

Progress in Vaccination against *Haemophilus influenzae* type b in the Americas

M. Carolina Danovaro-Holliday*, Salvador Garcia, Ciro de Quadros, Gina Tambini, Jon K. Andrus

Worldwide, *Haemophilus influenzae* type b (Hib) causes at least 3 million cases of severe disease each year. Approximately 400,000 children die annually due to pneumonia or meningitis caused by Hib [1]. Severe neurological sequelae occur in 15% to 30% of those who survive Hib meningitis [2]. Other, less frequent, manifestations of Hib are epiglottitis, septic arthritis, osteomyelitis, and septicemia [1–3].

Current polysaccharide–protein conjugate Hib vaccines are highly efficacious and safe. Primary series of two or three doses protect approximately 95% of infants [4–8]. Universal infant Hib immunization has proven to dramatically reduce Hib invasive disease [9–13] through direct vaccine protection and an important herd effect related to the reduction in Hib nasopharyngeal carriage in the community [12,14–16]. Adverse events are rare, and Hib vaccine is contraindicated only for persons with hypersensitivity to any of the vaccine's components [8,17].

The World Health Organization (WHO) recommends the introduction of Hib vaccines worldwide [1]. Furthermore, the Global Alliance for Vaccines and Immunization (GAVI Alliance)—an organization that aligns public and private resources in a global effort to create greater access to the benefits of immunization—considers Hib vaccine introduction in the world's poorest countries to be a top priority [18].

Prior to vaccine introduction, an estimated 20,000 cases of Hib meningitis were estimated to occur in countries of Latin America and the Caribbean (LAC) annually, based on an overall Hib meningitis incidence

Summary Points

- Hib vaccine introduction in countries of Latin America and the Caribbean has substantially reduced morbidity and mortality due to invasive Hib infections.
- All Latin American and Caribbean countries but one include Hib vaccine in their routine immunization schedule for infants.
- Factors that favored this region-wide Hib vaccine adoption include strong political will, data supporting Hib disease burden and impact in early adopting countries, and experience exchange among countries.
- Financial sustainability when introducing the more expensive Hib vaccine was critical for ensuring successful vaccine introduction in all countries.
- Efforts are still needed to improve vaccination coverage and to strengthen invasive bacterial disease surveillance in developing countries.

of 35 per 100,000 children aged 0–4 years [19]. Another 20,000 cases of invasive Hib disease were estimated to occur in the United States annually [20]. Most cases occurred in children aged less than 24 months, with at least 60% of cases occurring in children aged 0–11 months in half of the studies. The annual mortality rate for Hib meningitis in children aged less than five years was estimated to be around two per 100,000 in the Western Hemisphere [21].

In this article, we review the progress of vaccine introduction, lessons learned, and remaining challenges regarding Hib vaccination in the Americas, with emphasis on LAC countries. We expect that this updated and summarized information on Hib vaccination will serve as a useful reference to public health officials and policy makers from other regions

who face the challenge of introducing Hib and other new or underutilized vaccines.

Methods

To assess the progress accomplished by LAC countries in Hib vaccination and the remaining challenges, we reviewed the Pan American Health Organization (PAHO)'s Technical Advisory Group (TAG) on Vaccine-preventable Diseases recommendations; annual country immunization reports to PAHO; Hib-containing vaccine purchase records from PAHO's Revolving Fund; and Hib isolation data from selected countries participating in a Regional Laboratory Network for Surveillance of Bacterial

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Abbreviations: DTaP, diphtheria-tetanus-acellular pertussis vaccine; DTP, diphtheria-tetanus-pertussis vaccine; DTP3, third dose of DTP vaccine; EPI, Expanded Program on Immunization; GAVI, Global Alliance for Vaccines and Immunization; Hib, *Haemophilus influenzae* type b; Hib3, third dose of Hib vaccine; LAC, Latin America and the Caribbean; PAHO, Pan American Health Organization; RF, Revolving Fund; SIREVA, *Sistema Regional de Vacunas*; TAG, Technical Advisory Group on Vaccine-preventable Diseases; WHO, World Health Organization

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Meningitis and Pneumonia (*Sistema Regional de Vacunas*, or SIREVA). We examined data from 1997 to 2006.

