals who initiate vaccination at ages 15 through 26 years.

The paucity of official data on HPV vaccine coverage in Latin America limits this analysis, but these substantial 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 better evaluate national trends and implement more efficient strategies according to local situations. Brazil is one country that experiences a notable variance in vaccine adherence, with higher rates of vaccine uptake observed in more developed areas of the country where CC is less incident¹⁹ and lower rates of vaccine uptake where CC incidence is historically higher. For example, in states in the Northeast

FIGURE 1. Reduction in Uptake of First Dose in the Years Following the Introduction of HPV Vaccination in Latin American Countries

Infographic: Brazilian Society of Clinical Oncology, SBOC, 2017.



region of Brazil, where CC 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.²⁰ According to the Brazilian Ministry of Health, only 4% of Brazilian cities had 80% or more of the target population vaccinated; in 44% of the cities, vaccine uptake ranged between 50% and 80%, and it was less than 50% in 52% of the remaining locations. In 2017, 79.21% of girls between age 9 and 14 years had received the vaccine first dose and 48.74% received the second one; 43.8% of boys age 12 to 13 years (1.6 million) received the first dose.

In light of trends like 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.

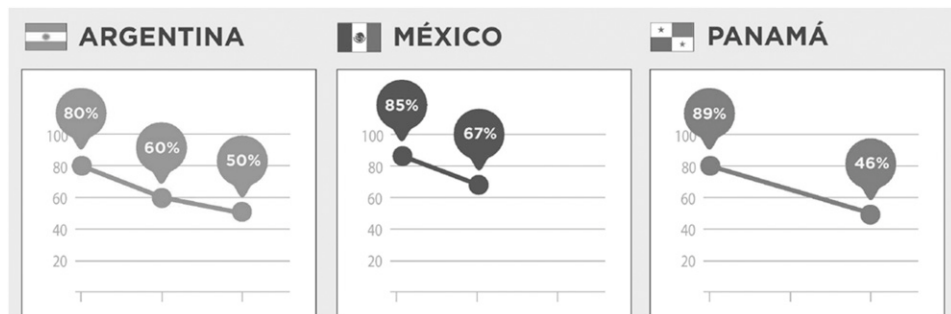
FEASIBLE SOLUTIONS

According to parents and health care professionals,²¹ barriers to HPV vaccination are multifactorial but tend to fall into four 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 about CC and the importance of CC screening has hindered the success of Pap test programs throughout Latin America and in other low- and middle-income countries, limited knowledge about HPV and HPV-related diseases has been a barrier to achieving widespread vaccine uptake.²² In a recent Brazilian cross-sectional study, 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, about 94% reported that they would get vaccinated and/or vaccinate their teenage children if vaccines were available in the public health system.²³ The degree to which health care providers are recommending the vaccine is currently below that which is expected, even in high-income countries. In a North American survey regarding parental attitudes toward HPV vaccination, 30% of parents cited lack of knowledge or 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 doctor; among parents of girls, 13.0% reported that HPV vaccination had not been recommended.²¹ Several studies have shown that once they are educated that the HPV vaccine prevents cancer, parents and practitioners are more likely to support it.²⁴⁻²⁶ Additionally, the majority of parents in an Australian study agreed that a recommendation from their general practitioner would increase acceptance of the HPV vaccine,²⁷ and the authors of a study²⁸ from Virginia

FIGURE 2. Examples of Reduction in Compliance to a Second HPV Vaccine Dose in Latin American Countries

Infographic: Brazilian Society of Clinical Oncology, SBOC, 2017.



state that “physician recommendation is one of the strongest modifiable factors in promoting [HPV] vaccination.” Although these data come from high-income countries, 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 trustable references for parents, like doctors and schools, is an essential step to leverage HPV vaccination in Latin America.

Many parents also cite safety concerns as a main reason for declining to give their child the HPV vaccine.²⁷ However, data show that these concerns are misguided. According to the WHO, more than 200 million doses of HPV vaccines have been distributed globally as of January 2016, and the Global Advisory Committee on Vaccine Safety has not found any safety issue that would alter its current recommendations for the use of HPV vaccination. A French study of more than 2 million girls showed no difference in the prevalence of diseases potentially associated with the vaccine between vaccinated and unvaccinated cohorts except for Guillain-Barré syndrome, for which a small increase in risk was identified in the vaccinated group (less than 1 in 100,000 vaccinated).²⁹ 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.³⁰ Like the important role of the health care provider in recommending the HPV vaccine to parents, providers should also inform parents about its overall safety as part of their recommendation, to dispel these misconceptions and improve acceptance. There are two different streams of thought from the medical community on how to accomplish this. The first, as recommended by a study from Boston, Massachusetts, suggests longer vaccination appointments so health care providers have adequate time to educate parents about vaccine efficacy and safety. The second, which is discussed in a study from Washington, DC, proposes presenting the HPV vaccine in 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 is also an important concern in many low- and middle-income countries, owing to the costs associated both with procuring multiple doses of the vaccine and with 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 U.S. \$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 CC mortality.²⁶ For example, in Argentina, use of the quadrivalent vaccine was far below the threshold of 1 gross domestic product per capita (U.S. \$1,009) per quality-adjusted life-year gained,³² and two Brazilian studies also showed 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 increased from 3.13% of the target population (girls age 11–13) in 2013 to 92% in 2014, when the public health system began providing the vaccine.

Despite the improvements in the price per vaccine dose, it is just one key factor to consider when assessing HPV vaccine cost-effectiveness, and national governments must also take into account the additional resources required for vaccine delivery.³⁴ The WHO has stated that secure, sustainable financing is important for successful HPV vaccine implementation in Latin America, in part because of the need to deliver multiple doses to rural and remote populations. In the Peruvian experience, for example, vaccine delivery cost is approximately U.S. \$1.00 to \$1.30 per dose delivered (only around \$3.00 per girl fully vaccinated, in addition to the cost of the vaccine itself), but substantial 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, highlights the additional costs of vaccine delivery beyond just procuring the vaccine, and supports 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 notable similarities between Pap test 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 about HPV. Specifically, there is a general discomfort among both parents and

providers to discuss sex³⁶ 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 about Pap smears, 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 gets 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 will also depend on where vaccination is provided. Most other vaccines are required in the first 2 years of life,¹² when medical appointments are regular, 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 (utilizing both health facility 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.

CONCLUSION

Considered 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 about the vaccine and the diseases it prevents, questions of safety, financial constraints, and cultural barriers. As of 2019, the HPV vaccine is now available to more than 80% of adolescent girls in Latin America in the public health systems, but little information exists about adherence in the years following implementation. Proper strategies for vaccine implementation, including patient-provider communication and education, and integrated monitoring and evaluation strategies are needed in Latin America. Otherwise, HPV vaccine programs run the risk of repeating the problems associated with Pap test programs, an efficient, life-saving tool that is unfortunately underutilized for cancer prevention, in low- and middle-income countries. 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 is needed to attain a substantial impact in HPV-related cancers.

Given that HPV-associated cancers arise years, if not decades, after an initial infection and that existing vaccines have no therapeutic efficacy on preexisting CC, Latin American countries must continue to improve Pap test 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. Latin America must remain alert in the ongoing implementation of the HPV vaccine to address these barriers and ensure successful uptake throughout the region.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.2022.40.12000>

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