Prophylactic cancer vaccines: development and challenges for HBV and HPV vaccines in Latin America

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Abstract

Vaccines against hepatitis B virus (HBV) and human papillomaviruses (HPV) are two safe and highly effective vaccines that were developed at the end of the 20th century and can prevent human cancer. HBV vaccine prevents liver cancer, and HPV prevents cervical and other HPV-related cancers. Starting with the immunogen identification, 15 years were necessary to reach the industrial production of HBV vaccine, and 20 years, for the HPV vaccines. However, while HBV vaccines have been commercially available for over 40 years and are used in most countries, there are still significant challenges to achieve universal childhood immunization against hepatitis B. Similarly, HPV vaccines have been commercially available for 17 years, and yet, countries with higher cervical cancer still have the lowest HPV vaccination rates. We describe the development of HBV and HPV vaccines and discuss the challenges to reaching equitable access to these vaccines in Latin America.

Keywords: cancer vaccines; hepatitis B vaccines; human papillomavirus vaccines; cervical cancer; hepatocellular carcinoma; liver cancer; Latin America

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Resumen

Las vacunas contra el virus de la hepatitis B (VHB) y el virus del papiloma humano (VPH) son dos vacunas seguras y altamente efectivas que se desarrollaron a finales del siglo XX y pueden prevenir el cáncer humano. La vacuna contra el VHB previene el cáncer de hígado y la VPH previene el cáncer de cuello uterino y otros cánceres relacionados con el VPH. A partir de la identificación del inmunógeno, fueron necesarios 15 años para llegar a la producción industrial de la vacuna contra la hepatitis B y 20 años para las vacunas contra el VPH. Sin embargo, aunque las vacunas contra el VHB han estado disponibles comercialmente durante más de 40 años y se utilizan en la mayoría de los países, aún existen desafíos importantes para lograr la inmunización infantil universal contra la hepatitis B. De manera similar, las vacunas contra el VPH han estado disponibles comercialmente durante 17 años; sin embargo, en países con incidencias altas de cáncer de cuello uterino, todavía existen tasas bajas de vacunación contra el VPH. Se describe el desarrollo de las vacunas contra el VHB y el VPH, y se discuten los desafíos para lograr un acceso equitativo a estas vacunas en América Latina.

Palabras clave: vacunas contra el cáncer; vacunas contra hepatitis B; vacunas contra Papillomavirus; cáncer de cuello uterino; carcinoma hepatocelular; cáncer de hígado; América Latina

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Vaccines against the hepatitis B virus (HBV) and human papillomaviruses (HPV) are two safe and highly effective prophylactic vaccines that can prevent human cancer. The HBV vaccine prevents liver cancer, and the HPV vaccine prevents cervical cancer (CC) and other HPV-related cancers. However, despite the fact that the HBV and HPV vaccines have been commercially available for over 40 and 17 years, respectively, and are used in most countries, they have not yet reached the countries that need them the most.[1,2] We briefly describe the development of the HBV and HPV vaccines, summarize their coverage in Latin America (LA), and discuss the challenges to reaching global equitable access to these vaccines.

HBV vaccine

In the early 1960s, Blumberg discovered the "Australia Antigen" (now called HBsAg) in the serum of an Australian Aboriginal person. It was later shown that this antigen was associated with HBV infection.[3] Seroepidemiological studies also demonstrated the causal role of the HBV in liver cancer,[4,5] and the International Agency for Research on Cancer (IARC) classified HBV chronic infection as carcinogenic to humans.[6]

The first HBV vaccine was developed in 1975.[7] Vaccine development was unconventional because the HBV could not be grown efficiently in cell cultures. The immunizing antigen was isolated from HBsAg positive sera of asymptomatic carriers, purified, and inactivated, and aluminum hydroxide was used as an adjuvant. This plasma-derived vaccine was shown to be highly immunogenic, efficacious, and safe both in adults[8] and infants.[9] It could also be associated with other vaccines included in the expanded program of immunization (EPI), facilitating its administration, in search of achieving universal vaccination coverage and thus reducing mortality and morbidity rates caused by vaccine-preventable diseases.[10] Follow-up of immunized infants proved the long-term protection against HBsAg carriage.[11] Plasma-derived vaccines produced by MSD and Pasteur Production became commercially available in the early 1980s.