PAHO is an international public health agency with more than 100 years of experience in working to improve health and living standards of the countries of the Americas. PAHO serves as the WHO Regional Office for the Americas, and provides technical assistance to all countries and territories in the Western Hemisphere. However, most of PAHO's technical cooperation is targeted to the poorer countries of LAC [22]. PAHO's TAG is comprised of eight immunization and vaccine experts who meet biennially, in the presence of Member States' immunization representatives, to provide recommendations on vaccination policy and strategies to improve countries' vaccination efforts [22].

Since the 1980s, Member States submit annual immunization reports to PAHO, using a standardized form, the PAHO-WHO/UNICEF Joint Reporting Form (previously known as EPI tables). This form includes data on:

- all routine vaccines included in country immunization schedules;
- vaccine presentation;
- annual administrative coverage rates (for Hib, number of third doses of Hib vaccine given divided by the number of children aged less than one year);
- surveillance data (i.e., number of Hib meningitis cases);
- immunization financing indicators, such as the percentage of all routine vaccine expenditures financed with government funds (this excludes any external financing from donors, but may include loans);
- existence of a budget line for vaccine purchase; and
- existence of immunization-related legislation.

The Revolving Fund (RF) is the mechanism for bulk purchase of vaccines and immunization supplies, managed by PAHO, since 1979, to serve Member States. PAHO annually consolidates vaccine orders from countries that wish to participate and conducts an international bid open to all vaccine manufacturers. PAHO procures vaccines with money drawn from the RF, and countries reimburse the RF for purchases made on their behalf [23,24].

SIREVA was started in 1993 to monitor the distribution of pneumococcal serotypes causing severe disease and the antimicrobial resistance patterns of pneumococci in six countries. Subsequently, SIREVA expanded its mandate to conduct laboratory surveillance for other agents that cause meningitis and pneumonia, such as Hib and meningococcus.

PAHO Recommendations Regarding Hib Immunization

To control Hib invasive disease and reduce Hib carriers in the Americas, PAHO's TAG recommends, since 1997, that Member States:

- introduce Hib vaccine into the routine universal infant immunization schedule;
- establish sustainable financial mechanisms to maintain vaccination against Hib; and
- monitor and report vaccination coverage and Hib cases in order to evaluate the impact of the intervention.

To help ensure sustainability of Hib vaccination, TAG has also recommended purchasing Hib vaccine in combination with diphtheria-tetanus-pertussis vaccine (DTP) or DTP/hepatitis B vaccine through the RF, as this can result in significant cost savings.

Progress in Hib Vaccine Introduction

By the end of 2006, all countries of the Americas, except Haiti, had included Hib in their infant immunization schedule (Table 1). As a result, over 98% of the 16 million children born annually in the Americas live in countries routinely using Hib-containing vaccines. Canada (1986) and the United States (1991) were among the first countries to introduce Hib vaccine. Bermuda (1989), the Cayman Islands (1992), and the Dutch territories (1995) were first in the Caribbean. Uruguay and Chile followed in 1994 and 1996, respectively. Uruguay conducted an aggressive catch-up introduction of Hib vaccine for all children aged one to four years, whereas Chile started vaccinating one birth cohort at a time [11,25]. Argentina followed in 1997. However, most countries and territories ($n = 20$) introduced Hib vaccine between 1998 and 2000, more than ten years after the

vaccine was first licensed in 1987. In 2006, Dominica was the last country to introduce Hib vaccine.

Most countries include only three doses for children aged less than one year. However, Canada, the French Departments and the Dutch territories in the Caribbean, the United States, and eight LAC countries and territories include a booster dose during the second year (Table 1).

In most countries, Hib vaccination was introduced nationwide. Due mostly to limited resources, countries such as Brazil, Guatemala, and Peru started vaccinating in selected populations or geographical areas. The use of Hib vaccine through the private sector in the region, in some cases years before introduction into the regular immunization program, has been widespread, but not quantified [11].

Lessons Learned

Logistics. One of the lessons learned with Hib vaccine introduction in the Americas is that the selection of a vaccine formulation (combination versus monovalent) and presentation (one- versus ten-dose vials) is essential. It has an impact on the price, vaccine wastage percentage, cold chain space, need for reconstitution, and training activities for health care workers [11,25,26].

