EXPERT REVIEWS

Pertussis in Latin America: epidemiology and control strategies

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Pertussis is a serious respiratory disease in infants that can also affect children and adults. Vaccination against pertussis was introduced in the 1950s and in the 1990s a resurgence of pertussis was observed worldwide. The aim of this work is to summarize the recent data concerning pertussis disease in different countries of Latin America. In this geographic region, pertussis is nationally notifiable and cases should be reported to the appropriate health department/Ministry. Though the surveillance systems are not the same among Latin America countries, over recent decades an increasing number of cases have been detected. Most of these cases correspond to patients younger than 6 months old who received fewer than three doses of vaccine. However, cases in adolescent and adults have also been detected. For this situation, which is not peculiar to Latin America countries, several explanations have been proposed.

KEYWORDS: *Bordetella pertussis* • epidemiology • Latin America • vaccination • whooping cough

Background of pertussis in Latin America

Bordetella pertussis is the main causative agent of pertussis or whooping cough, a respiratory disease that continues to be a serious public health problem. Pertussis remains in fifth place in the list of deaths attributed to vaccine-preventable diseases in children less than 5 years of age around the world. It causes significant morbidity and mortality in both developing and developed nations [1–3]. According to WHO, there are an estimated 16 million cases of the disease and approximately 195,000 deaths occur worldwide every year, 95% of which take place in developing countries [4].

In Latin America, the annual number of suspected pertussis cases over the last 10 years has ranged from 1500 to 43,000 [5,6], with significant increases in the number of cases in Argentina [7], Brazil [8], Mexico [9], Chile [10], Colombia [11], Paraguay [12], Peru [13] and Uruguay [14] among others. In this region as in other countries, infants younger than 1 year old and particularly those younger than 6 months, bear the largest disease burden. Severe morbidity and mortality are most common in infants [15–17]. For example, in Argentina, 76 deaths were registered in 2011 [18] and between 2008 and 2012 in Brazil, 185 pertussis-related deaths occurred in children less than 4 years of age. In Costa Rica, the disease has a direct impact on infant mortality and in 2006, eight infants younger than 1 year old died [19]. Though surveillance in adolescents and adults is weak, cases in those groups were also recorded [7,20,21]. The vaccination schedule against pertussis in Latin American countries consists of 3 primary doses with a booster in the second year of life, and a second booster dose at preschool age [22]. At present, this vaccination schedule including boosters, with the exception of Mexico and Costa Rica, was performed with the whole-cell pertussis (wP) vaccine (Table 1). In the last years, the coverage of the third dose of pertussis vaccines (DTP3, D and T because the vaccine also contains Diphtheria and Teranus components) as well as DTP1 and DTP2, is over 90% in most areas of the region. Moreover, recently in response to the resurgence of pertussis, several countries of the region have added new pertussis boosters on adolescent and adult population. These new boosters in elder groups are performed with acellular vaccines (aP) (Table 1).

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Table 1. Official vaccination schedule used in Latin American countries 2012.

Country	Primary series 2, 4, 6 months	Booster 15–18 months	Booster 4–6 years	Adolescents	Pregnant	Postpartum	HCW
Argentina	DTwP-HB-Hib	DTwP-Hib	DTwP	Tdap	Tdap	Tdap	Tdap
Brazil	DTwP-HB-Hib	DTwP	DTwP	NO	NO	NO	NO
Chile	DTwP-HB-Hib	DTwP-HB-Hib	Tdap	Tdap	NO	NO	NO
Colombia	DTwP-HB-Hib	DTwP	DTwP	NO	Tdap	NO	NO
Costa Rica	DTaP-Hib-IPV	DTaP-Hib-IPV	DTaP-IPV	NO	Tdap	Tdap	NO
El Salvador	DTwP-HB-Hib	DTwP-HB-Hib	DTwP	NO	NO	NO	NO
Guatemala	DTwP-HB-Hib	DTwP	DTwP	NO	NO	NO	NO
Honduras	DTwP-HB-Hib	DTwP	DTwP	NO	NO	NO	NO
Mexico	DTaP-Hib-IPV	DTaP-Hib-IPV	DTwP	NO	Tdap	NO	NO
Panama	DTwP-HB-Hib	DTwP-Hib	DTwP	Tdap	Tdap	Tdap	Tdap

DTwP: Diphtheria, tetanus pertussis; HB: Hepatitis; HCW: Healthcare workers; Hib. *Haemophilus influenzae* type B; IPV. Inactivated poliovirus vaccine; NO: Not used.

Possible transmission routes

Pertussis is a very contagious disease that is spread from person to person. Individuals with pertussis usually spread the disease by coughing or sneezing while in close contact with others, who then breathe in the bacteria. The study performed by Wendelboe *et al.* provides solid evidence that among infants for whom a source case was identified, household members were mainly responsible for the transmission of *B. pertussis* to this high-risk group [23]. In accordance with this study, data from Mexico showed that out of the total number of mothers (70 mothers) of children with confirmed pertussis, 26% had a positive PCR for *B.* pertussis [24]. Preliminary data from Argentina provided by the National Laboratory of Reference for pertussis (VacSal, IBBM FCE UNLP) showed that in 32% of cases, parents were the source of infection [25]. According to other data from a multicenter study that included Latin American countries (Brazil, Costa Rica and Uruguay), in 27% of children who were hospitalized with pertussis in pediatric intensive care units, the source of transmission was the mother. In Costa Rica, among household contacts of patients admitted to the National Children's Hospital, *B. pertussis* was identified by PCR in 69% of the studied household contacts, and 33% of patients had more than one possible source of contact [26].

Epidemiological surveillance & diagnostic methods

In Latin America, it is mandatory to notify pertussis nationally and cases should be reported to the National Health Ministry for each of the respective countries. Epidemiological surveillance in most of the Latin American countries is based on the recommendations of international organizations such as WHO [27] and the CDC [28]. The different countries of Latin America have considered adaptations in clinical criteria including age stratification and cough duration. Following the identification of a clinical case, a case report form is completed using information collected during patient and physician interviews. Specimens are collected and routinely shipped to a laboratory for diagnosis. The laboratory criteria for diagnosis are mainly based on isolation of *B. pertussis* from clinical specimen and/or through PCR for *B. pertussis*. Although direct fluorescent antibody testing is sometimes used in some Latin American countries, neither WHO nor the CDC recommends it as a diagnostic method.

Table 2 presents a summary of the criteria used by different Latin American countries for pertussis surveillance.

Epidemiological situation of pertussis in different Latin American countries

The countries selected for this section were not globally representative, but were chosen on the basis that they were able to provide data on vaccine coverage and trends in pertussis disease burden over time. The countries were selected to include representation from those with (i.e., Argentina, Brazil, Costa Rica, Chile, Colombia and Mexico) or without (i.e., Central American countries) an apparent pertussis resurgence. Whereas laboratory surveillance is established in the former countries, the latter do not seem to have these facilities, which might be one reason for their low numbers of reported cases.

Argentina

Since 2002, a sustained increase in cases of pertussis has been recorded, not only in children, but also in adolescents and adults [7,29,30]. The incidence of the disease in 2003 was 1.8 per 100,000 inhabitants, then rose in 2005 to 5.7 cases per 100,000 and in 2011 to 8.3 cases per 100,000, increasing 46% in 6 years (Figure 1) [29,30].

In 2011, 3332 confirmed cases were recorded; 54% of confirmed cases had a laboratory diagnosis positive for *B. pertussis* (84% by PCR), while 46% had a clinical report with an epidemiological link. The incidence rate in infants under 1 year of age was 374 cases per 100,000 [7].

The mortality rate in infants under 1 year of age was 0.09 per 1000, and the case-fatality rate was 2.4%. Of the 76 infants who died during 2011, 93% were under 3 months of age. In 92% of the deaths, infants had not been vaccinated, 5% had received only 1 dose and 3% had received only 3 doses [31].

Brazil

Since the 1990s, the incidence of pertussis cases has shown a significant reduction due to the expansion of pertussis vaccine coverage. In the beginning of that decade, vaccine coverage was about 70% and the incidence was 10.6 per 100,000 inhabitants. In the 1998–2000 period, the coverage increased to 95% and the incidence decreased to 0.9 per 100,000 inhabitants. With the maintenance of high vaccine coverage variations, an incidence of 0.72 per 100,000 inhabitants in 2004 and of 0.32 per 100,000 inhabitants in 2010 was observed. However in mid-2011 (>95% DTP3 coverage), there was a sudden increase in the number of cases; incidence exceeded the upper limit expected when compared with the 2006–2010 period. Throughout 2012, the number of cases by epidemiological week remained higher than expected. According to data recorded in the National Notifiable Diseases (SINAN) in 2012, 15,428 suspected pertussis cases were reported in the country. From these, 4453 (28.9%) were confirmed, representing an increase of 97% against the same period in 2011, when 2258 cases were confirmed [32]. The states that had a higher incidence of pertussis in 2012 were Espirito Santo state, with an incidence of 20.6 per 100,000 inhabitants and Rio Grande do Sul state, with 7.2 per 100,000 inhabitants. The age group with the largest number of cases and highest incidence were children under 1 year of age. This age range corresponds to about 70% of cases of pertussis in the country. In 2012, the incidence rate in children younger than 1 year was 105.6 per 100,000 inhabitants, while in 2011 it was 61.6 per 100,000 inhabitants (Table 3). In 2012, the number of deaths increased to 74 cases, while in 2011 it was 56 [32]. Between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age: 125 had never been vaccinated, 20 had received one dose, 2 had received 2 doses, 1 case had received 3 doses and 2 cases had received 3 doses plus the first booster. The immunization status was unknown for 35 of the deaths.

