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Pertussis in Latin America: Recent epidemiological data presented at the 2017 Global Pertussis Initiative meeting ☆

Daniela Hozbor [a,*], Rolando Ulloa-Gutierrez [b], Cristina Marino [c], Carl Heinz Wirsing von König [d], Tina Tan [e], Kevin Forsyth [f]

[a] Instituto de Biotecnología y Biología Molecular, Facultad de Ciencias Exactas, Universidad Nacional de La Plata-CONICET, La Plata, Argentina
[b] PediaClinic, Centro de Especialidades Pediátricas, San José, Costa Rica
[c] Medico Infectólogo, Hospital Militar Central, Bogotá, Colombia
[d] Labor:Medizin Krefeld MVZ, Krefeld, Germany
[e] Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[f] Flinders University and Flinders Medical Centre, Bedford Park, Adelaide, Australia

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ABSTRACT

The Global Pertussis Initiative (GPI) is an expert scientific forum that publishes consensus recommendations for pertussis monitoring, prevention, and treatment across many regions of the world. Here, we report on the regional 2017 GPI meeting on the Americas, focusing on Latin America. Information on current pertussis epidemiology, surveillance, vaccine strategies, diagnostic capabilities, disease awareness, and major local obstacles was presented by researchers from Argentina, Brazil, Colombia, Costa Rica, El Salvador, Mexico, Peru, Puerto Rico, Uruguay, and Venezuela. Pertussis outbreaks have occurred during the last decade in the majority of participant countries and have been followed by improvements in surveillance. In the countries that introduced maternal immunization during pregnancy, a reduction in the infant case fatality rate has been detected. All countries need to maintain and improve pertussis surveillance to reach primary vaccination coverage >90%. Moreover, countries without maternal immunization programs should strongly consider them.

1. Introduction

Pertussis, or whooping cough, is a respiratory disease that most commonly occurs in infants less than 1 year of age but can affect all age groups [1,2]. Symptoms can be particularly severe and the disease can be fatal in infants, in contrast to adolescents and adults in whom symptoms are usually mild [2]. Vaccination is the best strategy to control this highly contagious disease. The first vaccine developed against pertussis still in use is the whole-cell vaccine (wP) based on standardized cultures of *Bordetella pertussis* strains, the etiologic agent of the disease [3]. After the massive wP vaccination program was introduced in the 1940s, the morbidity and mortality associated with the disease were reduced significantly [4]. However, with years of use of wP, reports regarding its reactogenicity profile led to widespread apprehension, which prompted the development of acellular vaccines (aP) containing purified antigenic-protein components of *B. pertussis* (1, 2, 3, or 5 immunogens) [3,4]. aP vaccines are broadly accepted because of their lower reactogenicity, especially in industrialized countries where wP vaccines of the primary series (3 doses in infancy) have been replaced by aP [5].

Currently, it is well known that the immunity induced by both types of vaccines, though not the same, are both protective. While aP vaccines mainly induce a Th2-skewed response [6], wP vaccines induce a robust Th1 profile [6] and the proliferation of respiratory

Abbreviations: aP, acellular pertussis; CDC, Centers for Disease Control and Prevention; DTaP, diphtheria, tetanus, acellular pertussis; DTP3, third dose of diphtheria, tetanus, pertussis vaccine; DTP4, fourth dose of diphtheria, tetanus, pertussis vaccine; DTwP, diptheria, tetanus, whole-cell pertussis; GPI, Global Pertussis Initiative; LAPP, Latin American Pertussis Project; PAHO, Pan American Health Organization; PCR, polymerase chain reaction; SINAN, Sistema de Informação de Agravos de Notificação (National Notifiable Diseases); Tdap, tetanus-reduced diphtheria toxoid-acellular pertussis; WHO, World Health Organization; wP, whole-cell pertussis.

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* Corresponding author at: Laboratorio VacSal Instituto de Biotecnología y Biología Molecular, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, CONICET La Plata, Calles 50 y 115, 1900 La Plata, Argentina.
E-mail address: hozbor.daniela@gmail.com (D. Hozbor).