Currently, 34 countries use Hib in the form of a DTP-Hib-hepatitis B combination vaccine, or pentavalent (only available in one-dose vials) (Table 1). Of 17 countries and territories that started using monovalent Hib vaccine, only Canada and the United States have not switched to a combination vaccine, although in both countries, Hib combinations are often available as alternatives.

Hib vaccine in a combination formulation offers several advantages. Combination vaccines reduce the number of injections, thereby lowering the risk of injection complications and adverse events and reducing missed vaccination opportunities. In addition, parents and health care workers show greater acceptance of combination vaccines [27,28]. Combination Hib vaccine tends to be less expensive than monovalent Hib vaccine, thus contributing to the sustainability of immunization programs [27,28–30].

Financing Hib vaccination. Although universal vaccination with Hib vaccine

Table 1. Hib Vaccination in the Americas, 1991–2007

Country/Territory	Year Hib Introduced	Vaccine Used When Introduced ^a	Vaccine used in 2007 ^a	Routine Childhood Schedule 2007			
				1st Dose	2nd Dose	3rd Dose	Booster
Anguilla	1998	Hib	Pentavalent	3 m	5 m	7 m	
Antigua & Barbuda	2000	Pentavalent	Pentavalent	2 m	4 m	6 m	
Argentina	1997	DTP-Hib	DTP-Hib	2 m	4 m	6 m	18 m
Bahamas ^b	1998	Hib	Pentavalent	2 m	4 m	6 m	
			DTP-Hib				15 m
Barbados ^b	2000	Pentavalent	Pentavalent	3 m	4.5 m	6 m	
Belize	2001	DTP-Hib	Pentavalent	2 m	4 m	6 m	
Bermuda	1989	Hib	DTaP-IPV-Hib	2 m	4 m	6 m	15–18 m
Bolivia	2000	Pentavalent	Pentavalent	2 m	4 m	6 m	
Brazil	1999	Hib	DTP-Hib	2 m	4 m	6 m	
British Virgin Islands	1999	Hib	Pentavalent	2 m	4 m	6 m	
Canada ^c	1986	Hib	Hib or DTaP-IPV-Hib	2 m	4 m	6 m	18 m
Cayman Islands	1992	Hib	DTaP-IPV-Hib	2 m	4 m	6 m	
			DTaP-Hib				15 m
Chile	1996	Hib/ DTP-Hib	Pentavalent	2 m	4 m	6 m	
Colombia	1998	Hib	Pentavalent	2 m	4 m	6 m	
Costa Rica	1998	Hib	Pentavalent	2 m		6 m	
			Hib		4 m		15 m
Cuba	1999	Hib	Pentavalent	2 m	4 m	6 m	
			Hib				18 m
Dominica ^d	2006	Pentavalent	Pentavalent	2 m	4 m	6 m	
Dominican Republic	2001	Pentavalent	Pentavalent	2 m	4 m	6 m	
Ecuador	2003	Pentavalent	Pentavalent	2 m	4 m	6 m	
El Salvador	2002	Pentavalent	Pentavalent	2 m	4 m	6 m	
Grenada	2000	Pentavalent	Pentavalent	6–8 w	16–20 w	24–28 w	
Guatemala ^e	2005	Pentavalent	Pentavalent	2 m	4 m	6 m	
Guyana	2001	Pentavalent	Pentavalent	2 m	4 m	6 m	
Haiti	Not introduced						
Honduras	1999	Hib	Pentavalent	2 m	4 m	6 m	
Jamaica	2003	Pentavalent	Pentavalent	6 w	3 m	5–6 m	
Mexico	1998	Pentavalent	Pentavalent	2 m	4 m	6 m	
Montserrat	1999	Hib	Pentavalent	2 m	4 m	6 m	
Nicaragua	1999	Pentavalent	Pentavalent	2 m	4 m	6 m	
Panama	2000	Pentavalent	Pentavalent	2 m	4 m	6 m	
			DTP-Hib				18 m
Paraguay	2002	Pentavalent	Pentavalent	2 m	4 m	6 m	
Peru ^f	2005	Pentavalent	Pentavalent	2 m		4 m	
			Hib		3 m		
St. Kitts & Nevis	2000	Pentavalent	Pentavalent	2 m	4 m	6 m	
St. Lucia	2002	Pentavalent	Pentavalent	3 m	5 m	7 m	
St. Vincent & Grenadines	2003	Pentavalent	Pentavalent	2 m	4 m	6 m	
Suriname	2005	Pentavalent	Pentavalent	2 m	4 m	6 m	
Trinidad & Tobago	1999	Hib	Pentavalent	3 m	4–5 m	6 m	
Turks & Caicos ^g	1999	Hib	Pentavalent	2 m	4 m	6 m	
Uruguay	1994	Hib	Pentavalent	2 m	4 m	6 m	12 m
United States ^h	1991	Hib	Hib or combination	2 m	4 m	6 m	12–15 m
Venezuela	2000	Hib	Pentavalent	2 m	4 m	6 m	