Table 2. Clinical and laboratory criteria used by different countries in Latin-America.

Country	Surveillance system	Clinical case definition according to WHO/CDC	Methodologies used in laboratory diagnosis				Final classification of case				
			Culture	*PCR*	*Serology*	*IFD*	*Use of the epidemiological link for case classification*	*Suspect*	*Probable*	*Confirmed*	*Discarded*
Argentina	MUPN	Yes[1]	✓	✓	✓	×	✓	×	✓	✓	✓
Brazil	MUPN	Yes	✓	✓	×	×	✓	✓	×	✓	✓
Colombia	MUPN	Yes[1,4]	✓	✓	×	✓	✓	×	✓	✓	✓
Costa Rica	MUPN	Yes[1]	✓	✓	×	×	✓	✓	[5]	✓	×
Chile	MUPN	Yes[1]	✓	✓	×	✓	✓	✓	✓	✓	✓
Ecuador	MUPN	Yes	✓	✓	×	✓	✓	ND	✓	✓	×
Mexico	MUPN	Yes[1]	✓	✓	×	×	✓	✓	✓	✓	✓
Paraguay	MUPN	Yes	✓	✓	×	×	✓	✓	✓	✓	✓
Peru	MUPN	Yes[1]	✓	✓	×	✓	✓	✓	✓	✓	✓
Uruguay	MUPN	Yes	✓	✓	×	×	✓	✓	×	✓	×
Venezuela	MUPN	Yes	✓	✓	×	×	✓	×	✓	✓	×

[1]In the clinical case definition, symptoms are differentiated according to patient age. For neonates and infants, the duration of cough is not included in the clinical case definition.
[4]Instead of a 14-day duration of cough, 1 or 2 weeks are used in the definition.
[5]Case compatible with clinical case definition.
✓: Used; ×: Not used; MUPN: Mandatory universal passive notification; ND: No data available.

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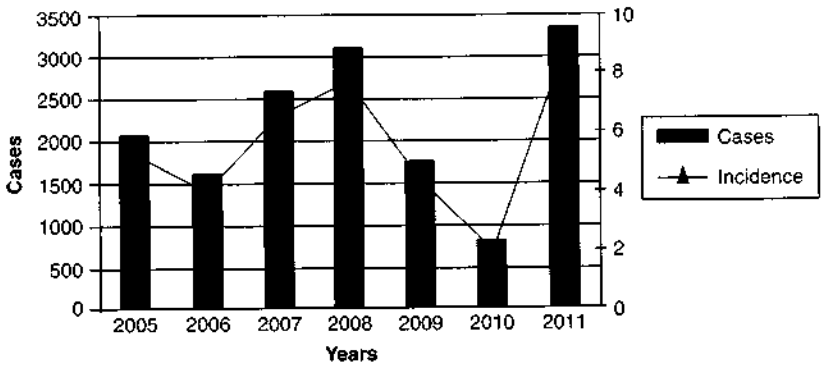

Figure 1. Number of pertussis cases and incidence rate per year in Argentina.
Period 2005–2011.

The entire epidemiological situation detected in 2012 could be due to the observed decrease in national vaccination coverage in infants due to supply issues. From 2006 to 2012, the number of municipalities with >95% DTP3 coverage decreased from 83 to 55% with non-homogenous coverage throughout the country. Causes for this decline were mainly operational issues, as social acceptance of vaccination in Brazil is high.

Chile

Since 2002, the incidence rate has been stable at approximately 7 cases per 100,000. In 2010, this value began to increase and in 2011 the incidence rate reached 15 cases per 100,000.

Table 3. Pertussis incidence rate and mortality by age group.

	2011			2012		
Age (years)	*Cases*	*Incidence*[†]	*Deaths*	*Cases*	*Incidence*	*Deaths*
Less than 1	1,687	61.6	54	2924	105.9	74
1–4	208	1.9	1	721	6.4	0
5–9	80	0.5	0	307	2.0	0
10–14	71	0.4	0	181	1.0	0
15–19	42	0.2	0	77	0.4	0
20–29	67	0.2	0	95	0.3	0
30–39	46	0.2	0	88	0.3	0
40–49	35	0.1	1	39	0.2	0
50–59	9	0.0	0	12	0.1	0
60–69	8	0.1	0	8	0.1	0
70–79	1	0.0	0	0	0.0	0
80 and over	0	0.0	0	1	0.0	0
Total	2254	1.2	56	4453	2.3	74

Brazil, 2011 and 2012 (per 100,000 inhabitants).
[†]Per 100,000 inhabitants.
Data taken from Sinan/UVRI/CGDT/DEVEP/SVS/MS. Data subject to revision

During 2011, the incidence rate in infants under 1 year of age was 517.8 per 100,000 inhabitants. The annual case-fatality rate in 2009, 2010 and 2011 was 1.0, 0.9 and 0.6%, respectively [33].

During the first 3 months of 2012, there was an increase of approximately 50% in the number of cases in infants, totaling 643 cases, compared with only 338 cases for the same period in 2011. The most affected regions all over Chile were Antofagasta, Coquimbo, Valparaiso, Maule, Los Rios and Los Lagos.

The number of deaths in 2011 and 2012 was 16 and 13, respectively; 7 deaths occurred in each 2010 and 2009. Mortality was highest in 2- to 3-month-old infants in 2011 and 2012 (47.6 per 1,000,000 births in 2012).

Colombia

According to the reports of the Instituto Nacional de Salud, the global pertussis incidence rate increased, ranging from 0.32 per 100,000 in 2005 to 2.19 per 100,000 in 2011. The number of confirmed cases has also increased significantly since 2011, when 830 cases were confirmed. In 2012, the incidence rate was 6.7 per 100,000 inhabitants [11]. In that year, 65.5% of the cases occurred in infants under 1 year of age (mainly younger than 6 months). In 2011, 34 deaths in infants under 1 year of age were reported in Colombia and 65 deaths in 2012 [34].

Costa Rica

Over the last 20 years, three epidemic outbreaks have been reported (in 1997/1998, 2001/2002 and 2006/2007), the last of which was the most severe and included 13 laboratory-confirmed deaths. Figure 2 shows the incidence rate per 100,000 inhabitants by age group, where the highest value was recorded in infants under 1 year old. During the 2006/2007 epidemic period, an increase in the mortality rate among children under 1 year was detected. In 2007, the death rate of pertussis was 11.2 per 100,000 live births. This value was higher than the one detected during the 1980–1982 triennium with a rate of 9.7 per 100,000, representing more than 1% of all deaths in children under 1 year in Costa Rica [35].

In April 2007, Costa Rica implemented the strategy of postpartum vaccination, which resulted in a dramatic

reduction in the number of deaths caused by pertussis: 2 deaths occurred in 2009 and no deaths in 2010 [36]. More recently, in February 2013, postpartum acellular vaccine (Tdap vaccine) was switched to vaccination during pregnancy.

Mexico

During the 2000–2011 period, pertussis showed fluctuations in the number of cases as described in other countries, with epidemic cycles every 3–5 years (Figure 3).

The last outbreak was recorded in 2009, with 579 confirmed cases. In 2010, the number of cases decreased but then in 2011 increased to 455 (up 19%). The latter increase may be due, at least in part, to the fact that in 2011 PCR assay began to be used as a diagnostic test for pertussis. The increase continued in 2012 with 752 confirmed cases.

Similar to most reports in the literature, 83% of the cases occurred in infants younger than 1 year of age [37]. The recently reported mortality rates are the highest reported over the last few years in Mexico. Official national data are not available, however, a recent prospective study conducted during a 1-year period in seven pediatric centers in Mexico showed that 6.5% of children died from pertussis complications [24].

Central American countries

Countries from Central America reported clinical cases and only few laboratory-confirmed cases of pertussis. In 2011, El Salvador reported 11 confirmed cases with an incidence rate of 0.10 per 100,000 inhabitants. On the other hand, in 2011 Honduras reported four confirmed cases with a rate of 0.01 per 100,000 inhabitants. In 2012, Guatemala has reported an increase in cases and issued an epidemiological alert [38]. For this country in 2011, the incidence of pertussis was less than 0.3 per 100,000 inhabitants and in 2012 the incidence rate was 1.8 per 100,000 inhabitants. In Panama, Nieto Guevara and colleagues reported that in the 2001–2008 period, 759 suspected cases were admitted to the Children's Hospital and 180 cases out of the total were confirmed by PCR and culture [39]. The hospitalization rate was 14.4 per 10,000 admissions, being higher in the group younger than 3 months (42.76 per 10,000 admissions, 75% out of the total).