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tissue-resident memory CD4 T cells [7]; therefore, the former has a more rapid decay in induced immunity and possibly a reduced impact on transmission compared with currently available wP vaccines [1]. Based on this evidence, the World Health Organization (WHO) published a position paper on this subject and wrote the following:

A switch from wP to aP vaccines for primary infant immunization should only be considered if the inclusion in the national immunization schedules of additional periodic booster or maternal immunization can be assured and sustained [8].

National programmes currently using aP vaccine may continue using this vaccine but should consider the need for additional booster doses and strategies to prevent early childhood mortality such as maternal immunization in case of resurgence of pertussis [8].

In the last few decades in different countries that use different types of vaccines and immunization schedules, the number of pertussis cases increased to levels that were of concern to health authorities [9]. There are an estimated 24.1 million cases of the disease and approximately 160,700 deaths occurring worldwide every year in children younger than 5 years of age, of which 95% take place in developing countries [10]. To explain this apparent heightened prevalence of pertussis, several causes have been proposed. These include an increased awareness of health care workers to detect the disease, resulting in more perceived and diagnosed cases, as well as improvements in diagnostic methodologies. Additionally, low vaccine coverage, waning immunity conferred by vaccination and/or natural infection, change to aP vaccine without ensuring boosters, and evolution of the pathogen may all contribute to increased prevalence [9,11–13]. The impact of each of these possible causes varies between countries, but beyond the causes necessary to be identified in each region to implement improvements, it is clear that pertussis today represents a disease that requires particular attention.

In Latin America, vaccination was introduced in the 1950s in some countries and in the 1970s in others [14]. As in other regions, there were low notification rates for an extended period of time. However, in the 1990s, the number of pertussis cases increased significantly in the region [15]. During the last 2 decades, pertussis outbreaks have been reported in different Latin American countries [14]. In particular, an important outbreak was detected in 2011–2012 in many countries of the region with a significant number of infant deaths [16,17]. The reported pertussis data of this region are relatively scarce. The Global Pertussis Initiative (GPI) Roundtable Meeting was convened in Cancun, Mexico, on November 11–13, 2017, with participants from 12 countries, including Argentina, Brazil, Canada, Colombia, Costa Rica, El Salvador, Mexico, Peru, Puerto Rico, United States, Uruguay, and Venezuela. The main objective was to review the current pertussis situation in the Americas, particularly Latin America, analyzing the local epidemiology; current vaccination schedule recommendations and practices; challenges, barriers, and obstacles for effective implementation; surveillance; and diagnosis. Here, we report the output of this meeting related to Latin America.

2. Methods: Pertussis surveillance and diagnosis

Since 2009, Argentina, Brazil, Chile, Colombia, Mexico, and Panama have been part of the Latin American Pertussis Project (LAPP), which is a collaboration between the ministries of health of those countries, the Centers for Disease Control and Prevention (CDC), the Pan American Health Organization (PAHO), and the Sabin Vaccine Institute [18]. The project's specific objectives are to expand laboratory capacity for the identification of the etiologic agent of the disease, to strengthen laboratory-based pertussis surveillance, and to standardize and improve pertussis reporting within each country. These objectives are all aligned with those of the GPI, an expert scientific forum that publishes consensus recommendations for pertussis monitoring, prevention, and treatment in several world regions. Here we present the main data discussed at the Latin American regional GPI meeting, held in Mexico in November 2017.

Epidemiological surveillance in the participant Latin American countries is based on the recommendations of international organizations such as the WHO [19], the PAHO [20], and the CDC [21]. Some countries such as Argentina, Brazil, and Colombia have considered adaptations in clinical criteria, including age stratification and cough duration. The laboratory criteria for diagnosis are mainly based on isolation of *B. pertussis* from clinical specimens and/or through polymerase chain reaction (PCR) for *B. pertussis* DNA (Table 1). Serology is used in 2 countries: Argentina and Chile.

3. Pertussis vaccines

To reduce the risk of severe pertussis in infants, 7 of the participant countries of Latin America use wP (Table 2). Costa Rica, Mexico, and Puerto Rico replaced all doses with aP vaccines [14].

Over the last several years, due to pertussis resurgence, additional protection strategies recommended by GPI and other international institutions have been considered [22,23]. These strategies include incorporation of a booster dose in adolescents as well as implementation of immunization of health care workers who take care of infants (Table 2). Following the 2011–2012 outbreaks, maternal and/or postpartum immunization was introduced in those countries with the outbreaks (Table 2).