The theoretical concerns about the safety of blood products, the inconsistency as a source of raw material and the advances in recombinant DNA technology led to the development of second-generation recombinant vaccines in which the HBsAg was produced in the yeast *Saccharomyces cerevisiae*.[12,13] The ability to produce immunogenic HBsAg in genome-free particles was a breakthrough. It allowed for the large-scale production of HBV vaccine and created a blueprint for vaccines against other pathogens such as HPV. Extensive clinical trials in humans proved that the recombinant HBV vaccine was safe and had a comparable anti-HBV response and similar protective efficacy as the human plasma-derived vaccine.[14-16] In 1986, the USA Food and Drug Administration approved the recombinant HBV. Since then, it has gradually replaced the plasma-derived HBV vaccine. Currently, there are 12 HBV vaccines prequalified by the World Health Organization (WHO): four as a single dose, and seven in a pentavalent combination (table I).[17]

Efficacy of HBV vaccine against primary liver cancer

In 1984, Taiwan launched the world's first universal vaccination program for HBV.[18] Vaccination first started with infants whose mothers were HBsAg carriers and was later extended to all newborns and unvaccinated preschool and primary-age children.[19] This program effectively reduced the prevalence of HBsAg from 9.8% to 0.7% in people older than 15 years[1] and the incidence of primary liver cancer (PLC) from 0.92 to 0.23 per 10 000 person-years among children and young adults. Vaccine failure to prevent hepatocellular carcinoma (HCC), the most common form of liver cancer, was associated with HBV transmission from highly infectious mothers to infants not vaccinated at birth.[20] Similar results have been published from China; Korea and Alaska.[21-23]

The reduction of HCC by immunization was also researched in Gambia. The Gambian Hepatitis Intervention Study (GHIS) was launched in 1986 to evaluate the effectiveness of HBV vaccination in childhood for preventing infection, chronic liver disease, and HCC in high-risk populations.[24] A high efficacy of the HBV vaccine has been reported for the prevention of the HBsAg carrier status;[25,26] long-term follow-up for HCC as an endpoint is ongoing.

Fraction of cancer attributable to HBV

HBV is responsible for 39.5% of liver cancer deaths and for 22.5% of deaths from cirrhosis.[27] In 2020, the incidence rate of liver cancer in LA and the Caribbean was 4.8 per 100 000 inhabitants, much higher than the world rate of 2.2 per 100 000 inhabitants, with the highest incidence rates reported from Guatemala and Nicaragua, and it was the first cause of death in Central America[28] (table II).[29,30]

HBV vaccination in LA

In 1991, the WHO recommended including HBV vaccination in national immunization programs in all countries with an HBsAg carrier prevalence of 8% or higher

Table I
CURRENTLY APPROVED HBV VACCINES

Prequalified	*Commercial name*	*Manufacturer*
01/01/87	Engerix	GlaxoSmithKline Biologicals SA
11/12/01	Heberbiovac HB	Centro de Ingeniería Genética y Biotecnología
12/11/04	Hepatitis B Vaccine (rDNA) (Adult)	Serum Institute of India Pvt. Ltd.
26/05/10	Diphtheria, Tetanus, Pertussis, Hepatitis B and *Haemophilus influenzae* type b Conjugate Vaccine*	Serum Institute of India Pvt. Ltd.
18/05/12	None used on labelling for supply through UN agencies. Also marketed with labelled commercial name ComBE Five (Liquid)*	Biological E. Limited
02/10/13	Easyfive-TT*	Panacea Biotec Ltd.
29/04/14	Shan-5*	Sanofi Healthcare India Private Limited
19/12/14	Hexaxim*	Sanofi Pasteur
19/12/14	Pentabio*	PT Bio Farma (Persero)
10/02/16	Eupenta*	LG Chem Ltd
21/01/20	Euvax B	LG Chem Ltd
15/07/22	Mosquirix‡	GlaxoSmithKline Biologicals SA