Source: Country Reports to PAHO, unless otherwise stated. Territories not routinely reporting to PAHO—French Guiana, Guadeloupe, Martinique, Aruba, and the Netherlands Antilles—include Hib in their routine infant immunization schedule (not shown).

^aHib refers to monovalent Hib vaccine; pentavalent to combination DTP-Hib-hepatitis B vaccine.

^bSchedule obtained from WHO Vaccine-Preventable Diseases: Monitoring System. WHO, 2004.

^cPolysaccharide vaccine Hib for children aged ≥24 months introduced in 1986. Hib conjugated vaccines for infants introduced in 1992.

^dThe country has purchased pentavalent vaccine for introduction in late 2006.

^ePentavalent vaccine introduced for the social security beneficiaries in 1999 (*Instituto Guatemalteco del Seguro Social*). Introduced in 2005 for the rest of the country.

^fStarted using Hib vaccine in parts of the country as early as 1997, but Hib vaccine became part of the schedule for the entire country only in 2005.

^gSchedule changed in 2006 from pentavalent at 6, 12, and 18 weeks.

^hCombination DTaP-hepatitis B-IPV and Hib-hepatitis B may be offered as options. Schedule obtained from CDC Web site at: <http://www.cdc.gov/nip/recs/child-schedule.htm>.

IPV, inactivated polio vaccine; m, months; w, weeks; y, years.

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is highly cost-beneficial in both developed and developing settings [31–33], Hib vaccine price is higher than the traditional vaccines of the

Expanded Program on Immunization (EPI). The price of Hib vaccine is more than double the measles-mumps-rubella vaccine, the most expensive

among the traditional EPI vaccines (US\$3.15 versus US\$1.4 per dose). Therefore, financial sustainability has been a critical consideration for

countries introducing Hib vaccination into their routine immunization schedule. To ensure sustainability, PAHO recommends purchasing Hib vaccine in combination with DTP or DTP/hepatitis B vaccine through the PAHO RF, and advocates for countries to issue legislation ensuring a budget line for vaccine purchase and other expenses of the immunization program.

In 2006, all but three of the LAC countries using Hib (Bolivia, the Dominican Republic, and Nicaragua) financed more than 95% of their public sector routine vaccine expenses using government funds. Also, in most LAC countries (27 of 31 with data available) at least 90% of the national immunization program's recurring costs were financed using government funds. All LAC countries using Hib vaccine have reported having a budget line for vaccine purchase (the Dominican Republic, Jamaica, and Saint Kitts and Nevis include vaccines in a budget line for medication purchase).

Of the six GAVI-eligible countries in LAC (countries with a gross national income of less than US\$1,000 per capita), Guyana was the only one to introduce Hib vaccine (as pentavalent) using GAVI support. In 2006, Guyana took over the full financing of this vaccine. Other low-income countries have introduced pentavalent with support from other aid agencies.

As of 2006, 26 LAC countries reported having some immunization-related legislation, and three more were in the process of adopting such laws. In countries with legislation, laws and decrees have been used as a way to secure a budget line for vaccines and sustain vaccine introduction [34]. Among the Hib vaccine early adopters, Hib introduction followed ministerial and presidential decrees in Chile and Uruguay [25]. No information regarding the specific relation between Hib vaccine introduction and legislation is available for other countries.