Pertussis vaccines used in the Latin America region

To reduce the risk of severe pertussis in infants, WHO recommends a three-dose primary series, with the first dose administered at 6 weeks of age; subsequent doses should be given 4–8 weeks apart, at the age of 10–14 weeks and 14–18 weeks. The last dose of that primary series should be completed by the age of 6 months. In addition, a booster dose is recommended for children aged 1–6 years, preferably during the second year of life. The booster should be given ≥6 months after the last primary dose. With this four-dose schedule (primary series plus booster), at least 6 years of protection against pertussis are expected [22].

The Advisory Committee on Immunization Practices (ACIP) of the US CDC and other international entities have

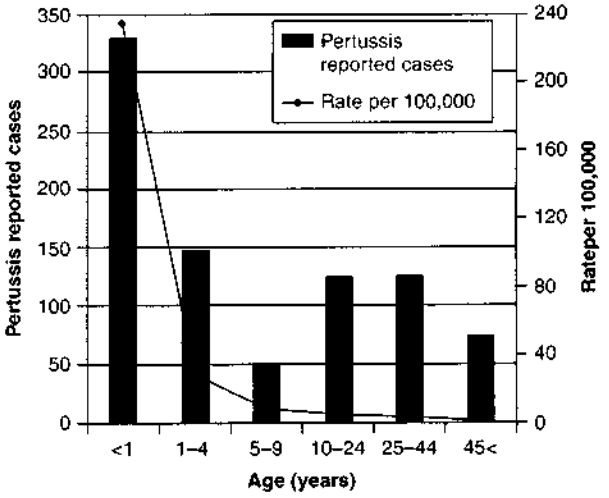

Figure 2. Number of pertussis cases and incidence rate per age group in Costa Rica during the outbreak of 2006/2007. Data taken from Epidemiologic Department, Ministry of Health Costa Rica.

also recommended a booster for adolescents and adults in order to improve disease control [40–42].

In order to accomplish all these recommendations, in the Latin American region two types of vaccines are used (Table 1): wP based on standardized cultures of *B. pertussis* strains and aP composed of two (pertussis toxin and filamentous hemagglutinin), three (pertussis toxin, filamentous hemagglutinin and pertactin) or five immunogens (pertussis toxin, filamentous hemagglutinin, pertactin and fimbriae-2 and -3) [43]. Whole-cell vaccines combined with diphtheria and tetanus toxoids or with tetanus, diphtheria and other vaccines such as *Haemophilus influenzae* type B (Hib, DTwP Hib) or Hib and hepatitis B

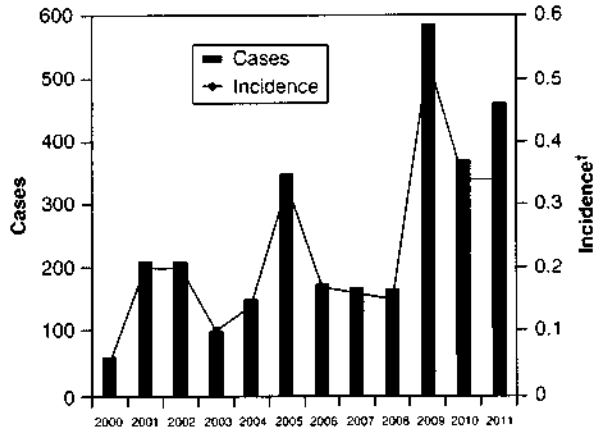

Figure 3. Number of pertussis cases and incidence rate by year. Mexico 2000–2011.
†Per 100,000 inhabitants.
Data taken from SINAVE/DGE/S.S. Pertussis Mentoring System.

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(DTwP Hib HB) were used until 2007 in all Latin American countries for the 3 doses of primary series given at 2, 4 and 6 months (Table 1), the first booster dose at 18 months of age and the fifth dose at age 4–7 years of age. In 2007 and 2009, Mexico and Costa Rica respectively, replaced all doses by the wP vaccine by DTaP-Hib-IPV (Pentaxim from Sanofi). Mexico and Costa Rica administer the two-component pertussis vaccine combined with Hib and IPV of French origin. In Costa Rica, pentavalent DTaP-Hib-IPV in a five-dose schedule has been used since September 2010.

Over the last few years, since the resurgence of pertussis, different protection strategies have also been considered: universal adult immunization; selective immunization of mothers and close family contacts of newborns; selective immunization of healthcare workers; selective immunization of childcare workers; universal immunization of adolescents; pre-school booster at 4–6 years of age and reinforcement and/or improvement of current infant and toddler immunization strategies [44]. Because immunization programs vary widely from country to country, no single strategy is likely to be appropriate for all.

In the next section, some features of each vaccination strategy are indicated, as well as which countries in Latin America have implemented the strategy described.

Universal adult vaccination

With the universal immunization of adults 19 years of age and older it is expected to reduce pertussis incidence in adults but also in young infants through herd immunity. However, up to now there are no data available showing that this strategy would meet these objectives. At present, this strategy has not been implemented in any of Latin America countries.

Immunization of mothers, family & close contacts of newborns (Cocoon strategy)

For this strategy, two main vaccination schedules were considered: maternal vaccination during pregnancy (during the third trimester) or vaccination of mothers, fathers, family members and other close contacts perinatally. Maternal vaccination during pregnancy might reduce pertussis transmission from mother to newborn and have the advantage of transferring antibodies to the infant via the placenta. In 2011, this strategy was recommended for all pregnant women after 20 weeks of gestation by ACIP [45].

In Latin America, Argentina, Colombia and Mexico have implemented this strategy in 2012.

At the end of 2012, the ACIP modified the recommendation for Tdap vaccination during pregnancy so that a dose of Tdap is to be given between 27 and 36 weeks during each pregnancy, regardless of the interval between pregnancies [46]. This strategy is not yet implemented in Latin American region.

The second vaccination schedule consists of postpartum vaccination of parents and all close contacts of the newborn.

Mathematical epidemiological models, showed that this strategy could yield the expected reduction in pertussis disease in infants [36]. In fact, some reports confirming that this strategy significantly reduces transmission to infants were recently published [47].

The only country of Latin America that vaccinated fathers and mothers was Costa Rica during the 2006/2007 outbreaks.

Selective immunization of healthcare & childcare workers

Vaccinating healthcare workers, primarily to prevent nosocomial transmission to infants and immune-compromised persons, may be cost-effective if high coverage rates are obtained. Countries with demonstrable nosocomial transmission are encouraged to implement such vaccination, especially among staff in maternity and pediatric units if it is economically and logistically feasible.

Argentina and Panama implemented the immunization of healthcare workers who took care of infants in 2010.

Preschool booster vaccination

With the administration of a booster dose at 4–6 years of age, it is expected that immunity will be extended into adolescence and also into infants since it is expected to reduce the transmission from siblings to young infants. However, Hviid *et al.* reported that the effectiveness of pre-school booster vaccination as an intervention to prevent pertussis hospitalization of 0- to 1-year-old children is modest [48].

Though this strategy seems to have a modest impact in infants, it is effective in reducing pertussis incidence in individuals with 4–6 years of age. In fact, it has been observed that after the introduction of a booster dose for 4- to 6-year-old children, the disease burden in preschool and school children decreased [49].

All the countries in Latin America currently have implemented vaccination at preschool age, from 4 to 6 years old.

Universal immunization of adolescents

With a booster dose in adolescents, it is expected to extend the immunity against pertussis and reduce the prevalence of the disease (and thereby transmission) in this age group, indirectly reducing transmission to vulnerable infants. However, in the absence of universal adult vaccination, adolescent vaccination will not sufficiently control the transmission to infants. In fact, modeling data from Argentina estimate that a Tdap booster at 11 years of age reduces the incidence in infants, but to a very small extent [49]. The calculated decrease does not exceed 5% in any of the epidemiological scenarios considered in the study [49].

In Latin America, the countries that have incorporated this strategy are Argentina (2010), Panama (2010) and Uruguay (2012). It should be stressed that the strategies of these countries cover only one age cohort per year (11–12 years).

Reinforce and/or improve the current infant & toddler immunization strategy

The most important way to reduce the incidence of pertussis in children is to ensure high vaccination coverage of the primary immunization schedule. Efforts to increase the coverage

of current programs are made in Latin American countries, and because of that there have been improvements in this regard.

The schedules used by different countries in Latin America in 2012 are summarized in Table 1.

Possible causes of pertussis resurgence in Latin America

Several causes have been proposed in order to explain the resurgence of pertussis. Among others, some possible reasons are the suboptimal coverage rates of vaccination, the waning of immunity conferred by vaccination and/or natural infection, the reduction in the number of natural boosters and the adaptability of the bacteria to the immunity conferred by the vaccines. Other more noticeable causes are the higher awareness of the disease, and the improvements in epidemiological surveillance and diagnostic tests [50–52]. In relation to the introduction of new diagnostic methodologies, which undoubtedly impacted on pertussis surveillance, Latin American countries have been incorporating molecular diagnosis based on PCR: Argentina in 2004, Costa Rica in 2007, in some states of Brazil in 2008 and Mexico in 2011. This technology is currently being introduced in other countries [53,54].