In Latin America, vaccination coverage rates have improved since the introduction of the DTwP (diphtheria, tetanus, whole-cell pertussis) vaccines in the extended program of immunization of many countries in the 1970s. Fig. 1A shows the DTP3 coverage rates for 2013 through 2017. In 2016, the DTP3 coverage rate, which is commonly used as an indicator of immunization program performance, was greater than 90% for Costa Rica (97%), Mexico (97%), Uruguay (95%), El Salvador (93%), Argentina (92%), and Colombia (91%). However, rates for Brazil, Peru, and Venezuela were lower: 89%, 86%, and 84%, respectively. Additionally, the DTP3 coverage rate declined in some countries (Argentina, El Salvador, Mexico, Panama, Peru, and Venezuela) in 2017. It is noteworthy that in some parts of Argentina and Brazil, reported DTP3

Table 1
Pertussis Diagnosis in Latin America: 2015 [21].

PCR	Culture + PCR	RT-PCR	Culture + RT-PCR	Culture + PCR + Serology	Culture + PCR + Serology + IFD
Costa Rica	Bolivia Brazil (PCR: 2 states) El Salvador Guatemala Honduras Uruguay Venezuela	Peru Suriname	Colombia Mexico Panama Paraguay	Argentina	Chile

IFD, immunofluorescence detection; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction.

Table 2
Vaccination schedule for Pertussis in Latin America [14].

Country	Primary Series[b] 2, 4, 6 months	Booster 15–18 months	Booster 4–6 years	Adolescents[c]	Pregnant	Postpartum	HCW[d]
Argentina	DTwP-HepB-Hib	DTwP-Hib	DTwP	Tdap	Tdap	Tdap	Tdap
Brazil	DTwP-HepB-Hib	DTwP	DTwP	NO	Tdap	NO	NO
Colombia	DTwP-HepB-Hib IPV (1), bOPV (2,3)	DTwP, bOPV	DTwP, bOPV	NO	Tdap	NO	NO
Costa Rica	DTaP-Hib-IPV	DTaP-Hib-IPV	DTaP-IPV	NO	Tdap	NO	NO
El Salvador	DTwP-HepB-Hib	DTwP-HepB-Hib	DTwP	NO	Tdap	NO	NO
Mexico	DTaP-Hib-IPV	DTaP-Hib-IPV	DTwP	NO	Tdap	NO	NO
Panama	DTaP-IPV-HepB-Hib	DTwP-Hib	DTwP	Tdap	Tdap	Tdap	Tdap
Peru[a]	DTwP	DTwP	NO	NO	NO	NO	NO
Puerto Rico	DTaP	DTaP	DTaP	Tdap	Tdap	Tdap	Tdap
Uruguay	DTwP-Hib-HepB	DTwP-Hib-HepB	DTwP	Tdap	Tdap	NO	Tdap
Venezuela	DTwP-Hib HepB	DTwP-Hib-HepB	DTwP-Hib-HepB	NO	NO	NO	NO

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bOPV, bivalent oral poliovirus vaccine; DTaP, diphtheria, tetanus, acellular pertussis; DTwP, diphtheria, tetanus, whole-cell pertussis; HepB, hepatitis B; HCW, health care workers; Hib, *Haemophilus influenzae* type B; IPV, inactivated poliovirus vaccine; NO, not used; Tdap, tetanus, diphtheria, acellular pertussis.
[a] Peru primary series: 2, 3, and 4 months.
[b] Hexavalent vaccine containing DTaP (diphtheria, tetanus, acellular pertussis), IPV (inactivated polio), hepatitis B, and Hib (*Haemophilus influenzae* type B) was introduced in 2014 for infant doses at 2, 4, and 6 months.
[c] A booster dose in adolescents was incorporated in the calendars of Puerto Rico (2009), Argentina (2010), Panama (2010), and Uruguay (2012).
[d] In 2010, Argentina, Panama, and Puerto Rico implemented the immunization of health care workers who take care of infants.