HBV: Hepatitis B virus.
* Pentavalent: Diphtheria-Tetanus-Pertussis-Hepatitis B-*Haemophilus influenzae* type b.
‡ Includes *Plasmodium falciparum* and Hepatitis B.
Source: adapted from the World Health Organization's List of Prequalified Vaccines.[17]

by 1995 and extending it to all countries by 1997. In 2019, the HBV vaccine for infants was introduced nationwide in 189 Member States, while 109 of these introduced one dose of the HBV vaccine to newborns within the first 24 hours of life.[30] The recommended scheme is three doses: at birth, at one month, and at six months of age.[31]

The WHO reports that global full-scheme coverage of the HBV vaccine increased considerably, from 29% in 2000 to 80% in 2021. Global coverage of a single dose at birth was 43%. By 2021, the region of the Americas had 80% full-scheme coverage and 59% of birth dose vaccination.[28] However, the heterogeneity across countries is high, ranging from 56% in Venezuela to 87% in Nicaragua for the complete schedule, and 37% in Venezuela to 99% in Cuba for the first dose at birth (table II).

HPV vaccine

In the early 1980s, laboratory studies identified HPV DNA in biopsies of CC.[32] Epidemiological studies then confirmed that infection by a small subset of genitally transmitted HPVs, mainly HPV16 and HPV18, was the central cause of CC.[33-35] The 1995 IARC monograph established HPV16 and HPV18 as group 1 carcinogens.[36]

The development of the HPV vaccine faced similar challenges to those of the HBV vaccine because the HPV does not grow in cell cultures. In the early 1990s, several researchers proved that the expression of L1 protein of animal and human papillomavirus in recombinant expression systems resulted in the self-assembly of this protein into virus-like particles (VLPs) that morphologically and antigenically mimicked the viral particle and induced high titers of neutralizing antibodies.[37-40] This evidence was reviewed in the first expert meeting on papillomavirus vaccines in 1994, which stimulated commercial interest in HPV vaccine development.[41]

Currently, 6 prophylactic VLP-based HPV vaccines have been licensed; four have been prequalified by the WHO, three are bivalent, two are quadrivalent, and one is nonavalent (table III).[17] All HPV vaccines contain VLPs against HPV types 16 and 18, which are responsible for 70% of CC; the nonavalent vaccine contains VLPs against HPV types 16,18, 31, 33, 45, 52, and 58, which cause 90% of CC, and the quadrivalent and nonavalent vaccines contain HPV 6 and 11 VLPs to protect against anogenital warts.[42]

Efficacy and effectiveness of HPV vaccines

Randomized phase 3 clinical trials conducted in various countries and involving over 100 000 women, men, and children have demonstrated that 3 doses of Gardasil-4,

Table II
Liver cancer incidence in 2020 and HBV vaccination coverage in countries of Latin America 2019 and 2021

Population	Incidence	HBV vaccine coverage*			
		2019		2021	
	ASIR (world)	Birth dose %	Complete %	Birth dose %	Complete %
Latin America and the Caribbean	4.8				
Guatemala	15.6	48	85	48	79
Nicaragua	10.6	NIB	98	NIB	87
Haiti	9.2	NIB	51	NIB	51
Dominican Republic	7.6	81	87	66	83
El Salvador	6.6	76	81	73	79
Puerto Rico	6.1	ND	ND	ND	ND
Costa Rica	6.1	87	97	78	94
Bolivia	6.0	NIB	75	NIB	70
Honduras	6.0	78	88	72	77
Peru	5.4	82	88	77	82
Mexico	5.3	ND	56	ND	80
Chile	4.8	65	96	98	98
Ecuador	4.6	71	85	61	68
Brazil	4.5	77	72	62	68
Panama	4.3	85	88	86	74
Cuba	3.8	99	99	99	99
Argentina	3.7	77	83	73	76
Colombia	3.5	81	92	88	86
Venezuela	3.2	52	64	37	56
Guyana	3.1	35	99	58	91
Jamaica	3.0	NIB	96	NIB	89
Trinidad and Tobago	3.0	NIB	93	NIB	94
Paraguay	2.7	NIB	86	NIB	70
Uruguay	2.7	NIB	94	NIB	89
Saint Lucia	1.3	85	92	94	80