Regarding vaccination, coverage rates have been improved since the introduction of the wP vaccine (Diphtheria, Tetanus, Pertussis [DTwP]) in the extended program of immunization in the 70s. At present, the DTwP coverage is greater than 90%, although in some locations (i.e., locations from Brazil and Argentina) it does not exceed 80% [55]. At this point, however, it is important to point out some observations about pertussis that would presage the difficulty in achieving control. Currently used vaccines, wP or aP, provide good protection against severe and typical pertussis, but substantially less against milder coughing illness suggesting that although vaccination prevented disease or at least its severest manifestations, transmission of infection continued. The immunity from vaccination waned and that protection against infection was less complete than against the severest manifestations of disease. Another critical observation is that the cyclic nature of pertussis epidemics remained largely unchanged after the widespread use of vaccination.

In recent years, the epidemiology of the disease in many countries including some from Latin America was complicated because the disease is now increasing in adolescents and adults, probably due to the fast waning immunity post-immunization. Adult or adolescent pertussis is usually not as severe as infant disease and is generally not life threatening. However, it may still cause significant morbidity transmitting the disease to unvaccinated infants. Because of this new epidemiological situation, adolescent booster immunization is recommended. However, for some countries where this strategy has been implemented some years ago, the incidence in infants remained largely unchanged, suggesting limited or absent herd benefit from adolescent and adult Tdap [56].

In addition to waning of vaccine-induced immunity, changes in the antigenic and genotypic characteristics of circulating *B. pertussis* strains are being described. In many countries of Latin America as in other countries, alleles of vaccine antigens expressed by circulating organisms largely differ from those expressed by the strains from which vaccines were originally derived (*ptx*P3, *prn*2 and *fim*3B for circulating bacteria and *ptx*P1, *prn*1 or 7, and *fim*3A for bacteria used in vaccine production) [2,57–60]. In some countries, the emergence of allelic variants coincides with disease resurgence, but in others it does not. It remains unclear whether the appearance of these predominant strains affects the efficacy of vaccines.

Expert commentary & five-year view

The assessment of the trends in the burden of pertussis in Latin America is complex, especially as regards comparisons between countries. This may be mainly due to differences in vaccination (type of vaccine and/or producer of vaccines) and the quality of the surveillance systems employed. Country-specific data mainly from Central American countries have provided no evidence of a resurgence of pertussis, probably due to their relatively weak epidemiological surveillance systems. Data from other countries of Latin America (Argentina, Brazil, Chile, Colombia and Mexico) have evidence of an increase in pertussis-related morbidity in recent years, as compared with previous periods. The increase in pertussis cases was mainly attributed to the increase in disease awareness, the increase in overall laboratory testing and the enhanced sensitivity of the PCR diagnostic methods, which are being used more widely. In all these countries, most cases were recorded in young infants who are not old enough to acquire protective immunity by vaccination, but cases in adolescents and adults were also detected. This increase in infant cases was associated with increased mortality.

In the majority of the Latin American countries, whole-cell vaccines are used for the primary series. Only Mexico and Costa Rica use aP for such doses. The DTP3 coverage was improved in all countries of the region, but there are still some populations with coverage below 80%. Moreover, in some countries, the national coverage has declined from 1 year to another (Brazil 2012). Undoubtedly, these weaknesses in vaccination coverage have a negative impact on the control of pertussis in these populations, especially considering the effectiveness of the current vaccines (both wP and aP) that do not exceed 85%.

The high number of doses that are recommended increases the likelihood of failure to achieve high coverage, especially in those regions with large populations and inequities regarding the scope of the health systems action.

Regarding those countries of Latin America that are using aP in the primary series, at present there is a particular concern on that since the DTaP vaccines do not provide protection for long [3]. Five studies done in the 1990s showed that DTwP vaccines have greater efficacy than DTaP vaccines. Recently, in a case–control study designed to assess the risk of pertussis among 10–17 year olds during the 2010–2011 outbreak in northern California, the researchers found that teenagers who had received four whole-cell vaccine doses were nearly six-times less likely to

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have been given a diagnosis of pertussis than those who had received all aP and nearly four-times less likely than those who had received a mix of vaccines [61]. It is proposed that the switch to the aP may partly explain the resurgence of pertussis [62].

In Mexico, where aP vaccine is used in its whole calendar, this faster waning immunity reported for other countries where the primary doses are performed with aP [59] was not yet detected. This could be due to the fact that the switch to aP vaccine is relatively recent. Therefore, the increase detected in this country was mainly attributed to the increase in overall laboratory testing, and the enhanced sensitivity of the PCR diagnostic methods being used more widely.

Finally, the potential contribution in pertussis epidemiology of genetic changes in circulating strains of *B. pertussis* should be considered. The genetic changes in three *B. pertussis* antigens, pertussis toxin, pertactin and fimbriae, detected in other regions, have also been observed over time in some countries of Latin America [58]. Studies in Argentina and also in the Netherlands and Australia suggested that genetic changes might have led to vaccine failures [59,63]. However, its real impact on pertussis epidemiology needs clarification.

Under this entire context, while the current vaccines are used in the best possible ways, a new generation of vaccines capable of overcoming the weaknesses associated with the current vaccines (low duration of the induced protective immunity, high number of doses needed to achieve adequate protection level, inability to subvert the phenomenon of pathogen adaptation) seems to be needed to improve the control of the disease. At present, several pathways deserve to be explored. One possibility is to promote the use of new, less reactogenic and improved wP vaccines [60,61]. However, the return to the whole-cell vaccine would be difficult to accept for the public opinion in countries that accepted the switch to the aP, out of concern about adverse reactions.

Another possibility is to improve the aP vaccine by including additional virulent factors of *B. pertussis* and/or an adjuvant, to drive a high Th1 response.

While new vaccine developments are expected, the implementation of strategies using the available vaccines considering the epidemiological, cultural and organizational characteristics of a region is recommended. In fact, several countries in Latin America have already implemented different protection strategies based on recommendations by ACIP, Pan American Health Organization and other organizations such as the Global Pertussis Initiative. Table 1 shows official vaccination schedules used in Latin America for direct and indirect protection in the last years.

At this point, it is important to emphasize the relevance that epidemiology has at the time of implementing a new control strategy. More solid laboratory data are needed. Because of that, consensus diagnostic methodologies integrated to surveillance should be encouraged in order to improve the availability of updated pertussis epidemiological surveillance data in Latin America. Laboratory methods should focus on enhanced specificity and cultures of the organisms should be retained so that the molecular characteristics can be assessed. The importance of on-time notification should also be reinforced.

Improvements in epidemiological and social data are expected to impact positively on the design of the control strategy. Then, and for any of the adopted strategies, it would be crucial to monitor their impact. Sustainable funding to monitor the execution of the new strategy should be a priority in countries where the strategy is implemented. The results achieved should be adequately delivered to both healthcare workers and the public in general. Political commitment from Latin American governments to invest in monitoring, in education regarding pertussis disease, in the benefits of control strategies and in vaccination should be encouraged.

Finally, to better control the disease in the region with current vaccines, following points should be considered:

- Optimize vaccine recommendations considering the epidemiology of the disease in the region. To do this, it is necessary to strengthen the epidemiological surveillance systems, including case definitions, algorithms, laboratory diagnostics and recording systems agreed and validated by international institutions.
- Continue to strengthening vaccination coverage, achieve early and timely vaccination (should consider starting the primary vaccination schedule as early as possible, ≥6 weeks of age) and maintain high levels of coverage (≥90%) with at least 3 doses of assured-quality pertussis vaccine. This strengthening should also focus on avoiding delays in the application of the dose, as these delays have been predicted to have a negative impact on controlling the disease [64]
- Immunization during pregnancy would be the most effective and easiest to be implemented with good coverage, and probably at a lower cost. Vaccination during the mothers' postpartum period may also be an alternative, although possibly with less impact on newborns. Despite the effectiveness of the cocoon strategy, it would be difficult to implement in Latin American countries due to the low percentage of close contacts that could get vaccinated and the high cost.
- Vaccination in adolescents could be a good strategy to reduce the incidence in their age group, but not for newborns.

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Key issues

- Though the surveillance systems differ among Latin American countries, an increasing number of pertussis cases have been detected over the last decades.
- In most of Latin American countries, whole-cell vaccines are used for the primary series. Only Mexico and Costa Rica use acellular vaccines for such doses. The DTP3 coverage was improved in all countries of the region, but there are still some populations with coverage below 80%.
- The strengthening of immunization coverage is essential to control the disease. This strengthening should also focus on avoiding delays in the application of the dose, as these delays have been predicted to have a negative impact on controlling the disease.
- In Latin America, as in other countries, infants younger than 1 year old and particularly those younger than 6 months, bear the largest disease burden.
- Immunization during pregnancy would be the most effective strategy to reduce the impact of pertussis disease in infants. Vaccination during the mothers' postpartum period may also be an alternative, although possibly with less impact on newborns.
- A new generation of vaccines capable of overcoming the deficiencies reported for current vaccines (low duration of the induced protective immunity, high number of doses needed to achieve adequate protection level, inability to subvert the phenomenon of pathogen adaptation) would improve the control of the disease.

