

HPV vaccine implementation and monitoring in Latin America

Silvana Luciani, MHS^c,⁽¹⁾ Laia Bruni MD, MPH, MHS^c,⁽²⁾ Irene Agurto, PhD,⁽¹⁾ Cuauhtémoc Ruiz-Matus, MD.⁽³⁾

Luciani S, Bruni L, Agurto I, Ruiz-Matus C.
HPV vaccine implementation and monitoring in Latin America.
Salud Publica Mex. 2018;60:683-692.
<https://doi.org/10.21149/9090>

Luciani S, Bruni L, Agurto I, Ruiz-Matus C.
Implementación y monitoreo de la vacuna contra el VPH en América Latina.
Salud Publica Mex. 2018;60:683-692.
<https://doi.org/10.21149/9090>

Abstract

Objective. To describe HPV vaccine program implementation, monitoring and evaluation experiences in Latin America. **Materials and methods.** We reviewed published articles in peer-reviewed journals and reports from government websites, as well as the PAHO/WHO/UNICEF Joint Reporting form and the ICO/IARC HPV Information Centre database. **Results.** By December 2016, 13 countries/territories in Latin America (56%) have introduced HPV vaccines. The majority have done so in the past three years, targeting 10-12 year old girls with a two dose schedule, through school programs. Vaccine coverage ranges from 30 to 87%. Safety monitoring is well established, but monitoring vaccine impact is not, and data are not available. **Conclusions.** Although Latin America is the most advanced developing region with HPV vaccine introduction, systems for its monitoring are weak and there is a paucity of consistently available coverage data for this vaccine. Challenges remain to introduce HPV vaccines in several countries, to achieve high coverage, and to strengthen monitoring, evaluation and reporting.

Keywords: immunization program; HPV vaccine; cervical cancer/prevention; monitoring

Resumen

Objetivo. Describir las experiencias con la implementación, monitoreo y evaluación de programas de vacunación contra VPH en América Latina. **Material y métodos.** Revisamos datos publicados en revistas, informes gubernamentales, así como los informes de monitoreo de programas de inmunizaciones de la OPS/OMS/UNICEF y del centro de información del VPH del ICO/IARC. **Resultados.** Hasta diciembre de 2016, 13 países/territorios en América Latina (56%) han introducido vacunas contra VPH. La mayoría lo han hecho en los últimos tres años, apuntando a niñas de 10 a 12 años con un calendario de dos dosis, a través de programas escolares. La cobertura de vacunas varía entre 30 y 87%. La vigilancia de la seguridad está bien establecida, pero el monitoreo del impacto de la vacuna no, y los datos no están disponibles. **Conclusiones.** Aunque América Latina es la región en desarrollo más avanzada en la introducción de la vacuna contra VPH, los sistemas para su monitoreo son débiles y hay una escasez de datos de cobertura disponibles. Sigue habiendo desafíos para introducir vacunas contra VPH en varios países, para lograr una alta cobertura y para fortalecer el monitoreo, la evaluación y la presentación de informes.

Palabras clave: programas de inmunización; vacuna contra HPV; cáncer cervicouterino/prevenición; monitoreo

- (1) Unit of Noncommunicable Diseases, Department of Noncommunicable Diseases and Mental Health, Pan American Health Organization. Washington, DC, USA.
(2) Cancer Epidemiology Research Program, Catalan Institute of Oncology, Barcelona, Spain.
(3) Unit of Comprehensive Family Immunization, Department of Family, Gender and Lifecourse, Pan American Health Organization. Washington, DC, USA.

Received on: September 13, 2017 • Accepted on: March 8, 2018

Corresponding author: Silvana Luciani. Pan American Health Organization. 525 23rd St NW Washington, DC, USA
E-mail: lucianis@paho.org

Immunization is the most cost-effective public health intervention, and more than 20 diseases can currently be prevented with the recommended scheduled childhood and adolescent vaccines. In Latin America, since the inception of the Expanded Program on Immunization (EPI) 40 years ago, countries and territories in this region have made significant advances against vaccine preventable diseases. In fact, the Americas is the first world region to eradicate smallpox, eliminate polio, rubella and congenital rubella syndrome, and most recently eliminate endemic measles transmission.¹ Another opportunity presents itself to significantly reduce, if not begin to eliminate a disease—cervical cancer—with the availability of HPV vaccines. Cervical cancer is the second most common female cancer in Latin America, with approximately 64 000 new cases and 26 000 deaths each year.² HPV infection causes virtually all cervical cancers, in addition to being a risk factor for other cancer types (anal, vaginal, vulvar, oropharyngeal, and penile cancers).³