Maintaining affordable prices is critical for vaccine introduction. The price of Hib vaccine purchased through the RF started at between US\$6 and US\$8.2 per dose in 1997 and dropped markedly, to between US\$2.18 and US\$2.60, at the end of 1998, as significantly more doses were

purchased. For 2007, the RF price is US\$3.15 per dose of the combination DTP-Hib (ten-dose vials) and US\$3.92 per dose of pentavalent (one-dose vials).

In 2006, all LAC countries but four procured Hib-containing vaccines through the RF: two used Hib-containing vaccines produced in their own countries (Brazil and Cuba) and two purchased directly from a vaccine manufacturer.

Regional laboratory network.

Having a regional laboratory network has been instrumental in monitoring the circulating Hib strains that cause bacterial meningitis and pneumonias. As of 2006, SIREVA included laboratories from 19 Latin American countries plus the Caribbean Epidemiology Centre, and continued to monitor trends in the circulating serotypes and antimicrobial resistance patterns of Hib, as well as pneumococcus and meningococcus [35].

Remaining Challenges

Hib vaccination coverage. PAHO recommends reaching coverage levels of at least 95% for all vaccines in all municipalities [36,37]. Throughout the past seven years, the overall reported administrative coverage (weighted average) with three doses of Hib vaccine (Hib3) in LAC has increased from 78% in 2000 to 94% in 2006 (with 19 and 37 countries reporting, respectively). However, the lower coverage reported in earlier years mostly reflects the partial use of Hib vaccine during the year of introduction. Hib3 coverage rates are comparable to those observed for the third dose of the diphtheria-tetanus-pertussis vaccine (DTP3). Use of combination vaccines contributes to this finding. No deterioration in DTP3 coverage during the year of Hib vaccine introduction is apparent from the coverage data available.

Coverage varies between and within countries. In 2006, reported coverage ranged from 83% to greater than 100%. Also, 42% of LAC municipalities (districts) reported coverage levels below 95%, using DTP3 as a proxy for Hib3. This finding illustrates that inequities in Hib vaccine use still exist in LAC countries.