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EXPERT REVIEWS

Pertussis in Latin America: epidemiology and control strategies

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Pertussis is a serious respiratory disease in infants that can also affect children and adults. Vaccination against pertussis was introduced in the 1950s and in the 1990s a resurgence of pertussis was observed worldwide. The aim of this work is to summarize the recent data concerning pertussis disease in different countries of Latin America. In this geographic region, pertussis is nationally notifiable and cases should be reported to the appropriate health department/Ministry. Though the surveillance systems are not the same among Latin America countries, over recent decades an increasing number of cases have been detected. Most of these cases correspond to patients younger than 6 months old who received fewer than three doses of vaccine. However, cases in adolescent and adults have also been detected. For this situation, which is not peculiar to Latin America countries, several explanations have been proposed.

KEYWORDS: *Bordetella pertussis* • epidemiology • Latin America • vaccination • whooping cough

Background of pertussis in Latin America

Bordetella pertussis is the main causative agent of pertussis or whooping cough, a respiratory disease that continues to be a serious public health problem. Pertussis remains in fifth place in the list of deaths attributed to vaccine-preventable diseases in children less than 5 years of age around the world. It causes significant morbidity and mortality in both developing and developed nations [1–3]. According to WHO, there are an estimated 16 million cases of the disease and approximately 195,000 deaths occur worldwide every year, 95% of which take place in developing countries [4].

In Latin America, the annual number of suspected pertussis cases over the last 10 years has ranged from 1500 to 43,000 [5,6], with significant increases in the number of cases in Argentina [7], Brazil [8], Mexico [9], Chile [10], Colombia [11], Paraguay [12], Peru [13] and Uruguay [14] among others. In this region as in other countries, infants younger than 1 year old and particularly those younger than 6 months, bear the largest disease burden. Severe morbidity and mortality are most common in infants [15–17]. For example, in Argentina, 76 deaths were registered in 2011 [18] and between 2008 and 2012 in Brazil, 185 pertussis-related deaths occurred in children less than 4 years of age. In Costa Rica, the disease has a direct impact on infant mortality and in 2006, eight infants younger than 1 year old died [19]. Though surveillance in adolescents and adults is weak, cases in those groups were also recorded [7,20,21]. The vaccination schedule against pertussis in Latin American countries consists of 3 primary doses with a booster in the second year of life, and a second booster dose at preschool age [22]. At present, this vaccination schedule including boosters, with the exception of Mexico and Costa Rica, was performed with the whole-cell pertussis (wP) vaccine (Table 1). In the last years, the coverage of the third dose of pertussis vaccines (DTP3, D and T because the vaccine also contains Diphtheria and Tetanus components) as well as DTP1 and DTP2, is over 90% in most areas of the region. Moreover, recently in response to the resurgence of pertussis, several countries of the region have added new pertussis boosters on adolescent and adult population. These new boosters in elder groups are performed with acellular vaccines (aP) (Table 1).

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Table 1. Official vaccination schedule used in Latin American countries 2012.

Country	Primary series 2, 4, 6 months	Booster 15–18 months	Booster 4–6 years	Adolescents	Pregnant	Postpartum	HCW
Argentina	DTwP-HB-Hib	DTwP-Hib	DTwP	Tdap	Tdap	Tdap	Tdap
Brazil	DTwP-HB-Hib	DTwP	DTwP	NO	NO	NO	NO
Chile	DTwP-HB-Hib	DTwP-HB-Hib	Tdap	Tdap	NO	NO	NO
Colombia	DTwP-HB-Hib	DTwP	DTwP	NO	Tdap	NO	NO
Costa Rica	DTaP-Hib-IPV	DTaP-Hib-IPV	DTaP-IPV	NO	Tdap	Tdap	NO
El Salvador	DTwP-HB-Hib	DTwP-HB-Hib	DTwP	NO	NO	NO	NO
Guatemala	DTwP-HB-Hib	DTwP	DTwP	NO	NO	NO	NO
Honduras	DTwP-HB-Hib	DTwP	DTwP	NO	NO	NO	NO
Mexico	DTaP-Hib-IPV	DTaP-Hib-IPV	DTwP	NO	Tdap	NO	NO
Panama	DTwP-HB-Hib	DTwP-Hib	DTwP	Tdap	Tdap	Tdap	Tdap

DTwP: Diphtheria, tetanus pertussis, HB: Hepatitis; HCW: Healthcare workers; Hib: *Haemophilus influenzae* type B; IPV: Inactivated poliovirus vaccine; NO: Not used

Possible transmission routes

Pertussis is a very contagious disease that is spread from person to person. Individuals with pertussis usually spread the disease by coughing or sneezing while in close contact with others, who then breathe in the bacteria. The study performed by Wendelboe *et al.* provides solid evidence that among infants for whom a source case was identified, household members were mainly responsible for the transmission of *B. pertussis* to this high-risk group [23]. In accordance with this study, data from Mexico showed that out of the total number of mothers (70 mothers) of children with confirmed pertussis, 26% had a positive PCR for *B.* pertussis [24]. Preliminary data from Argentina provided by the National Laboratory of Reference for pertussis (VacSal, IBBM FCE UNLP) showed that in 32% of cases, parents were the source of infection [25]. According to other data from a multicenter study that included Latin American countries (Brazil, Costa Rica and Uruguay), in 27% of children who were hospitalized with pertussis in pediatric intensive care units, the source of transmission was the mother. In Costa Rica, among household contacts of patients admitted to the National Children's Hospital, *B. pertussis* was identified by PCR in 69% of the studied household contacts, and 33% of patients had more than one possible source of contact [26].

Epidemiological surveillance & diagnostic methods

In Latin America, it is mandatory to notify pertussis nationally and cases should be reported to the National Health Ministry for each of the respective countries. Epidemiological surveillance in most of the Latin American countries is based on the recommendations of international organizations such as WHO [27] and the CDC [28]. The different countries of Latin America have considered adaptations in clinical criteria including age stratification and cough duration. Following the identification of a clinical case, a case report form is completed using information collected during patient and physician interviews. Specimens are collected and routinely shipped to a laboratory for diagnosis. The laboratory criteria for diagnosis are mainly based on isolation of *B. pertussis* from clinical specimen and/or through PCR for *B. pertussis*. Although direct fluorescent antibody testing is sometimes used in some Latin American countries, neither WHO nor the CDC recommends it as a diagnostic method.

Table 2 presents a summary of the criteria used by different Latin American countries for pertussis surveillance.

Epidemiological situation of pertussis in different Latin American countries

The countries selected for this section were not globally representative, but were chosen on the basis that they were able to provide data on vaccine coverage and trends in pertussis disease burden over time. The countries were selected to include representation from those with (i.e., Argentina, Brazil, Costa Rica, Chile, Colombia and Mexico) or without (i.e., Central American countries) an apparent pertussis resurgence. Whereas laboratory surveillance is established in the former countries, the latter do not seem to have these facilities, which might be one reason for their low numbers of reported cases.

Argentina

Since 2002, a sustained increase in cases of pertussis has been recorded, not only in children, but also in adolescents and adults [7,29,30]. The incidence of the disease in 2003 was 1.8 per 100,000 inhabitants, then rose in 2005 to 5.7 cases per 100,000 and in 2011 to 8.3 cases per 100,000, increasing 46% in 6 years (Figure 1) [29,30].

In 2011, 3332 confirmed cases were recorded; 54% of confirmed cases had a laboratory diagnosis positive for *B. pertussis* (84% by PCR), while 46% had a clinical report with an epidemiological link. The incidence rate in infants under 1 year of age was 374 cases per 100,000 [7].

The mortality rate in infants under 1 year of age was 0.09 per 1000, and the case-fatality rate was 2.4%. Of the 76 infants who died during 2011, 93% were under 3 months of age. In 92% of the deaths, infants had not been vaccinated, 5% had received only 1 dose and 3% had received only 3 doses [31].

Brazil

Since the 1990s, the incidence of pertussis cases has shown a significant reduction due to the expansion of pertussis vaccine coverage. In the beginning of that decade, vaccine coverage was about 70% and the incidence was 10.6 per 100,000 inhabitants. In the 1998–2000 period, the coverage increased to 95% and the incidence decreased to 0.9 per 100,000 inhabitants. With the maintenance of high vaccine coverage variations, an incidence of 0.72 per 100,000 inhabitants in 2004 and of 0.32 per 100,000 inhabitants in 2010 was observed. However in mid-2011 (>95% DTP3 coverage), there was a sudden increase in the number of cases; incidence exceeded the upper limit expected when compared with the 2006–2010 period. Throughout 2012, the number of cases by epidemiological week remained higher than expected. According to data recorded in the National Notifiable Diseases (SINAN) in 2012, 15,428 suspected pertussis cases were reported in the country. From these, 4453 (28.9%) were confirmed, representing an increase of 97% against the same period in 2011, when 2258 cases were confirmed [32]. The states that had a higher incidence of pertussis in 2012 were Espirito Santo state, with an incidence of 20.6 per 100,000 inhabitants and Rio Grande do Sul state, with 7.2 per 100,000 inhabitants. The age group with the largest number of cases and highest incidence were children under 1 year of age. This age range corresponds to about 70% of cases of pertussis in the country. In 2012, the incidence rate in children younger than 1 year was 105.6 per 100,000 inhabitants, while in 2011 it was 61.6 per 100,000 inhabitants (Table 3). In 2012, the number of deaths increased to 74 cases, while in 2011 it was 56 [32]. Between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age: 125 had never been vaccinated, 20 had received one dose, 2 had received 2 doses, 1 case had received 3 doses and 2 cases had received 3 doses plus the first booster. The immunization status was unknown for 35 of the deaths.