(a)

Country	2013	2014	2015	2016	2017
Argentina	94	94	94	92	86
Brazil	97	93	96	89	89
Colombia	91	90	91	91	92
Costa Rica	95	91	92	97	96
El Salvador	92	94	91	93	85
Mexico	83	87	87	97	85
Panama	80	80	73	86	81
Peru	88	88	90	89	83
Uruguay	95	95	95	95	NA
Venezuela	82	78	87	84	66

(b)

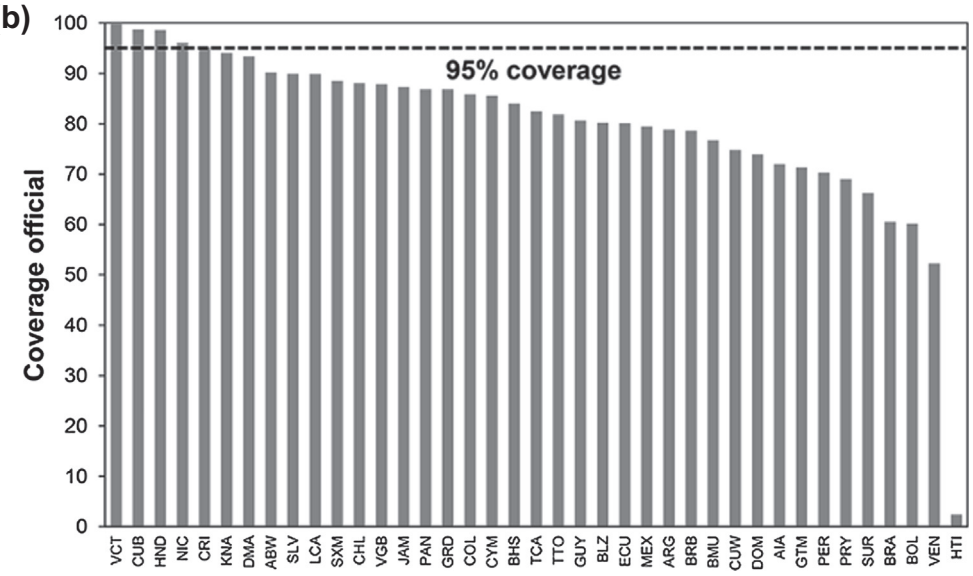

Fig. 1. DTP3 and DTP4 coverage by country [24]. (A) DTP3 coverage by country between 2013 and 2017. For most countries, there was improvement in coverage over those years. Moreover, some countries reached the recommended 95% coverage. NA, not available. (B) DTP4 coverage by country for 2016. Five countries reached 95% coverage. ABW, Aruba; AIA, Anguilla; ARG, Argentina; BHS, Bahamas; BLZ, Belize; BMU, Bermuda; BOL, Bolivia; BRA, Brazil; BRB, Barbados; CHL, Chile; COL, Colombia; CRI, Costa Rica; CUB, Cuba; CYM, Cayman Islands; DMA, Dominica; DOM, Dominican Republic; ECU, Ecuador; GRD, Grenada; GTM, Guatemala; GUY, Guyana; HND, Honduras; HTI, Haiti; JAM, Jamaica; KNA, Saint Kitts and Nevis; LCA, Saint Lucia; MEX, Mexico; NIC, Nicaragua; PAN, Panama; PER, Peru; PRY, Paraguay; SLV, El Salvador; SUR, Suriname; SXM, Sint Maarten; TCA, Turks and Caicos Islands; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VEN, Venezuela; VGB, British Virgin Islands.

coverage is lower than 80% [14]. Data on DTP4 coverage for Latin America are available from 2016 (Fig. 1B) [24]. In general, the coverage of this dose is lower than that of DTP3.

4. Epidemiological situation of pertussis in Latin America

Although pertussis is a vaccine-preventable disease and mass vaccination against it began more than 60 years ago, there are difficulties in achieving adequate control of the disease [25]. In particular, the currently used wP or aP vaccines provide good protection against severe and typical pertussis, but substantially less protection against milder coughing illness, suggesting that although vaccination prevented disease or at least its severest manifestations, transmission of infection continued [11,25]. As after natural infection, the immunity from vaccination wanes (faster for aP than for wP), and protection against infection is less complete than against the most severe manifestations of disease [11,12].