Sustainability of immunization programs. A major challenge

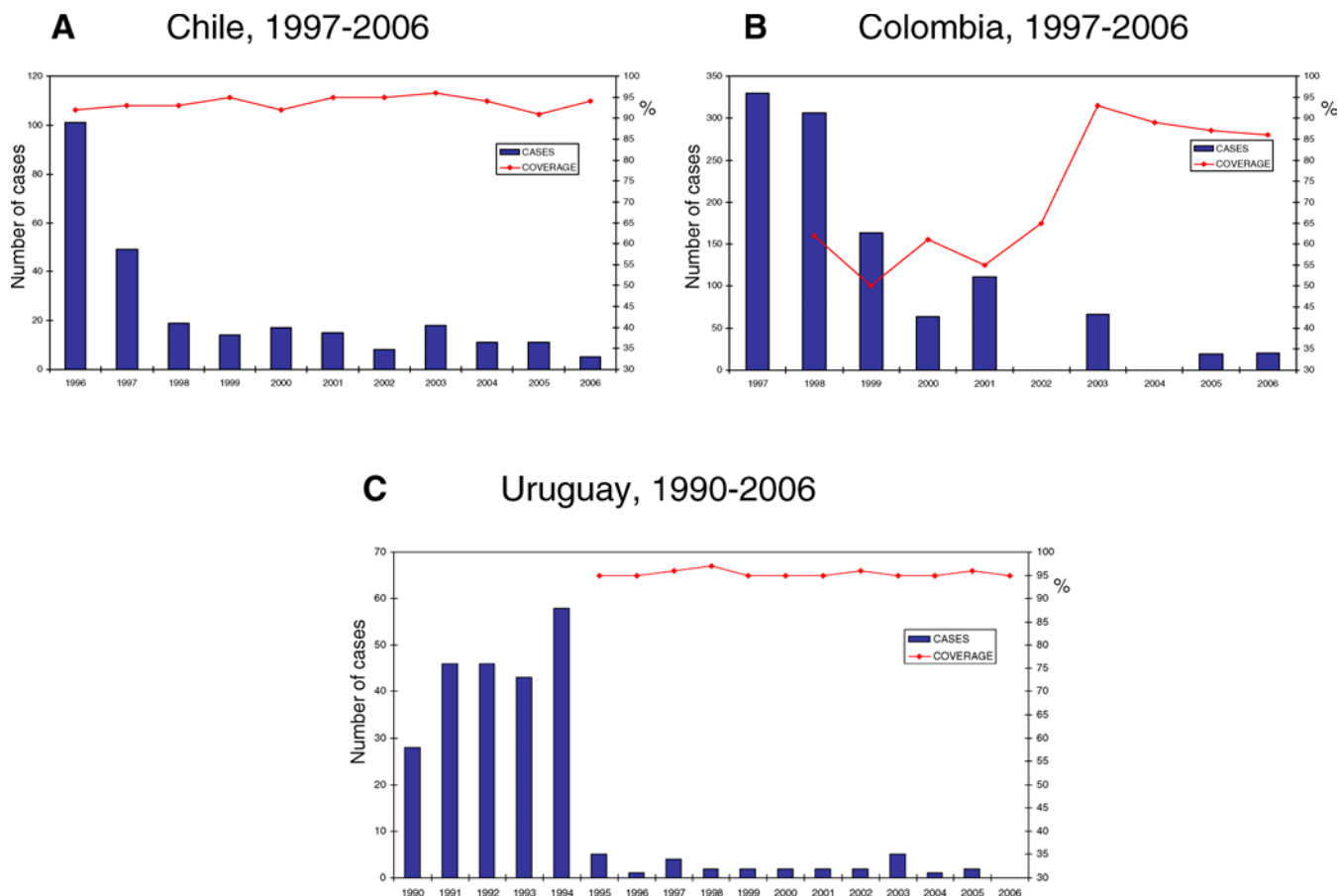
for countries of the Americas is maintaining Hib vaccination while adding new, more expensive vaccines into national routine schedules. PAHO is currently developing a regional policy framework to assist countries in the following areas: exploring mechanisms to find new approaches for sustainable financing, focusing on securing longer-term and reliable funding for immunization programs, particularly through the creation of fiscal space; strengthening vaccine legislation to reduce national transaction costs; and improving the efficiency of the RF and expanding participation in its services to ensure that countries can afford new-generation vaccines [34,37–39].

“Creating fiscal space” is an expression used for mobilizing additional resources without compromising existing priorities in health. Mechanisms used include: identifying new partners; enhancing tax collection procedures; raising additional revenues through national lotteries, as was done for new vaccine purchase in Costa Rica; and exempting vaccine purchases from import tax, since import taxes can raise the vaccine purchase cost by as much as 30% in some countries.

PAHO recently described model vaccine legislation based on an analysis of existing laws [34]. Some of the legislation components aim to secure resources for immunization programs and include: a budget line for vaccines; regulations guaranteeing timely and reliable disbursement of resources; tax exemptions for vaccines and immunization supplies; flexibility to contract with suppliers, including third parties such as the RF; and streamlined customs regulations to accelerate the importation process and reduce transaction costs.

Vaccination impact. The impact of Hib vaccine introduction has been well documented by reductions in Hib meningitis in selected countries of the Americas [9–11,25,40]. However, some countries are still lacking a surveillance of bacterial invasive disease that performs sufficiently well to document such impact.

A decrease in Hib meningitis has been well documented in Chile, Colombia, and Uruguay, in spite of differences in the introduction strategy and the coverage levels attained (Figure 1). Both Uruguay and Chile



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Figure 1. Coverage with Third Dose of Vaccine Containing Hib in Children Aged Less Than One Year and Number of Reported Hib Meningitis Cases by Year in Chile, Colombia, and Uruguay
 Source: Country reports to PAHO and XVI Meeting of PAHO's TAG, 2004. No Hib meningitis data were reported to PAHO from Colombia for 2002, and zero cases were reported from Uruguay in 2006.

reached coverage levels of greater than 90% since vaccine introduction, but only Uruguay had an aggressive catch-up strategy at vaccine introduction. The schedule in Uruguay calls for a booster dose at 12 months. Colombia initially achieved moderate coverage levels (50%–65%) that have increased to more than 86% over the last three years. Based on coverage levels achieved, 95% vaccine effectiveness, and the 20,000 cases estimated in the pre-vaccine era [19], PAHO estimates that Hib meningitis cases in LAC have decreased by approximately 85%.