HBV: hepatitis B virus.
ASIR: age-standardized Incidence rate per 100 000 population.
NIB: no immunization at birth for the country.
ND: no data.
* These data represent the official hepatitis B vaccination coverage reported annually through the WHO/UNICEF Joint Immunization Reporting Form (JRF). The data are updated as the country data are received. National, regional and global data are updated annually on July 15.[29]
Birth dose: including those given within and after 24 hours of birth, HB complete scheme defined as three doses.
Source: Adapted from the International Agency for Research on Cancer[29] and the World Health Organization. Immunization coverage.[30]

Gardasil-9, and Cervarix are safe and highly efficacious vaccines for the prevention of persistent HPV infection, high-grade cervical, vulvar, vaginal, anal and penial epithelial lesions, and genital warts, and the protection lasts at least 10 years.[43] These excellent results led to the introduction of these vaccines in national vaccination programs in 125 countries for girls and in 45 countries for girls and boys.

In real-world settings, a systematic review of ten years showed maximal reductions of 90% for HPV 6/11/16/18 infection, genital warts, and 85% for high-grade histologically proven cervical abnormalities.[2] Evidence of the protective effect of the quadrivalent vaccine for invasive CC has been recently reported. Among 10- to 30-year-old Swedish girls and women, HPV vaccination was associated with a substantial reduction of invasive CC, the cumulative incidence of cervical cancer was 47 cases per 100 000 persons among women who had been vaccinated and 94 cases per 100 000 persons among those who had not been vaccinated.[44]

Table III
CURRENTLY APPROVED HPV VACCINES

Vaccine	Gardasil 4	Cervarix	Gardasil 9	Cecolin	Walrinvax	Cervavac
Year licensed	Merck & Co 2006	GSK 2007	Merck & Co 2014	Xiamen Innovax Biotech China 2019	Biotech China 2022	Indian Serum Inst 2021
VLP types	6/11/16/18	16/18	6/11/16/18/ 31/33/45/52/58	16/18	16/18	6/11/16/18
Age *Sex*	9+ years Girls and boys	9+ years Girls and boys	9+ years Girls and boys	9+ years Girls	9+ years Girls	9+ years Girls and boys
Indication	Lesions and cancer of cervix, vulva, vagina and anus, warts	Lesions and cancer of cervix, vulva, vagina and anus	Lesions and cancer of cervix, vulva, vagina and anus, warts	Cervical lesions and cervical cancer	Cervical lesions and cervical cancer	Lesions and cancer of cervix, vulva, vagina and anus, warts
Market	Global (WHO Prequalification)	Global (WHO Prequalification)	Global (WHO Prequalification)	China (WHO Prequalification)	China	India

HPV: Human papillomaviruses.
WHO: World Health Organization.
Source: adapted from the World Health Organization's List of Prequalified Vaccines.[17]

Attributable fraction of cancer to HPV

In 2017, the fraction of cancer attributable to HPV was estimated on 100% for CC, 88% for anal cancer, 30.8% for oropharyngeal cancer, 2.4% for laryngeal cancer, and 2.2% for oral cavity cancer.[45] Estimates for 2020 reported the highest incidence and mortality rates for CC in Bolivia, Paraguay, and Guyana, and the lowest, in Puerto Rico (table IV).[46]