HPV vaccines were first licensed in 2006, and by early 2016 over 200 million doses of HPV vaccines had been applied around the world, with validating evidence of its safety.⁴ HPV vaccines in use around the world include a bivalent vaccine (Cervarix, GSK, Belgium) protecting against infection from HPV types 16/18; a quadrivalent vaccine (Gardasil, Merck, USA) protecting against infection from HPV types 6/11/16/18; and a recently approved nonavalent vaccine (Gardasil 9, Merck, USA) protecting against infection from HPV types 6/11/16/18/31/33/45/52/58).⁵

WHO recommends HPV vaccines to be introduced into national immunization programs if cervical cancer prevention is a public health priority, if it is programmatically feasible, has sustainable financing, and is cost-effective.⁶ For the Americas region, the Pan American Health Organization (PAHO) Technical Advisory Group on Vaccine Preventable Diseases recommended, in 2013, using 2- and 3-dose extended HPV immunization schedule for girls aged 9-13 years.⁷ Furthermore, the Regional Plan of Action on Immunization, endorsed by the Ministers of Health of the Americas during the 2015 PAHO Directing Council, calls for, among other things, strengthening platforms for universal vaccination, and monitoring the introduction of new vaccines including HPV vaccines.¹

Monitoring HPV vaccines, as is the case with other vaccines, includes monitoring coverage, safety, and impact. Because of the well established EPI programs in Latin America, immunization program performance, safety and coverage is routinely performed through organized information systems. Immunization coverage monitoring is routinely done using administrative

data from immunization registries, vaccination cards and tally sheets, or surveys and records from health service providers, and reported annually through the PAHO/WHO/UNICEF Joint Reporting Form (JRF) for Immunization. Vaccine safety is routinely monitored through immunization program systems for adverse events. Vaccine impact monitoring is more commonly performed through surveillance and special studies. However, HPV vaccines, unlike other vaccines, involve a much more complex process for impact monitoring, as it requires robust clinical, laboratory, and surveillance infrastructure, including cancer registries. While establishing HPV vaccine monitoring processes is not a prerequisite for the initiation of an HPV vaccination program, monitoring coverage and safety are fundamental aspects for any immunization program.

In this article, we review the experiences in Latin American countries with HPV vaccine monitoring following its introduction in the region. We examine how HPV vaccines are currently being implemented and monitored, as well as the challenges and barriers to routinely monitor vaccine coverage and impact.

Materials and methods

Latin American countries were included in this analysis as follows: Mexico and Central America (Mexico, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama); South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Peru, Paraguay, Venezuela, and Uruguay); and Latin Caribbean (Cuba, Dominican Republic, Haiti, Martinique, and Puerto Rico).

We searched and retrieved published articles in peer reviewed journals, as well as official documents from government websites on information and reports related to national immunization programs and HPV vaccine monitoring, surveillance and evaluation from Latin American countries. PubMed, Science Direct and Google Scholar databases were searched from November to December 2016 using the following search terms: "human papillomavirus" OR "HPV" AND "vaccine" OR "immunization" AND "Latin America". The search included English and Spanish language articles published after January 1, 2007. Websites from the World Health Organization, Pan American Health Organization, and Ministries of Health from Latin American countries were reviewed from November to December 2016 and reports on immunization programs and HPV vaccination were retrieved from these sites.

For HPV vaccine coverage, we reviewed the WHO/UNICEF Joint Reporting Form database and the PAHO Immunization Annual Report. However, no data on HPV

vaccine coverage were reported in these systems. Therefore, we consulted the HPV information database of the Catalan Institute of Oncology (ICO) and the International Agency for Research on Cancer (IARC), and extracted and updated relevant regional data from a previous global analysis of HPV vaccine coverage, for which the detailed methods were published elsewhere.⁸ Coverage data were identified through a systematic review of the literature and official government websites from Latin-American HPV national immunization programs, up to December 2016. We retrieved information on the year of introduction, the target ages, the schedule, implementation strategy (either primary or catchup) and approach (organized or opportunistic), and collected age-specific data on one, two and three-dose HPV vaccine coverage for each country. To estimate the coverage and number of vaccinated females, the retrieved coverage data were converted into birth-cohort specific coverages, with missing data imputed using an algorithm, and applied to global population estimates and cervical cancer projections by country and income level.