Table 2. Clinical and laboratory criteria used by different countries in Latin-America.

Country	Surveillance system	Clinical case definition according to WHO/CDC	Methodologies used in laboratory diagnosis				Final classification of case				
			Culture	*PCR*	*Serology*	*IFD*	*Use of the epidemiological link for case classification*	*Suspect*	*Probable*	*Confirmed*	*Discarded*
Argentina	MUPN	Yes[1]	✓	✓	✓	×	✓	×	✓	✓	✓
Brazil	MUPN	Yes	✓	✓	×	×	✓	✓	×	✓	✓
Colombia	MUPN	Yes[1,†]	✓	✓	×	✓	✓	×	✓	✓	✓
Costa Rica	MUPN	Yes[1]	✓	✓	×	×	✓	✓	[§]	✓	×
Chile	MUPN	Yes[1]	✓	✓	×	✓	✓	✓	✓	✓	✓
Ecuador	MUPN	Yes	✓	✓	×	✓	✓	ND	✓	✓	×
Mexico	MUPN	Yes[1]	✓	✓	×	×	✓	✓	✓	✓	✓
Paraguay	MUPN	Yes	✓	✓	×	×	✓	✓	✓	✓	✓
Peru	MUPN	Yes[1]	✓	✓	×	✓	✓	✓	✓	✓	✓
Uruguay	MUPN	Yes	✓	✓	×	×	✓	✓	×	✓	×
Venezuela	MUPN	Yes	✓	✓	×	×	✓	×	✓	✓	×

[1]In the clinical case definition, symptoms are differentiated according to patient age. For neonates and infants, the duration of cough is not included in the clinical case definition.
[†]Instead of a 14-day duration of cough, 1 or 2 weeks are used in the definition.
[§]Case compatible with clinical case definition.
✓: Used; × Not used; MUPN: Mandatory universal passive notification; ND: No data available.

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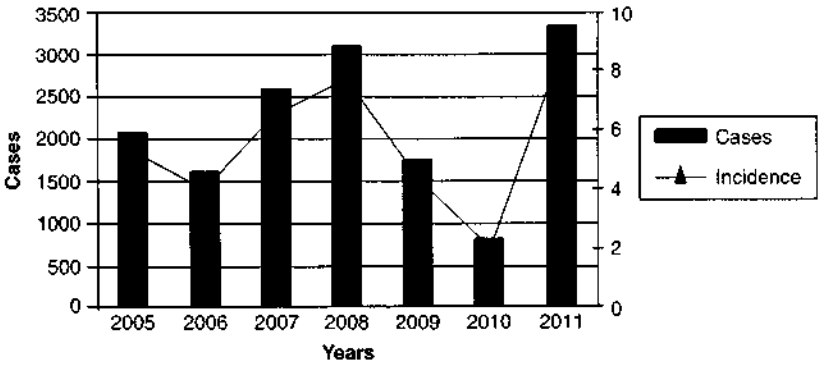

Figure 1. Number of pertussis cases and incidence rate per year in Argentina. Period 2005–2011.

The entire epidemiological situation detected in 2012 could be due to the observed decrease in national vaccination coverage in infants due to supply issues. From 2006 to 2012, the number of municipalities with >95% DTP3 coverage decreased from 83 to 55% with non-homogenous coverage throughout the country. Causes for this decline were mainly operational issues, as social acceptance of vaccination in Brazil is high.

Chile

Since 2002, the incidence rate has been stable at approximately 7 cases per 100,000. In 2010, this value began to increase and in 2011 the incidence rate reached 15 cases per 100,000.

Table 3. Pertussis incidence rate and mortality by age group.

	2011			2012		
Age (years)	Cases	Incidence†	Deaths	Cases	Incidence	Deaths
Less than 1	1,687	61.6	54	2924	105.9	74
1–4	208	1.9	1	721	6.4	0
5–9	80	0.5	0	307	2.0	0
10–14	71	0.4	0	181	1.0	0
15–19	42	0.2	0	77	0.4	0
20–29	67	0.2	0	95	0.3	0
30–39	46	0.2	0	88	0.3	0
40–49	35	0.1	1	39	0.2	0
50–59	9	0.0	0	12	0.1	0
60–69	8	0.1	0	8	0.1	0
70–79	1	0.0	0	0	0.0	0
80 and over	0	0.0	0	1	0.0	0
Total	2254	1.2	56	4453	2.3	74

Brazil, 2011 and 2012 (per 100,000 inhabitants).
†Per 100,000 inhabitants.
Data taken from Sinan/UVRI/CGDT/DEVEP/SVS/MS. Data subject to revision.

During 2011, the incidence rate in infants under 1 year of age was 517.8 per 100,000 inhabitants. The annual case-fatality rate in 2009, 2010 and 2011 was 1.0, 0.9 and 0.6%, respectively [33].

During the first 3 months of 2012, there was an increase of approximately 50% in the number of cases in infants, totaling 643 cases, compared with only 338 cases for the same period in 2011. The most affected regions all over Chile were Antofagasta, Coquimbo, Valparaiso, Maule, Los Rios and Los Lagos.

The number of deaths in 2011 and 2012 was 16 and 13, respectively; 7 deaths occurred in each 2010 and 2009. Mortality was highest in 2- to 3-month-old infants in 2011 and 2012 (47.6 per 1,000,000 births in 2012).

Colombia

According to the reports of the Instituto Nacional de Salud, the global pertussis incidence rate increased, ranging from 0.32 per 100,000 in 2005 to 2.19 per 100,000 in 2011. The number of confirmed cases has also increased significantly since 2011, when 830 cases were confirmed. In 2012, the incidence rate was 6.7 per 100,000 inhabitants [11]. In that year, 65.5% of the cases occurred in infants under 1 year of age (mainly younger than 6 months). In 2011, 34 deaths in infants under 1 year of age were reported in Colombia and 65 deaths in 2012 [34].

Costa Rica

Over the last 20 years, three epidemic outbreaks have been reported (in 1997/1998, 2001/2002 and 2006/2007), the last of which was the most severe and included 13 laboratory-confirmed deaths. Figure 2 shows the incidence rate per 100,000 inhabitants by age group, where the highest value was recorded in infants under 1 year old. During the 2006/2007 epidemic period, an increase in the mortality rate among children under 1 year was detected. In 2007, the death rate of pertussis was 11.2 per 100,000 live births. This value was higher than the one detected during the 1980–1982 triennium with a rate of 9.7 per 100,000, representing more than 1% of all deaths in children under 1 year in Costa Rica [35].

In April 2007, Costa Rica implemented the strategy of postpartum vaccination, which resulted in a dramatic

reduction in the number of deaths caused by pertussis: 2 deaths occurred in 2009 and no deaths in 2010 [36]. More recently, in February 2013, postpartum acellular vaccine (Tdap vaccine) was switched to vaccination during pregnancy.

Mexico

During the 2000–2011 period, pertussis showed fluctuations in the number of cases as described in other countries, with epidemic cycles every 3–5 years (Figure 3).

The last outbreak was recorded in 2009, with 579 confirmed cases. In 2010, the number of cases decreased but then in 2011 increased to 455 (up 19%). The latter increase may be due, at least in part, to the fact that in 2011 PCR assay began to be used as a diagnostic test for pertussis. The increase continued in 2012 with 752 confirmed cases.

Similar to most reports in the literature, 83% of the cases occurred in infants younger than 1 year of age [37]. The recently reported mortality rates are the highest reported over the last few years in Mexico. Official national data are not available, however, a recent prospective study conducted during a 1-year period in seven pediatric centers in Mexico showed that 6.5% of children died from pertussis complications [24].

Central American countries

Countries from Central America reported clinical cases and only few laboratory-confirmed cases of pertussis. In 2011, El Salvador reported 11 confirmed cases with an incidence rate of 0.10 per 100,000 inhabitants. On the other hand, in 2011 Honduras reported four confirmed cases with a rate of 0.01 per 100,000 inhabitants. In 2012, Guatemala has reported an increase in cases and issued an epidemiological alert [38]. For this country in 2011, the incidence of pertussis was less than 0.3 per 100,000 inhabitants and in 2012 the incidence rate was 1.8 per 100,000 inhabitants. In Panama, Nieto Guevara and colleagues reported that in the 2001–2008 period, 759 suspected cases were admitted to the Children's Hospital and 180 cases out of the total were confirmed by PCR and culture [39]. The hospitalization rate was 14.4 per 10,000 admissions, being higher in the group younger than 3 months (42.76 per 10,000 admissions, 75% out of the total).