Vaccine production in LA

LA and the Caribbean have not been able to overcome some of the longstanding challenges in expanding the research, development, and production of vaccines in terms of public health and national security.[47] It has been reported that, with the exception of a few successful production experiences in some LA countries, the sub-region has been characterized by its dependence on imports to cover the needs of the Expanded Vaccination Programs.[48] Currently, the Butantan Institute in Sao Paulo, Brazil, is the only one in LA that produces and sells the HPV vaccine.[49]

HPV vaccination in LA

Despite the overwhelming evidence of HPV vaccine effectiveness and safety, vaccination coverage is suboptimal in LA. According to WHO data, the global coverage of the HPV vaccination in women (last dose administered) has increased from 3% in 2010 to 12% in 2021. The region that achieved the highest coverage by 2021 is the Americas, with 37%, followed by Europe, with 23%; the region with the lowest coverage is Southeast Asia, with an average of 1%. In LA, vaccination coverage is heterogeneous, and there are significant drops in vaccination rates after the f Covid-19 pandemic, ranging from 1% in México to 67% in Brazil (in 2021, for countries that report complete coverage on a yearly in basis) (table IV).[30]

HPV vaccine dose regimens

HPV vaccines were originally approved as 3-dose regimens, and girls between 9 and 14 years of age have been the key target population.[50] Subsequently, *ad-hoc* analyses of clinical trials in Costa Rica and India showing high levels of protection against persistent HPV infection with 1 and 2 doses, and two randomized trials in Kenya and Tanzania confirming these results, led WHO to issue "permissive or Off-label recommendation" to use 1- or 2-dose regimens in girls and boys under 20 years of age.[51] Three doses are recommended for HIV patients and other Immunocompromised individuals.[52]

Vaccine recommendations for boys are based on the evidence of a rapid increase of other HPV-attributable cancer, such as anal and head and neck cancers, and on increasing herd immunity. Still, only thirteen countries in the Region of Americas have included boys as their primary target population.[53]

Table IV
Cervical cancer incidence in 2020 and HPV vaccination coverage for women in countries of Latin America 2019 and 2021

Population	Incidence	HPV vaccine coverage*			
		2019		2021	
	ASIR (World)	First dose %	Last dose %	First dose %	Last dose%
Latin America and the Caribbean	14.9				
Bolivia	36.6	80	70	60	36
Paraguay	34.1	53	54	23	17
Guyana	29.5	42	20	3	2
Peru	22.2	82	76	ND	53
Venezuela	22.2	ND	ND	ND	ND
Nicaragua	21.3	ND	ND	ND	ND
Guatemala	20.3	42	24	34	15
Trinidad and Tobago	19.8	18	9	19	8
Honduras	19.5	78	59	75	53
Dominican Republic	17.9	11	6	27	8
Argentina	16.7	87	59	79	53
Saint Lucia	16.6	ND	ND	ND	ND
Ecuador	16.0	82	54	30	3
Colombia	14.9	31	10	39	11
Panama	14.0	85	73	ND	ND
Cuba	13.9	ND	ND	ND	ND
El Salvador	13.1	ND	ND	43	24
Brazil	12.7	77	67	81	67
Mexico	12.6	94	95	1	1
Uruguay	11.7	77	38	55	17
Costa Rica	11.7	98	39	77	59
Haiti	11.6	ND	ND	ND	ND
Chile	11.1	92	82	67	57
Puerto Rico	8.0	ND	ND	ND	ND

ASIR: Age-standardized incidence rate per 100 000 population.
ND: No data.
* These data represent official human papillomavirus (HPV) vaccination coverage reported annually through the WHO/UNICEF Joint Immunization Reporting Form (JRF). Data are updated as country data are received. National, regional and global data will be updated annually on July 15.[29]
Source: Adapted from the International Agency for Research on Cancer[29] and the World Health Organization. Immunization coverage.[30]

Discussion

Vaccines targeting oncogenic viruses, such as HPV and HBV, are exceptional examples of potential successful prevention of virus-associated cancers, such as CC and HCC,[54] and vaccination against HPV has the potential to prevent 75% of CC.[55] It is difficult to establish correlations between the incidence rates of HCC and CC with the coverage rates of the two vaccines, without taking into account other important determinants for the two cancers, such as alcohol, tobacco, and aflatoxins for HCC, and parity and screening for CC.[56] Furthermore, vaccination coverage rates are subject to bias, as information is not systematically gathered across all LA countries.