Results

Overview of HPV vaccine introduction in Latin America

By December 2016 in Latin America, 12 countries and 1 territory (13/23, 56%) had introduced HPV vaccines into their national immunization program and an additional country (Bolivia) had plans to introduce it in early 2017 (table I). HPV vaccines were first introduced nationally in Puerto Rico (2006) and Panama (2008), and it wasn't for three more years that other countries began to introduce this vaccine into their national immunization programs (table I).^{2,9} The quadrivalent HPV vaccine is more commonly used in these countries. While all South American countries have introduced the HPV vaccine, with the exception of Venezuela, countries in Central America and Latin Caribbean are lagging behind. In total, nine countries remain to introduce HPV vaccines: Costa Rica, Cuba, Dominican Republic, El Salvador, Haiti, Guatemala, Martinique, Nicaragua, and Venezuela.

Table I
YEAR OF HPV VACCINE INTRODUCTION AND SELECTED COUNTRY CHARACTERISTICS, COUNTRIES IN LATIN AMERICA, AT DECEMBER 2016

Year of HPV vaccine introduction in national immunization program	Country/territory	Population* size (in thousands, 2016, data available at time of preparation of the article)	GNI* (US\$ per capita, 2014 data available at time of preparation of the article)	National health expenditure* (public, as % of GDP)	Cervical cancer [‡]	
					Incidence rate (per 100 000 women, 2012, data available at time of the preparation of the article)	Mortality rate (per 100 000 women 2012, data available at time of the preparation of the article)
2006	Puerto Rico	3 681	19 310	...	11.4	2.8
2007	-					
2008	Panama	3 990	11 130	5.9	18.7	7.1
2009	-					
2010	-					
2011	Argentina	43 847	13 480	2.7	20.8	8.3
	Peru	31 774	6 360	3.3	32.7	12.0
2012	Mexico	128 632	9 870	3.3	23.3	8.0
	Colombia	48 654	7 970	5.4	18.7	8.0
2013	Uruguay	3 444	16 350	6.1	18.9	7.1
	Paraguay	6 725	4 400	4.5	34.2	15.7
2014	Brazil	209 568	11 790	3.8	16.3	7.3
	Chile	18 132	14 910	3.9	12.8	6.0
2015	Ecuador	16 385	6 090	4.5	29.0	14.0
2016	Honduras	8 190	2 270	4.4	29.4	14.1
	Belize	367	4 350	3.9	32.7	14.9
2017	Bolivia (Planned)	10 888	2 870	4.6	47.7	21.0

GNI= gross national income; GDP=gross domestic product

Source:

* Pan American Health Organization⁹

‡ Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al.²

In all countries, HPV vaccines are publicly available at no cost to the client and delivered through organized national immunization programs, which includes active outreach to a clear target population according to an organized plan. The majority of countries vaccinate girls, using a 2 or 3 dose schedule, in the recommended age

group of 9-13 years of age (table II). Boys are included in the HPV vaccine programs in Panama and Puerto Rico, and Argentina and Brazil would include boys in their programs in 2017. The preferred delivery strategy is a school-based one, together with delivery at health centers. Opportunistic catch up for girls up to 26 years

Table II
HPV VACCINE IMPLEMENTATION, COUNTRIES IN LATIN AMERICA, AT DECEMBER 2016

Country/ territory	Year of introduction	Strategy	Targeted age and sex	Delivery strategy	Schedule	National system to monitor vaccine adverse events
Argentina	2011	Primary organized	11 year old females (males from 2017 on)	health center	2 doses	yes
	2014	Special groups	11-26 HIV positive or transplant recipient (both sexes)	health center	3 doses	-
Belize	2016	Primary organized	10 year old females	school	2 doses	yes
Bolivia	2017	Planned introduction 2017 in 10-12 year old females	-	-	-	yes
Brazil	2014	Primary organized	9-13 year old females	school and health center	2 doses	yes
		Special groups	14-26 year old HIV positives			-
	2017	Planned introduction in 2017: Primary or- ganized for 9-13 year old males, 9-26 HIV positives (males) and catch-up for 14 year old unvaccinated females or who did not complete the 2-dose schedule	-			
Chile	2014	Primary organized	9 year old females	school (grade 4)	2 doses	yes
	2015-16 only	Organized catch-up	11-13 year old females	school (grade 6-8)		-
Colombia	2012	Primary organized	9 year old females	school (grade 4)	3 doses exten- ded (0-6-60m)	yes
		Oppor- tun-istic catch-up	9-17 year old females	school (grade 4-11), special campaigns for unschooled/remote areas	-	
Ecuador	2015	Primary organized	9-11 year old females	school and health center	2 doses	yes
Honduras	2016	Primary organized	11 year old females	school and health center	2 doses	yes
Mexico	2012	Primary organized	10-11 year old females (schooled), 11 years old females (unschooled)	school (grade 5) and health center	2 doses	yes
Panama	2008	Primary organized	10 year old both sexes (males since 2016)	school and health centers	2 doses	yes
Paraguay	2013	Primary organized	10 year old females	school	3 doses	yes
Peru	2011	Primary organized	9-12 year old females	school (grade 5 or 6) and health cen- ter (unschooled)	2 doses	yes
Puerto Rico	2006	Primary opportun-istic	11-12 year old both se- xes (males since 2011)	health center	3 doses (2 doses from 2017)	yes
		Opportun-istic catch-up and special po- pulations	<26 year old females <21 year old males	health center	3 doses (2 doses <15 yo from 2017)	yes
Uruguay	2013	Primary organized	12 year old females	health center	3 doses	yes