Another critical observation is that the cyclic nature of pertussis epidemics remained largely unchanged after the widespread use of vaccination. Undoubtedly, vaccination coverage rates, delays in vaccination, and vaccination schemes and their changes (eg, type of vaccines and age group) modify the epidemiology of the disease. Epidemiological data from each of the participant countries at the meeting are presented next. An overview of some of the reporting and surveillance systems employed in several of the participant countries can be seen in Supplementary Table 1.

4.1. Argentina

In Argentina, after a long period of low pertussis incidence, a sustained increase in cases has been recorded since 2002 in infants and adolescents [26]. In 2011, an outbreak was detected with 2821 confirmed cases; the incidence in infants <1 year of age was 344/100,000, and 76 infant deaths were reported [16]. In response to this epidemiological situation, vaccination of pregnant women with aP-containing vaccines was introduced in 2012 and became mandatory in 2014 [27]. Pertussis incidence decreased from 4.8/100,000 in 2012 to 1.4/100,000 in 2014, and the case fatality ratio decreased from 1.7% to 1.1% [28]. In 2016, another outbreak was detected (incidence 3.9/100,000), but was not accompanied by increased case fatality ratios (0.6%) [28]. These data suggest that maternal immunization reduces the severity of pertussis cases that would otherwise be fatal. In agreement with these data, it was recently reported that no fatal cases were detected in a pediatric hospital from Buenos Aires after the pregnancy aP recommendation was implemented [29].

4.2. Brazil

In Brazil, until 2015, vaccine coverage for the 1-year booster vaccination was 85–91% but fell to 64% in 2016; this decrease may have been due to the introduction of a new vaccine registration system in 2016, rather than vaccination coverage determined by the number of vaccines used. Tdap (tetanus-reduced diphtheria toxoid-acellular pertussis) vaccination during pregnancy was introduced in 2014. A retrospective study showed that pertussis incidence increased significantly from 2012 up to 2014, peaking between spring and midsummer [30]. According to the National Notifiable Diseases (Sistema de Informação de Agravos de Notificação [SINAN]) in 2012, 15,428 suspected pertussis cases were reported. Of these, 4453 (28.9%) were confirmed, representing an increase of 97% compared with the same period in 2011, when 2258 cases were confirmed [31]. The age group with the highest incidence was children <1 year of age (105.6/100,000). In 2012, the number of deaths increased to 74 from 56 in 2011 [32]. The increase in incidence coincided with the introduction of pentavalent vaccine and with several states experiencing a relative reduction in vaccination coverage [30]. Surveillance data from 2010 to 2016 show that most cases occurred in infants <5 months old; 91% of pertussis-related deaths were in infants <3 months old. This trend continued during the 2015 outbreak, with most cases in patients <5 years of age [32].

4.3. Colombia

Colombia also experienced a pertussis outbreak in 2011–2012. Despite good vaccine coverage rates, there was an increasing trend in pertussis during those years. In 2011, the incidence was 2.2/100,000 and it was 8.5/100,000 in 2012 [33]; 65.5% of cases occurred in infants <1 year of age, particularly among those <6 months. In 2011, 35 deaths in infants <1 year of age were reported and 65 infant deaths were reported in 2012 [34]. This led to the introduction of Tdap maternal vaccination in Bogotá in 2013. From 2014, maternal vaccination was offered nationwide to pregnant women from 27 to 29 weeks' gestation, reaching maternal vaccination coverage rates of ~90%. The number of pertussis-related deaths has decreased from 74 in 2012 to 5 at the end of 2017 [33]. A retrospective study in Bogotá showed a 100% reduction in mean pertussis mortality prior to and after the introduction of maternal vaccination, with a mean mortality rate of 6/100,000 in 2005–2012 versus 0/100,000 in 2014–2015 [35].

4.4. Costa Rica

In 2006, a severe pertussis outbreak occurred with a pertussis-related death rate of 11.2/100,000 live births in Costa Rica [36]. Postpartum cocoon vaccination was introduced nationwide in May 2007, and there was a rapid decline in pertussis cases in the following months. The annual number of deaths has fallen to 0–2 since 2007 (unpublished data). In 2010, Costa Rica switched from TDwP to TDaP for the primary series of vaccination, and postpartum Tdap was switched to vaccination during pregnancy after week 20 of gestation in 2013.