Despite the fact that the HBV and HPV vaccines are safe and efficacious, uptake remains low. Faced with the controversies generated by vaccination, the case for compulsory childhood immunization against HPV and HBV is based mainly on an argument of best interests to promote the health of the individual child and the future adult,[57] which is aimed at the immunization for the prevention not only of infectious diseases but also of two types of cancer with significant prevalence in the world.

In the case of the HBV vaccine, a barrier identified for neonatal vaccination in LA is the lack of information and inadequate supply.[58] Successful experiences from various countries reveal that HCC related to HBV in children has been almost eradicated after the introduction of HBV vaccination in infants; this is considered a successful experience in countries such as Taiwan, South Korea, China, and Alaska.[20-23] Failure of HBV vaccination in the prevention of HCC has been linked to incomplete immunization and lack of immunization at birth in infants born from HBsAg-positive mothers.[11] Thus, in LA screening of mothers for HBsAg must be improved, and their babies, immunized at birth. Another

possibility to increase the HBV vaccine coverage is the use of pentavalent vaccines which have been reported to increase vaccine coverage significantly.[59]

For the HPV vaccine, acceptance is consistently lower than for other vaccines. Barriers to achieving high rates of HPV vaccination persist in many countries of LA,[53] including high vaccine costs, health communication difficulties, and hesitancy. Very low vaccination coverage does not allow herd immunity,[60] which is key in the case of HPV. The very long duration of protection observed[61] can also be used to vaccinate at a younger age, for example, promoting vaccination in schools at age 8 and 9 years (as in the UK), and even to implement preschool immunization,[62] allowing vaccination to no longer be associated with the start of sexual activity and to be applied at an age when demyelinating diseases rarely occur.[63] HPV immunization programs have been seriously damaged in some countries, including Colombia, by rumors spread by anti-vaccine groups, based on media reports of psychogenic events which occur at much higher rates in adolescent girls than in other age groups.[52] In addition, vaccination rates from 2019 to 2021 declined considerably after the Covid-19 pandemic, for example in Mexico the vaccine coverage was 95% in 2019 and dropped to 1% in 2021 (table IV). The health emergency contributed to the decline, with a shortage in vaccine availability. The HPV vaccination campaign in this country was only reactivated in November 2022.

In response to these challenges, the WHO set a goal of reducing HBV infections by 90% and reducing HBV-related deaths by 65% by 2030[64] and of eliminating CC as a public health issue by 2030, by vaccinating against HPV 90% of girls by age 15, screening with the HPV test 70% of women at 35 and 45 years of age, and treating 70% of women with precancer and CC.[65] The off-label WHO recommendation of using 1 dose for girls and boys aged 9 to 20 years[52] will simplify logistics, reduce costs and contribute to improve coverage. Although few countries are adopting the single dose strategy, additional research is needed to confirm that 1 dose confers a similar degree of protection to that of 2 or 3 doses, not only for persistent HPV infection but also for precancerous lesions and cancer, and that this protection is long lasting.

It has been a long way between establishing causality of HBV and HPV infection and cancer and the development of these vaccines. Despite solid evidence on the efficacy and safety of HBV and HPV vaccines, complete scheme coverage is heterogeneous and unsatisfactory across LA countries. There is an urgent need to develop specific action plans to increase vaccination uptake, reduce vaccine hesitancy, and provide equitable access.

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

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