Source: Data from official government documents and websites of the corresponding Ministry of Health national immunization program
Date and location: December 2016, Washington DC USA

old presenting at a clinic or designated immunization center is available in only five countries (table II). In some countries, notably Colombia, Ecuador, Mexico and Panama, targeted delivery strategies were reported to reach vulnerable populations, for instance in isolated, rural areas or indigenous communities, through mobile services and special outreach campaigns.

Vaccine procurement has been facilitated by the PAHO Revolving Fund, a regional pooled procurement mechanism that enables countries to access high-quality vaccines, syringes and related supplies for their populations at the lowest price and not dependent on purchase size. Through the PAHO Revolving Fund, HPV vaccines are currently available at 8.50 and 9.80 dollars for the bivalent and quadrivalent HPV vaccine, respectively. All Latin American countries are utilizing this mechanism to purchase their HPV vaccines, with the exception of Mexico and Brazil, which utilize their own national procurement mechanisms for HPV vaccines.

Decision making processes used for HPV vaccine introduction have been only partially described and appear to be based on the cost effectiveness of the vaccine. In 10 countries* the decision making process was facilitated by PAHO, through the ProVAC initiative. This included country based assessments of cervical cancer burden, review of evidence with stakeholders on HPV vaccines (immunogenicity, efficacy, duration of protection, serotypes covered, safety) and an evaluation of its cost-effectiveness using local data on cervical cancer burden, treatment costs, and health service utilization. For the latter, the PAHO CERVIVAC tool was applied and it provided country specific information on HPV vaccine program costs, number of deaths averted, DALYs averted, and cost per DALY averted, among others, in order to determine the investment value of introducing the HPV vaccine in their national immunization program. HPV vaccination was shown to be very cost effective in all 10 countries which conducted the PROVAC study.

Systems for monitoring and evaluation of HPV vaccines

All Latin American countries have a national Expanded Program on Immunization (EPI), which includes vaccine monitoring systems that routinely collect information

on indicators of vaccine coverage by type of vaccine and age group, as well as planning and logistics information such as supply management, cold chain management, and financial planning. In addition, all Latin American countries have adverse events monitoring systems that routinely monitor and report on any adverse events associated with vaccination. Ministries of Health annually complete a standardized questionnaire, using the WHO-UNICEF Joint Reporting Form on immunization coverage and submit the data to PAHO. The data is then collated and a regional bulletin on Immunization in the Americas is published annually by PAHO, making vaccine coverage information publically available and widely disseminated.

For HPV vaccines, EPI programs have begun to monitor and report on coverage by doses administered to females 9-15 years of age or older for each of the recommended doses in a calendar year. However, very limited data on HPV vaccine coverage were found from the Ministry of Health national immunization reports, or the PAHO Immunization Bulletin, signaling major gaps in monitoring of coverage. Coverage data were located for only 8 [Argentina, Brazil, Colombia, Mexico, Panama, Peru, Puerto Rico, Uruguay] of the 13 Latin American countries/territories using HPV vaccines in their national programs.

A framework for a surveillance system to monitor HPV vaccine impact for Latin America and the Caribbean has been proposed. It includes routine data collection on indicators on prevalence of HPV genotypes in sexually-active adolescents, prevalence of precancerous cervical lesions, and cervical cancer incidence and mortality and HPV genotype prevalence in invasive cancer (table III).¹⁰ To enable impact monitoring, however, HPV laboratories capable of processing HPV tests with quality assurance procedures are necessary. Public HPV laboratories were reported in at least eight Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Mexico, Paraguay, Peru), signaling the need to improve HPV laboratory infrastructure in the region. The Argentina National Institute of Infectious Diseases serves as a regional reference HPV laboratory, and is part of the WHO global HPV Laboratory Network. This regional reference laboratory provides technical support to improve the availability and quality of laboratory services for effective surveillance and monitoring of HPV vaccines. In addition, to enable longer term impact, monitoring population-based cancer registries is required to be able to track, and report on cervical cancer incidence. All Latin American countries note having data on cancer mortality, although only 10 countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba,

* Argentina, Belize, Brazil, Bolivia, Costa Rica, Guatemala, Honduras, Nicaragua, Paraguay, Uruguay.