4.5. El Salvador

In El Salvador, there was a significant increase in the number of confirmed cases of pertussis in 2012, with the majority of reported cases in infants ≤6 months old (64/71 cases; 90%), particularly those ≤2 months old (53/71 cases; 75%) (National Surveillance data, unpublished). In the past 6 years, pertussis-related mortality has increased from 1.4% to 12.5% (National Surveillance data, unpublished); three quarters of these deaths were in infants <4 months old. A pertussis vaccination booster dose for pregnant women was introduced in 2014, reaching coverage rates up to 75%, but has fluctuated since then due to vaccine supply issues.

4.6. Mexico

In 2011, when positive PCR testing was added to the national operational definition of pertussis in Mexico, a 19% increase in reported cases was observed. The increase continued in 2012 with 752 confirmed cases. The majority of the detected cases occurred in infants <1 year of age [14]. Official national data of pertussis-associated mortality are not available; however, a recent prospective study conducted during a 3-year period in 11 hospital centers showed that 6.7% of children died from pertussis complications [37]. Consequently, maternal vaccination was recommended, but coverage has been inadequate due in part to economic hardship in Mexico from 2012 to 2013 and a vaccine supply shortage from 2014 to 2016.

4.7. Peru

In 2014, the national coverage for primary vaccination was 88.3% in Peru. Between 2011 and 2012, a 20-fold increase in the incidence of pertussis cases was registered, with the highest disease burden in infants <1 year, representing 38% of cases despite national immunization coverage of 92% in this age group. In a study performed during this outbreak, pertussis was found to be significantly higher in patients who had 0–3 vaccine doses of the pentavalent vaccine alone than in those who had 4–5 vaccine doses of the pentavalent vaccine plus DTwP boosters (94.3% vs 5.7%, respectively; $P < 0.00001$) [17].

4.8. Puerto Rico

In Puerto Rico, coverage of the pertussis primary vaccination series has been higher than the recommended 95% target. The high coverage was achieved because children were not allowed to start school until their vaccination schedule was up to date. Sixty percent of residents are covered by the government plans and the remaining 40% of residents are covered by private insurance. In 2015, there were 10 cases of pertussis reported nationwide and 12 in 2016 (unpublished data).

4.9. Uruguay

The biggest outbreak in recent years in Uruguay was detected in 2011–2012, with most cases in infants <1 year of age. The overall mortality rate for infants <1 year old was 9.3 per 1000 births (0.93%) in 2012 [38], and the case fatality rate was 1–4% during this outbreak. Maternal aP vaccination during pregnancy was introduced during the 2011–2012 outbreak, but was discontinued shortly thereafter. Another pertussis outbreak was detected in 2015. Since the 2015 outbreak, aP vaccination has also been given to new mothers who were not vaccinated during pregnancy, family contacts of neonates, and health care workers, especially those in contact with neonates and infants.

4.10. Venezuela

Incidence in 2011 was reported to be 217% greater than in 2012 in Venezuela. The majority of cases were detected in infants <1 year, but a consistent number of cases occurred in those >5 years, including adolescents and adults, and were a source of transmission for the most susceptible age group. Vaccination coverage rates in 2017 dropped to 67.8% for children <1 year of age and 41.9% for the booster in children 5 years of age, with significant underreporting in the last few years due to the ongoing crisis in the country (unpublished data).

5. Summary and conclusions

Pertussis immunization has led to a decrease in the number of cases over many years since the introduction of widespread immunization. However, a notable increase in pertussis incidence was detected in many countries of the region since 2004. From 2006 to 2015, most reported pertussis cases were in infants younger than 1 year of age, but increases have been seen in all age groups (Fig. 2). Argentina, Chile, Costa Rica, and Uruguay had the highest incidence of pertussis in infants during that time period (Fig. 3) (unpublished data). In recent years, the number of pertussis-related deaths was highest in 2009 and 2012 (Fig. 4) (unpublished data). Moreover, Argentina, Brazil, Colombia, El Salvador, Peru, and Uruguay detected outbreaks during 2011–2012, as was reported for other countries of the Americas (eg, Canada [39] and the United States [40]). The majority of cases in such outbreaks were detected in infants younger than 1 year of age. The specific reasons for these outbreaks were unknown, but contributing factors include vaccine coverage below 95% and delays in vaccine administration.