In recent years, the number of Hib isolates from children aged less than two years has decreased in selected countries, from 92 in 2000 to 30 in 2005 in Brazil, from 30 in 2000 to eight in 2005 in Colombia, from 53 in 2000 to four in 2005 in the Dominican Republic, and from 44 in 2000 to two in 2005 in Venezuela. In these four countries, the number of pneumococci and meningococci isolates

has remained stable over the same time period [35]. Hib isolates continue to be obtained from countries using Hib vaccine. However, neither SIREVA nor PAHO routinely collect data on the vaccination status of Hib cases reported.

Only a few LAC countries have been able to demonstrate that Hib vaccine has been effective against pneumonia in children aged less than two years. Hib vaccine has reduced the incidence of hospitalized pneumonia by about 20% in Chile [41,42]. For radiologically diagnosed pneumonia, vaccine effectiveness has been estimated at 31% in central Brazil and up to 55% in a case-control study conducted in Colombia [43,44].

Hib surveillance remains one of the most important challenges in LAC. To promote the strengthening of routine surveillance, PAHO recommends the integration of Hib into the routine surveillance of bacterial meningitis and pneumonias [3]. As done in the

Central American sub-region, this will require adapting WHO's generic protocol for population-based Hib surveillance [3,45,46]. Currently, case definitions and surveillance procedures vary by country, limiting data comparability.

Monitoring the effectiveness of Hib vaccine in the routine immunization program is essential because vaccine efficacy may be affected by several factors, such as the use of booster doses, waning immunity, reduction of natural boosting due to reduced Hib transmission [47], and cold damage in storage units not maintained properly. Monitoring the changing epidemiology of *H. influenzae* disease in the post-vaccine era will also be important, as the role of invasive non-b type *H. influenzae* may become prominent [48]. The importance of continued Hib disease monitoring has been recently highlighted. In the United Kingdom, an unexpected increase in the incidence of Hib disease coincided

with the distribution of combination vaccines that contain acellular pertussis (diphtheria-tetanus-acellular pertussis-Hib vaccine, or DTap-Hib) [49–52]. In the Gambia, Hib seems to have reappeared in 2005–2006 after at least three years with no cases [53].

The added value of using a booster dose has been debated extensively because the majority of Hib disease burden in developing countries occurs before the age when the booster is usually administered (12–18 months) [1]. PAHO is currently assisting four countries to determine whether a booster dose during the second year of life is useful.

Efforts are in place to enhance the work done by SIREVA, including collecting more clinical and epidemiological data. This new initiative, known as “Network Surveillance System for the Bacterial Agents Responsible for Pneumonia and Meningitis” or SIREVA II, should provide a better understanding of the occurrence of cases in countries reporting high Hib coverage and the possibility of serotype replacement over time.

Conclusions

Although LAC countries lagged behind North America in their efforts to introduce Hib vaccine into their childhood immunization schedules, probably due mostly to financial considerations, all but Haiti had introduced this vaccine by the end of 2006. Even though the data available regarding Hib is not complete and comes from routine reporting by countries to PAHO, we believe that the main factors that favored the region-wide adoption of Hib vaccine in LAC are the safety and effectiveness of conjugated Hib vaccines; strong political will; the existence of data supporting a high Hib disease burden and vaccination impact in early adopters, and their lessons learned, shared through several publications and regional meetings; and PAHO’s efforts to ensure the affordability of Hib vaccines, mainly through the RF.

Striving to use Hib in combination with other antigens and considering mechanisms to ensure sustainability, such as vaccine laws or presidential decrees whenever possible, will accelerate introduction. The main challenges remaining in LAC countries

are to address low vaccination coverage in low-performing districts, ensure Hib vaccination while introducing other new and more expensive vaccines, and establish or strengthen Hib surveillance, better utilizing the well-established laboratory network. When considering the introduction of other new vaccines, LAC countries must take into account lessons learned from Hib introduction, in order to shorten the lag between vaccine development and widespread adoption in developing countries. ■

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Supporting Information

Text S1. Translation of the article into Spanish by MCD-H

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