Table III
SURVEILLANCE SYSTEM FRAMEWORK FOR MONITORING AND EVALUATION OF HPV VACCINES

Monitoring and evaluation	Indicator	Time frame (years after vaccine introduction)
Coverage	HPV vaccine coverage by age or birth cohort and by dose for a calendar year	Annual
HPV prevalence	HPV genotype prevalence in sexually-active adolescents	Short-term (5-10 years)
Cervical precancerous lesions	Prevalence of precancerous lesions (CIN 2+) HPV genotype prevalence in invasive cervical cancer	Medium-term (10-15 years)
Cervical cancer	Cervical cancer incidence Cervical cancer mortality HPV genotype prevalence in invasive cervical cancer	Long-term (≥20 years)

Source: World Health Organization. Report of the meeting on HPV vaccine coverage and impact monitoring¹⁰

Ecuador, Martinique, Paraguay, Peru) are reported as meeting the international standards for population-based cancer registries with quality, complete and timely incidence and mortality data, signaling the need to increase capacity in this area.

Reports on HPV vaccination coverage

In those countries with available data, HPV vaccine coverage was shown to range from a low of 30% in Uruguay for 14 year old girls, to a high of 81% in Panama for 14 and 15 year old girls, for the full dose schedule (2-3 doses according to national guidelines) in the last calendar year available. The median overall coverage observed in Latin America for at least 1 dose is 80%, while it is 55% for the full dose schedule (table IV).¹¹ For the case of boys, only Puerto Rico reported data on HPV vaccine coverage in this population, showing coverage in 2015 of 68% for 1 dose or more, and 31% coverage for the full 3 dose course, which was a lower coverage than for girls (76 and 50% respectively).

Based on these reported coverage rates, and using an algorithm to impute missing data, we estimate that around 11 million girls in South America and six million girls in Central America and Mexico, most of whom are currently aged 10-14 years, had been vaccinated against HPV by December 31 2016. Given this situation and based on the actual cervical cancer incidence and mortality rates, we estimate that approximately 230 000 new cases of cervical cancer and almost 100 000 deaths from cervical cancer have been averted in Latin America, assuming long term protection and 100% effectiveness

against HPV16 and 18, which are responsible for 70% of the cervical cancer cases.

Reports on HPV vaccine safety

The most common adverse reactions to HPV vaccination reported in Latin America, as elsewhere, have been injection site and muscle pain. Some allergic reactions have been observed, along with syncope in vaccinated girls. In three Latin American countries (Brazil, Colombia, Peru) extensive media coverage was given to events of girls recently vaccinated against HPV reporting headache, paresthesia of the lower or upper limbs, respiratory distress, chest pain and fainting. The media reports linked the events to HPV vaccination, which led to strong negative public reaction, reduced acceptance of the HPV vaccine and in the case of Peru, temporarily halted the program's implementation. Investigations were conducted in each country, and none of the events were found to be associated with the HPV vaccine. These cases highlight the importance for health professionals and authorities to be aware of the possibility of mass psychogenic illness related to HPV vaccination in adolescent girls or the administration of any other vaccines in this population; and for the public and the media to be educated and informed about HPV vaccines and their safety.

Reports on HPV vaccine impact

No reports on HPV vaccine impact in Latin America were found, perhaps due to the complexity of impact

Table IV
HPV VACCINATION COVERAGE IN FEMALES BY AGE, AT DECEMBER 2016
(ACCORDING TO NATIONAL GUIDELINES)

Country	Dose	10 year old %	11 year old %	12 year old %	13 year old %	14 year old %	15 year old + %
Argentina	Full course (2-3 doses)	-	-	-	56.2%	-	50.2
	1 dose +	-	-	-	-	-	86.0
Brazil	Full course (2-3 doses)	-	42.7	48.1	-	-	-
	1 dose +	-	78.0	50.3	85.7	-	-
Colombia	Full course (2-3 doses)	45.1	24.4	59.9	87.4	59.9	-
	1 dose +	61.1	81.0	87.6	98.0	87.6	-
Mexico	Full course (2-3 doses)	-	92	-	-	-	-
Panama	Full course (2-3 doses)	-	66.8	79.5	73.3	81.5	81.4
	1 dose +	-	-	-	-	-	89.0
Peru	Full course (2-3 doses)	55.5	30.0	-	-	-	-
	1 dose +	-	-	61.0	-	93	-
Puerto Rico	Full course (2-3 doses)	-	-	-	-	49.9	-
	1 dose +	-	-	-	-	76.0	-
Uruguay	Full course (2-3 doses)	-	-	-	-	30.0	40.0
	1 dose +	-	-	-	-	-	-

Source: Catalan Institute of Oncology/International Agency for Research on Cancer¹¹

monitoring as well as the early stage of HPV vaccine introduction in the majority of countries in this region.