Many countries experience significant surveillance challenges, mainly due to the clinical diagnosis definitions utilized, inconsistent laboratory confirmation, a lack of uniformly accessible detection techniques, or incomplete epidemiological notifications. This is likely to result in underreporting and underestimation of disease burden. Although circulation of pertussis in adolescents has been detected, surveillance in this age group is still inadequate, and therefore it is unclear whether the administration of adolescent boosters is important. More evidence for introducing this booster dose is required.

To reduce the number of cases in infants, maternal immunization has been introduced in many countries of the region during the last decade (Table 3). The data presented show that this strategy is having an impact not only in reducing the number of cases, but also in the number of deaths caused by the disease [28,29]. Although the data on this strategy are encouraging, recommendations are inconsistent, and several countries, including Brazil, Costa

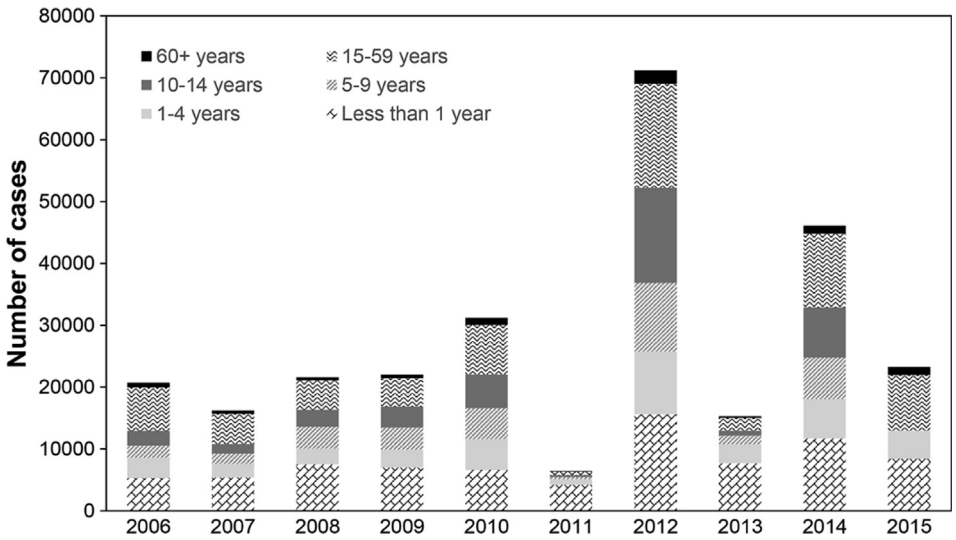

Fig. 2. Distribution of reported pertussis cases by age in the Americas: 2006–2015. Pertussis cases are being detected in all age groups (unpublished data).

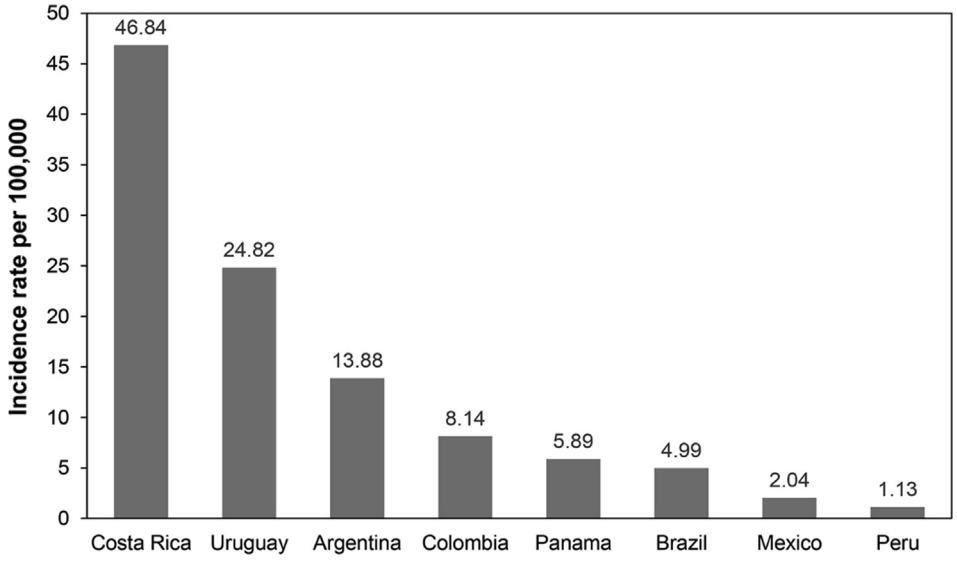

Fig. 3. Pertussis incidence rate in infants (<1 year) in Latin America: 2006–2015 (unpublished data).