Pertussis vaccines used in the Latin America region

To reduce the risk of severe pertussis in infants, WHO recommends a three-dose primary series, with the first dose administered at 6 weeks of age; subsequent doses should be given 4–8 weeks apart, at the age of 10–14 weeks and 14–18 weeks. The last dose of that primary series should be completed by the age of 6 months. In addition, a booster dose is recommended for children aged 1–6 years, preferably during the second year of life. The booster should be given ≥6 months after the last primary dose. With this four-dose schedule (primary series plus booster), at least 6 years of protection against pertussis are expected [22].

The Advisory Committee on Immunization Practices (ACIP) of the US CDC and other international entities have also recommended a booster for adolescents and adults in order to improve disease control [40–42].

In order to accomplish all these recommendations, in the Latin American region two types of vaccines are used (Table 1): wP based on standardized cultures of *B. pertussis* strains and aP composed of two (pertussis toxin and filamentous hemagglutinin), three (pertussis toxin, filamentous hemagglutinin and pertactin) or five immunogens (pertussis toxin, filamentous hemagglutinin, pertactin and fimbriae-2 and -3) [43]. Whole-cell vaccines combined with diphtheria and tetanus toxoids or with tetanus, diphtheria and other vaccines such as *Haemophilus influenzae* type B (Hib, DTwP Hib) or Hib and hepatitis B

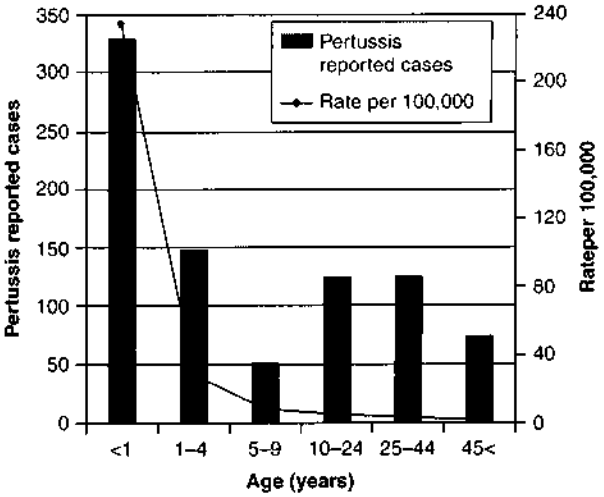

Figure 2. Number of pertussis cases and incidence rate per age group in Costa Rica during the outbreak of 2006/2007. Data taken from Epidemiologic Department, Ministry of Health Costa Rica.

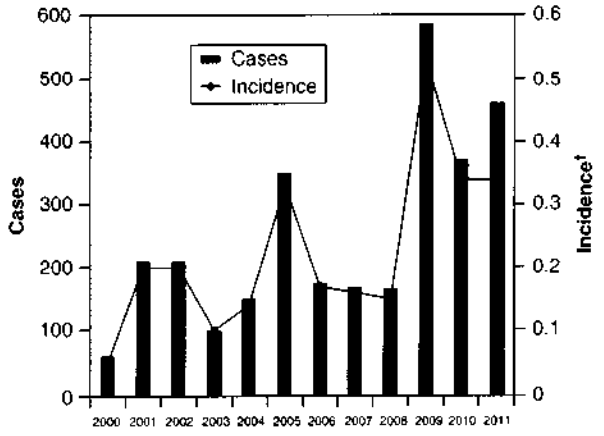

Figure 3. Number of pertussis cases and incidence rate by year. Mexico 2000–2011.
†Per 100,000 inhabitants.
Data taken from SINAVE/DGE/S.S. Pertussis Mentoring System.

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(DTwP Hib HB) were used until 2007 in all Latin American countries for the 3 doses of primary series given at 2, 4 and 6 months (Table 1), the first booster dose at 18 months of age and the fifth dose at age 4–7 years of age. In 2007 and 2009, Mexico and Costa Rica respectively, replaced all doses by the wP vaccine by DTaP-Hib-IPV (Pentaxim from Sanofi). Mexico and Costa Rica administer the two-component pertussis vaccine combined with Hib and IPV of French origin. In Costa Rica, pentavalent DTaP-Hib-IPV in a five-dose schedule has been used since September 2010.

Over the last few years, since the resurgence of pertussis, different protection strategies have also been considered: universal adult immunization; selective immunization of mothers and close family contacts of newborns; selective immunization of healthcare workers; selective immunization of childcare workers; universal immunization of adolescents; pre-school booster at 4–6 years of age and reinforcement and/or improvement of current infant and toddler immunization strategies [44]. Because immunization programs vary widely from country to country, no single strategy is likely to be appropriate for all.

In the next section, some features of each vaccination strategy are indicated, as well as which countries in Latin America have implemented the strategy described.

Universal adult vaccination

With the universal immunization of adults 19 years of age and older it is expected to reduce pertussis incidence in adults but also in young infants through herd immunity. However, up to now there are no data available showing that this strategy would meet these objectives. At present, this strategy has not been implemented in any of Latin America countries.

Immunization of mothers, family & close contacts of newborns (Cocoon strategy)

For this strategy, two main vaccination schedules were considered: maternal vaccination during pregnancy (during the third trimester) or vaccination of mothers, fathers, family members and other close contacts perinatally. Maternal vaccination during pregnancy might reduce pertussis transmission from mother to newborn and have the advantage of transferring antibodies to the infant via the placenta. In 2011, this strategy was recommended for all pregnant women after 20 weeks of gestation by ACIP [45].

In Latin America, Argentina, Colombia and Mexico have implemented this strategy in 2012.

At the end of 2012, the ACIP modified the recommendation for Tdap vaccination during pregnancy so that a dose of Tdap is to be given between 27 and 36 weeks during each pregnancy, regardless of the interval between pregnancies [46]. This strategy is not yet implemented in Latin American region.

The second vaccination schedule consists of postpartum vaccination of parents and all close contacts of the newborn.

Mathematical epidemiological models, showed that this strategy could yield the expected reduction in pertussis disease in infants [36]. In fact, some reports confirming that this strategy significantly reduces transmission to infants were recently published [47].

The only country of Latin America that vaccinated fathers and mothers was Costa Rica during the 2006/2007 outbreaks.

Selective immunization of healthcare & childcare workers

Vaccinating healthcare workers, primarily to prevent nosocomial transmission to infants and immune-compromised persons, may be cost-effective if high coverage rates are obtained. Countries with demonstrable nosocomial transmission are encouraged to implement such vaccination, especially among staff in maternity and pediatric units if it is economically and logistically feasible.

Argentina and Panama implemented the immunization of healthcare workers who took care of infants in 2010.

Preschool booster vaccination

With the administration of a booster dose at 4–6 years of age, it is expected that immunity will be extended into adolescence and also into infants since it is expected to reduce the transmission from siblings to young infants. However, Hviid *et al.* reported that the effectiveness of pre-school booster vaccination as an intervention to prevent pertussis hospitalization of 0- to 1-year-old children is modest [48].

Though this strategy seems to have a modest impact in infants, it is effective in reducing pertussis incidence in individuals with 4–6 years of age. In fact, it has been observed that after the introduction of a booster dose for 4- to 6-year-old children, the disease burden in preschool and school children decreased [44].

All the countries in Latin America currently have implemented vaccination at preschool age, from 4 to 6 years old.

Universal immunization of adolescents

With a booster dose in adolescents, it is expected to extend the immunity against pertussis and reduce the prevalence of the disease (and thereby transmission) in this age group, indirectly reducing transmission to vulnerable infants. However, in the absence of universal adult vaccination, adolescent vaccination will not sufficiently control the transmission to infants. In fact, modeling data from Argentina estimate that a Tdap booster at 11 years of age reduces the incidence in infants, but to a very small extent [49]. The calculated decrease does not exceed 5% in any of the epidemiological scenarios considered in the study [49].

In Latin America, the countries that have incorporated this strategy are Argentina (2010), Panama (2010) and Uruguay (2012). It should be stressed that the strategies of these countries cover only one age cohort per year (11–12 years).

Reinforce and/or improve the current infant & toddler immunization strategy

The most important way to reduce the incidence of pertussis in children is to ensure high vaccination coverage of the primary immunization schedule. Efforts to increase the coverage

of current programs are made in Latin American countries, and because of that there have been improvements in this regard.

The schedules used by different countries in Latin America in 2012 are summarized in Table 1.

Possible causes of pertussis resurgence in Latin America

Several causes have been proposed in order to explain the resurgence of pertussis. Among others, some possible reasons are the suboptimal coverage rates of vaccination, the waning of immunity conferred by vaccination and/or natural infection, the reduction in the number of natural boosters and the adaptability of the bacteria to the immunity conferred by the vaccines. Other more noticeable causes are the higher awareness of the disease, and the improvements in epidemiological surveillance and diagnostic tests [50–52]. In relation to the introduction of new diagnostic methodologies, which undoubtedly impacted on pertussis surveillance, Latin American countries have been incorporating molecular diagnosis based on PCR: Argentina in 2004, Costa Rica in 2007, in some states of Brazil in 2008 and Mexico in 2011. This technology is currently being introduced in other countries [53,54].