Discussion

2017 marks ten years since the first preventative HPV vaccine was approved for use. The Latin American region has advanced more than any other World region, except Western Europe, with HPV vaccine introduction.⁴ This has resulted in an estimated 17 million vaccinated girls aged 10-14 years, and almost 100 000 averted deaths from cervical cancer in Latin America. Unfortunately, the nine countries that still lag behind with HPV vaccine introduction are among those with the highest rates of cervical cancer and have populations that can most benefit from this vaccine.¹² Cervical cancer disproportionately affects women in lower socioeconomic groups, mainly due to lack of access to health services for screening, early diagnosis and treatment; thus to prevent further inequities associated with cervical cancer HPV, vaccine introduction is urgently needed in these lagging countries.

National Immunization Technical Advisory Groups (NITAG) play a key role in decision-making for new vaccine introduction, but their resources and capacity

vary across the region, including in the Latin American countries that have not yet introduced HPV vaccines.^{13,14} Factors such as disease burden or cost-effectiveness have been considered, but the institutional and political context, as well as the legislative and regulatory environment, media coverage and advocacy, have influenced adoption decisions and prevented more rapid uptake of HPV vaccines into policy.¹⁴ The PAHO ProVac Initiative has strengthened national capacities and NITAG functions to make better informed, evidence-based decisions, by developing tools for economic analysis, and forming multidisciplinary teams to use these decision-making tools for new vaccines, including HPV vaccines.¹⁵

Yet, other obstacles persist for a wider adoption in the Region. First, together with the pneumococcal vaccine, the HPV vaccine remains the most expensive EPI vaccine. Despite its proven cost-effectiveness, the vaccine cost is perceived as unaffordable in the context of limited EPI budgets. Second, public health priorities in Latin America focus on childhood illnesses—pneumonia and diarrhea—and maternal mortality and, consequently, public investments are directed at their prevention. As a result, other new vaccines have been prioritized for introduction, and all countries in Latin America now have rotavirus vaccine and conjugate

pneumococcal vaccine in their routine schedules.⁹ Finally, health professionals have limited understanding of HPV and cervical cancer and question its safety and efficacy, limiting wider adoption. For example, in Colombia general practitioners were noted to have very limited knowledge about HPV, cervical cancer and HPV vaccination, and in Argentina a study showed that 30% of specialized medical providers were not aware of the relationship between HPV and cervical cancer.^{16,17}

While cervical cancer prevention is the main objective, and females are the main target group of HPV vaccination programs in Latin America, equity issues have driven policy changes and boys are now included in HPV vaccine programs in three countries in the region and likely more in the near future. Although the expressed country specific reasons for these recent policy changes were not found in our search, reasons have been cited elsewhere and include protection against warts and HPV related cancer risk in boys, protection for high risk populations such as men who have sex with men, and effectiveness for other HPV related diseases.⁴ It is still too early to fully understand the programmatic implications of having gender neutral HPV vaccine programs, and whether it may challenge achieving high vaccine coverage, given the experiences to date with vaccinating girls only.

No specific regional targets have been set for HPV vaccination coverage. However, the Global Vaccine Action Plan 2011-2020 calls for a 90% national coverage and 80% in every district for all vaccines in national programs.¹⁸ This may be an ambitious target for Latin America for HPV vaccines based on the results illustrated in this analysis, and a separate global HPV vaccine coverage analysis showing an average of 71% coverage for Latin America and the Caribbean region.⁸ Challenges to achieving a higher coverage, especially in low and middle income countries, have been noted and include: difficulties with covering multiple age groups, requirements for multiple dose vaccine, reaching an adolescent population, and concerns about safety, efficacy and perceptions of association with increased sexual activity.^{19,20} The ongoing media stories questioning the safety of the HPV vaccine may also have affected coverage rates, as have been documented elsewhere.²¹ However, school-based delivery strategies, which are predominantly used in Latin America, have been cited as a more effective strategy to reach high vaccine coverage in this age group.²² In addition, Vaccination Week in the Americas, an annual immunization campaign coordinated by PAHO, has strengthened national immunization programs to reach populations with little access to regular health

services, and provides an opportunity to increase HPV vaccination coverage.²³

Perhaps more challenging, as noted by the scant information found for our analysis, is to mount and sustain surveillance systems for monitoring and evaluation of HPV vaccines, in order to accurately monitor coverage, safety and impact, using the indicators previously described. Monitoring and evaluation of vaccines requires adequate program databases and information systems, and ability to capture and link data. Here is where the challenges lie, because although EPI programs are well established with monitoring systems, they still need to be adapted to integrate issues specific to HPV vaccines, such as capturing data for multiple age groups, school settings as well as health clinics. Only two Latin American countries have more than seven years of HPV vaccine implementation experience, and can be expected to have robust and comprehensive monitoring systems. All other countries have about 2-3 years of implementation experience and it may still be relatively early to monitor complete coverage and impact.