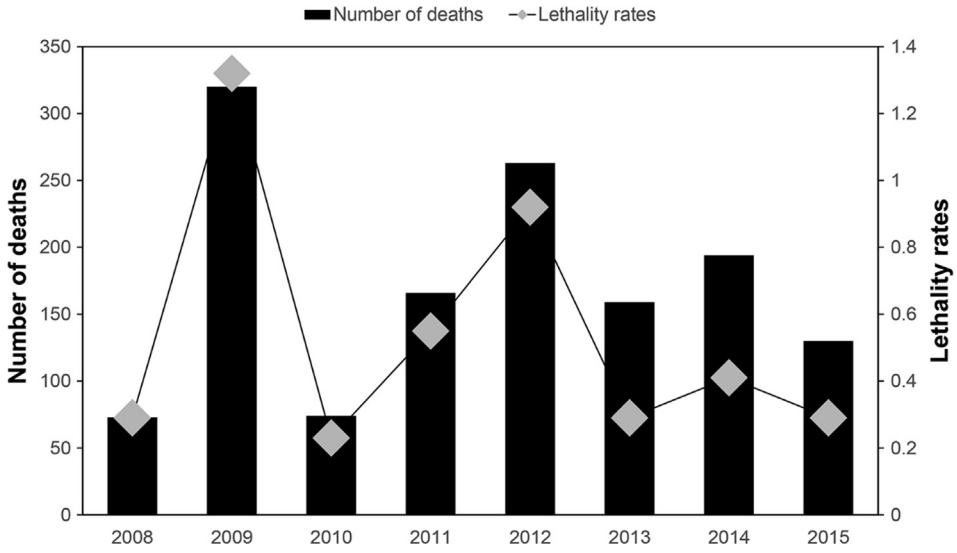

Fig. 4. Number of deaths and lethality rates due to pertussis infection in the Americas: 2008–2015 (unpublished data).

Table 3
Maternal vaccination coverage in Latin America: 2012–2016.

	Coverage (%)				
Country	2012	2013	2014	2015	2016
Argentina	51	67	66	61	65
Brazil	NA	NA	37	40	NA
Chile	78	83	88	88	88
Colombia	NA	81	36	74	75
Costa Rica	NA	NA	77	NA	NA
Mexico	NA	95	NA	52	96
Panama	100	16	100	100	100
Paraguay	NA	26	NA	NA	NA

NA, not available.
Source: unpublished data.

Rica, El Salvador, Mexico, and Uruguay, noted that implementation of maternal immunization needs to be improved with increased coverage warranted. In Venezuela, maternal immunization is not in the vaccination schedule.

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Conflicts of interest

The GPI is supported by Sanofi Pasteur SA and was established in 2001 to evaluate the ongoing problem of pertussis worldwide and to recommend appropriate pertussis control strategies. Sanofi Pasteur continues to fund this important initiative to provide a forum for scientific and policy-based discussions. The views and opinions expressed in this publication, which could include use of Sanofi Pasteur products that is inconsistent with current labeling or licensed indication, are solely those of the authors and do not reflect the position of Sanofi Pasteur SA.

Other potential conflicts of interest:

DH, RU, CM, and CHW are members of the GPI. TT and KF are co-chairs of the GPI.

RU: has received honorary fees as an invited speaker and attended pertussis meetings sponsored by Sanofi Pasteur & GlaxoSmithKline.

CHW: has received honoraria as a speaker from GlaxoSmithKline and MSD.

TT: has received grants and personal fees from Sanofi Pasteur, grants from Merck Inc. and Pfizer, and personal fees from GlaxoSmithKline.

KF: has received honoraria from Sanofi Pasteur.

Author contributions

All authors were responsible for idea generation, critical review, and input into the manuscript drafts, as well as approval of the final draft for submission. All authors had full access to the study data and take full ownership for the integrity of the data and accuracy of the data analysis.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.07.007.

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