Regarding vaccination, coverage rates have been improved since the introduction of the wP vaccine (Diphtheria, Tetanus, Pertussis [DTwP]) in the extended program of immunization in the 70s. At present, the DTwP coverage is greater than 90%, although in some locations (i.e., locations from Brazil and Argentina) it does not exceed 80% [55]. At this point, however, it is important to point out some observations about pertussis that would presage the difficulty in achieving control. Currently used vaccines, wP or aP, provide good protection against severe and typical pertussis, but substantially less against milder coughing illness suggesting that although vaccination prevented disease or at least its severest manifestations, transmission of infection continued. The immunity from vaccination waned and that protection against infection was less complete than against the severest manifestations of disease. Another critical observation is that the cyclic nature of pertussis epidemics remained largely unchanged after the widespread use of vaccination.

In recent years, the epidemiology of the disease in many countries including some from Latin America was complicated because the disease is now increasing in adolescents and adults, probably due to the fast waning immunity post-immunization. Adult or adolescent pertussis is usually not as severe as infant disease and is generally not life threatening. However, it may still cause significant morbidity transmitting the disease to unvaccinated infants. Because of this new epidemiological situation, adolescent booster immunization is recommended. However, for some countries where this strategy has been implemented some years ago, the incidence in infants remained largely unchanged, suggesting limited or absent herd benefit from adolescent and adult Tdap [56].

In addition to waning of vaccine-induced immunity, changes in the antigenic and genotypic characteristics of circulating *B. pertussis* strains are being described. In many countries of Latin America as in other countries, alleles of vaccine antigens expressed by circulating organisms largely differ from those expressed by the strains from which vaccines were originally derived (*ptx*P3, *prn*2 and *fim*3B for circulating bacteria and *ptx*P1, *prn*1 or 7, and *fim*3A for bacteria used in vaccine production) [2,57–60]. In some countries, the emergence of allelic variants coincides with disease resurgence, but in others it does not. It remains unclear whether the appearance of these predominant strains affects the efficacy of vaccines.

Expert commentary & five-year view

The assessment of the trends in the burden of pertussis in Latin America is complex, especially as regards comparisons between countries. This may be mainly due to differences in vaccination (type of vaccine and/or producer of vaccines) and the quality of the surveillance systems employed. Country-specific data mainly from Central American countries have provided no evidence of a resurgence of pertussis, probably due to their relatively weak epidemiological surveillance systems. Data from other countries of Latin America (Argentina, Brazil, Chile, Colombia and Mexico) have evidence of an increase in pertussis-related morbidity in recent years, as compared with previous periods. The increase in pertussis cases was mainly attributed to the increase in disease awareness, the increase in overall laboratory testing and the enhanced sensitivity of the PCR diagnostic methods, which are being used more widely. In all these countries, most cases were recorded in young infants who are not old enough to acquire protective immunity by vaccination, but cases in adolescents and adults were also detected. This increase in infant cases was associated with increased mortality.

In the majority of the Latin American countries, whole-cell vaccines are used for the primary series. Only Mexico and Costa Rica use aP for such doses. The DTP3 coverage was improved in all countries of the region, but there are still some populations with coverage below 80%. Moreover, in some countries, the national coverage has declined from 1 year to another (Brazil 2012). Undoubtedly, these weaknesses in vaccination coverage have a negative impact on the control of pertussis in these populations, especially considering the effectiveness of the current vaccines (both wP and aP) that do not exceed 85%.

The high number of doses that are recommended increases the likelihood of failure to achieve high coverage, especially in those regions with large populations and inequities regarding the scope of the health systems action.

Regarding those countries of Latin America that are using aP in the primary series, at present there is a particular concern on that since the DTaP vaccines do not provide protection for long [3]. Five studies done in the 1990s showed that DTwP vaccines have greater efficacy than DTaP vaccines. Recently, in a case–control study designed to assess the risk of pertussis among 10–17 year olds during the 2010–2011 outbreak in northern California, the researchers found that teenagers who had received four whole-cell vaccine doses were nearly six-times less likely to

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have been given a diagnosis of pertussis than those who had received all aP and nearly four-times less likely than those who had received a mix of vaccines [61]. It is proposed that the switch to the aP may partly explain the resurgence of pertussis [62].

In Mexico, where aP vaccine is used in its whole calendar, this faster waning immunity reported for other countries where the primary doses are performed with aP [59] was not yet detected. This could be due to the fact that the switch to aP vaccine is relatively recent. Therefore, the increase detected in this country was mainly attributed to the increase in overall laboratory testing, and the enhanced sensitivity of the PCR diagnostic methods being used more widely.

Finally, the potential contribution in pertussis epidemiology of genetic changes in circulating strains of *B. pertussis* should be considered. The genetic changes in three *B. pertussis* antigens, pertussis toxin, pertactin and fimbriae, detected in other regions, have also been observed over time in some countries of Latin America [58]. Studies in Argentina and also in the Netherlands and Australia suggested that genetic changes might have led to vaccine failures [59,63]. However, its real impact on pertussis epidemiology needs clarification.

Under this entire context, while the current vaccines are used in the best possible ways, a new generation of vaccines capable of overcoming the weaknesses associated with the current vaccines (low duration of the induced protective immunity, high number of doses needed to achieve adequate protection level, inability to subvert the phenomenon of pathogen adaptation) seems to be needed to improve the control of the disease. At present, several pathways deserve to be explored. One possibility is to promote the use of new, less reactogenic and improved wP vaccines [60,61]. However, the return to the whole-cell vaccine would be difficult to accept for the public opinion in countries that accepted the switch to the aP, out of concern about adverse reactions.

Another possibility is to improve the aP vaccine by including additional virulent factors of *B. pertussis* and/or an adjuvant, to drive a high Th1 response.

While new vaccine developments are expected, the implementation of strategies using the available vaccines considering the epidemiological, cultural and organizational characteristics of a region is recommended. In fact, several countries in Latin America have already implemented different protection strategies based on recommendations by ACIP, Pan American Health Organization and other organizations such as the Global Pertussis Initiative. Table 1 shows official vaccination schedules used in Latin America for direct and indirect protection in the last years.

At this point, it is important to emphasize the relevance that epidemiology has at the time of implementing a new control strategy. More solid laboratory data are needed. Because of that, consensus diagnostic methodologies integrated to surveillance should be encouraged in order to improve the availability of updated pertussis epidemiological surveillance data in Latin America. Laboratory methods should focus on enhanced specificity and cultures of the organisms should be retained so that the molecular characteristics can be assessed. The importance of on-time notification should also be reinforced.

Improvements in epidemiological and social data are expected to impact positively on the design of the control strategy. Then, and for any of the adopted strategies, it would be crucial to monitor their impact. Sustainable funding to monitor the execution of the new strategy should be a priority in countries where the strategy is implemented. The results achieved should be adequately delivered to both healthcare workers and the public in general. Political commitment from Latin American governments to invest in monitoring, in education regarding pertussis disease, in the benefits of control strategies and in vaccination should be encouraged.

Finally, to better control the disease in the region with current vaccines, following points should be considered:

- Optimize vaccine recommendations considering the epidemiology of the disease in the region. To do this, it is necessary to strengthen the epidemiological surveillance systems, including case definitions, algorithms, laboratory diagnostics and recording systems agreed and validated by international institutions.
- Continue to strengthening vaccination coverage, achieve early and timely vaccination (should consider starting the primary vaccination schedule as early as possible, ≥6 weeks of age) and maintain high levels of coverage (≥90%) with at least 3 doses of assured-quality pertussis vaccine. This strengthening should also focus on avoiding delays in the application of the dose, as these delays have been predicted to have a negative impact on controlling the disease [64]
- Immunization during pregnancy would be the most effective and easiest to be implemented with good coverage, and probably at a lower cost. Vaccination during the mothers' postpartum period may also be an alternative, although possibly with less impact on newborns. Despite the effectiveness of the cocoon strategy, it would be difficult to implement in Latin American countries due to the low percentage of close contacts that could get vaccinated and the high cost.
- Vaccination in adolescents could be a good strategy to reduce the incidence in their age group, but not for newborns.

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Key issues

- Though the surveillance systems differ among Latin American countries, an increasing number of pertussis cases have been detected over the last decades.
- In most of Latin American countries, whole-cell vaccines are used for the primary series. Only Mexico and Costa Rica use acellular vaccines for such doses. The DTP3 coverage was improved in all countries of the region, but there are still some populations with coverage below 80%.
- The strengthening of immunization coverage is essential to control the disease. This strengthening should also focus on avoiding delays in the application of the dose, as these delays have been predicted to have a negative impact on controlling the disease.
- In Latin America, as in other countries, infants younger than 1 year old and particularly those younger than 6 months, bear the largest disease burden.
- Immunization during pregnancy would be the most effective strategy to reduce the impact of pertussis disease in infants. Vaccination during the mothers' postpartum period may also be an alternative, although possibly with less impact on newborns.
- A new generation of vaccines capable of overcoming the deficiencies reported for current vaccines (low duration of the induced protective immunity, high number of doses needed to achieve adequate protection level, inability to subvert the phenomenon of pathogen adaptation) would improve the control of the disease.

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