Monitoring coverage for HPV vaccines is unlike doing it for other vaccines, given the multiple age groups, multiple doses and multiple delivery strategies through school-based programs and health facilities. There is clearly a need for standardization of coverage monitoring procedures, notably in standardizing the denominators used to calculate coverage, to allow for more accurate comparability between country data. There is also a need for more consistent and regular annual reporting of coverage data for this vaccine, through the PAHO/WHO/UNICEF Joint reporting form. But there are opportunities to improve coverage data through the use of electronic immunization registers, which are in the process of being established throughout Latin America and, once in place, will facilitate more accurate and timely coverage monitoring and reporting.

Monitoring HPV vaccine impact is not necessary for HPV vaccine introduction. It is a complex and resource intense process that requires HPV testing and HPV laboratory capacities, cervical cancer screening capacity and cancer registries.¹⁰ Genital warts, which develop relatively soon after HPV infection, can be monitored within a short period of time but it does not demonstrate vaccine impact on precursors to cervical cancer. Also it is only appropriate for the quadrivalent vaccine. In limited resource settings, the priority should be on developing surveillance systems to monitor cervical cancer impact, by monitoring changes in HPV genotype prevalence over the short term and changes in precancerous cervical lesions over the medium term.

Monitoring HPV genotype in sexually active population, possible after 5-10 years of vaccine introduction, can provide an early indicator of vaccine effectiveness, but it does require considerable resource commitment and is likely feasible in a few limited sites (e.g., sentinel surveillance). No reports from Latin America were found on changes in HPV genotype prevalence post HPV vaccination. But experiences from other countries indicate there are reductions. For example, prevalence of HPV infection for types 6/11/16/18 decreased by 86% after three doses among Australian women and by 89% after one or more dose in women in the USA within six years.²⁴

Monitoring precancerous cervical lesions, which develop many years after HPV infection, involves screening women and diagnosing those with cervical intraepithelial neoplasia (CIN), a precursor to cervical cancer and acceptable surrogate for measuring vaccine efficacy. However, this requires health service capacity, organized population-based cervical cancer screening programs and laboratory infrastructure, which are resource intensive. Furthermore, changes in screening practices could improve rates of detection of pre-cancerous lesions and may give misleading conclusions about vaccine impact. However, results from HPV vaccine impact monitoring studies from developed countries illustrate the promising impact that may be possible in Latin America. CIN (grade 2 or higher) has been reported to decline in cohorts of vaccinated females within five years by 75% in studies in Sweden, 73% in Denmark, 69% in Canada, and 57% in Queensland, Australia.²⁴

Monitoring reduction in cervical cancer is a much longer term undertaking, requiring 20 years or more. At this point in time, no studies are available on reductions in cervical cancer rates as a result of HPV vaccination, given that it has only been available for 10 years.

In conclusion, HPV vaccine introduction has been successful in Latin America, although challenges persist with achieving a high vaccination, as well as screening coverage, establishing monitoring and evaluation systems, and reporting on HPV vaccine coverage and effectiveness.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

1. Pan American Health Organization. Plan of Action on Immunization. Report to the 54th Directing Council [Internet]. 2015 [cited 2016 Dec 3]. Available from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=11087&Itemid=41537&lang=en

2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited 2016 Dec 3]. Available from: <http://globocan.iarc.fr>
3. Lowy DR, Schiller JT. Reducing HPV-associated cancer globally. *Cancer Prevention Research*. 2012;5(1):18-23. <https://doi.org/10.1158/1940-6207.CAPR-11-0542>
4. Brotherton JML, Zuber PLF, Bloem PJJ. Primary prevention of HPV through vaccination: Update on the current global status. *Curr Obstet Gynecol Rep*. 2016;5(3):210-23. <https://doi.org/10.1007/s13669-016-0165-z>
5. World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2016 conclusions and recommendations. *Wkly Epidemiol Rec*. 2016;48(2):579-80. [cited 2016 Dec 27]. Available from: http://apps.who.int/iris/bitstream/10665/251816/1/11VER9148_561-582.pdf?ua=1
6. World Health Organization. Human papillomavirus vaccines. WHO position paper. *Wkly Epidemiol Rec*. 2009;84(15):118-31.
7. Pan American Health Organization. Final report of the XXI Technical Advisory Group Meeting on Vaccine-preventable Diseases of the Pan American Health Organization. 2013. [cited 2016 Dec 3]. Available from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=1862&Itemid=2032&lang=en
8. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosc FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: A pooled analysis. *Lancet Glob Health*. 2016;4(7):453-63. [https://doi.org/10.1016/S2214-109X\(16\)30099-7](https://doi.org/10.1016/S2214-109X(16)30099-7)
9. Pan American Health Organization. Health Situation in the Americas: Core Indicators 2016. Washington, DC, USA: PAHO; 2016
10. World Health Organization. Report of the meeting on HPV vaccine coverage and impact monitoring [Internet]. 2010 [cited 2016 Dec 22]. Available from: http://www.who.int/immunization/hpv/learn/hpv_vaccine_coverage_and_impact_monitoring_report_who_2009.pdf
11. Catalan Institute of Oncology (ICO)/International Agency for Research on Cancer (IARC), Information Centre on HPV and Cancer. 2017 Statistics. Barcelona, Spain: ICO/IARC [cited December 3, 2016]. Available at: <http://www.hpvcentre.net/statistics.php>
12. Murillo R, Herrero R, Sierra MS, Forman D. Cervical cancer in Central and South America: Burden of disease and status of disease control. *Cancer Epidemiology*. 2016;44(Suppl 1):S121-30. <https://doi.org/10.1016/j.canep.2016.07.015>
13. de Oliveira LH, Toscano CM, Sanwogou NJ, Ruiz-Matus C, Tambini G, Roses-Periago M, et al. Systematic documentation of new vaccine introduction in selected countries of the Latin American Region. *Vaccine*. 2013;31(Suppl 3):C114-22. <https://doi.org/10.1016/j.vaccine.2013.05.032>
14. Burchett HE, Mounier-Jack S, Griffiths UK, Mills AJ. National decision-making on adopting new vaccines: A systematic review. *Health Policy Plan*. 2011;27(Suppl 2):39-49.
15. Jauregui B, Janusz CB, Clark AD, Sinha A, Garcia AG, Resch S, et al. ProVac Global Initiative: A vision shaped by ten years of supporting evidence-based policy decisions. *Vaccine*. 2015;33(Suppl 1):A21-7. <https://doi.org/10.1016/j.vaccine.2014.12.080>
16. Piñeros M, Cortés C, Trujillo L, Wiesner C. Conocimientos, aceptabilidad y actitudes sobre la vacuna contra el VPH en médicos generales, ginecólogos y pediatras en Colombia. *Rev Colomb Cancerol*. 2009;13(2):88-98.
17. Mazzadi A, Paolino M, Arrossi S. HPV vaccine acceptability and knowledge among gynecologists in Argentina. *Salud Publica Mex*. 2012;54(5):515-22. <https://doi.org/10.1590/S0036-36342012000500008>
18. World Health Organization. Global Vaccine Action Plan 2011-2020 [Internet]. 2013 [cited 2016 Dec 3]. Available from: http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

19. LaMontagne DS, Barge S, Le NT, Mugisha E, Penny ME, Gandhi S, et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. *Bull World Health Organ.* 2011;89(11):821-30. <https://doi.org/10.2471/BLT.11.089862>
20. Wigle J, Coast E, Watson-Jones D. Human papillomavirus (HPV) vaccine implementation in low and middle-income countries (LMICs): Health system experiences and prospects. *Vaccine.* 2013;31(37):3811-7. <https://doi.org/10.1016/j.vaccine.2013.06.016>
21. Gollust SE, LoRusso SM, Nagler RH, Fowler EF. Understanding the role of the news media in HPV vaccine uptake in the United States: Synthesis and commentary. *Hum Vaccin Immunother.* 2016;12(6):1430-4. <https://doi.org/10.1080/21645515.2015.1109169>
22. Paul P, Fabio A. Literature review of HPV vaccine delivery strategies: Considerations for school- and non-school based immunization program. *Vaccine.* 2014;32(3):320-6. <https://doi.org/10.1016/j.vaccine.2013.11.070>
23. Ropero-Álvarez AM, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C, Tambini G. Vaccination Week in the Americas: An Opportunity to integrate other health services with immunization. *J Infect Dis.* 2012;205(Suppl 1):S120-5. <https://doi.org/10.1093/infdis/jir773>
24. Garland SM, Kjaer SK, Munoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: A systematic review of 10 years of real-world experience. *Clinical Infectious Diseases.* 2016;63(15):519-27. <https://doi.org/10.1093/cid/ciw354>