

2019 Latin American Pertussis Workshop

Summary of Proceedings

Buenos Aires, Argentina | February 20-21, 2019



Acknowledgements

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Recommended citation:

Sabin Vaccine Institute. Latin American Pertussis Workshop: Summary of Proceedings. Washington, D.C.; 2019.

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Latin American
**PERTUSSIS
WORKSHOP**
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Introduction

From February 20 to 21, 2019, more than 70 pertussis leaders, technical experts and key stakeholders from 16 countries met in Buenos Aires, Argentina for the Latin American Pertussis Workshop to share recent findings and reflect on their experiences at the conclusion of the decade-long Latin American Pertussis Program (LAPP).

A collaborative effort between the Sabin Vaccine Institute (Sabin), the U.S. Centers for Disease Control and Prevention (CDC), the Pan American Health Organization (PAHO) and the ministries of health (MOHs) of Argentina, Brazil, Chile, Colombia, Mexico and Panama, LAPP was established in 2009 with the goal of expanding understanding of pertussis epidemiology in Latin America to inform strategies for controlling and preventing the disease.¹ Participants in the workshop included representatives of the three LAPP partner agencies, MOHs of the six LAPP countries and several other Latin American and Caribbean countries.

Through presentations, panel discussions and question-answer dialog, participants reflected on the state of pertussis epidemiology, prevention and control from local, national and global perspectives. They shared lessons learned through engagement in LAPP and considered the project's impact on pertussis vaccination and control strategies through its emphasis on capacity-building, training and research. Presentations of research findings on maternal vaccination strategies, as well as on molecular-level studies of the pathogen *Bordetella pertussis* and related species, provided context for decision-making and ongoing inquiry. The workshop concluded with a wide-ranging, open discussion of the future of pertussis vaccine strategies and research in Latin America.

Background

Pertussis, also known as whooping cough, is one of the world's most poorly controlled vaccine-preventable diseases.² Despite the widespread availability and uptake of pertussis vaccines, the disease continues to cause significant child mortality. An estimated 24 million people globally are infected with pertussis annually, with 160,000 children under 5 years of age dying from these infections.³ Illness and death due to pertussis occur most frequently among infants, particularly those under 6 months of age. Robust estimates of pertussis incidence and death are limited by a lack of reliable surveillance data and diagnostic capacity.⁴

Since 2002, many Latin America countries have reported increased numbers of pertussis cases.² However, the effects of pertussis in Latin America are uncertain due to limited published data on pertussis deaths and hospitalizations, country-specific differences in case definitions and variability in diagnostic testing practices.^{5 6} The recent increase of reported pertussis, against a backdrop of varied incidence reports among Latin America countries, highlights the need to reinforce epidemiologic and diagnostic capacity across the region.²

Recognizing the need for improved epidemiologic information to guide pertussis vaccination policies and surveillance recommendations⁷, LAPP was established in 2009 to strengthen both laboratory diagnostic capacity and epidemiologic surveillance in selected Latin American countries.² Sabin provided overall funding and project management, as well as logistical support and feedback for LAPP activities; CDC provided technical support of epidemiology and laboratory diagnostics in participating countries; and PAHO provided expertise on immunizations and coordination with the MOHs. In each country, national-level public health personnel, including staff from both the pertussis surveillance department and the national reference laboratory (NRL), engaged in LAPP activities.

Specifically, LAPP sought to expand laboratory capacity for identification of *B. pertussis* to strengthen laboratory-based pertussis surveillance and standardize and improve pertussis reporting within each country.² Initial in-country assessments of the pertussis surveillance system and laboratory capacity informed country-specific on-site laboratory and epidemiologic training, guidance and technical assistance, as well as participation in a laboratory quality control and quality assurance (QC/QA) program. Mentoring and ongoing communication with laboratory and surveillance country staff were emphasized throughout these activities.

Latin American Pertussis Project Model

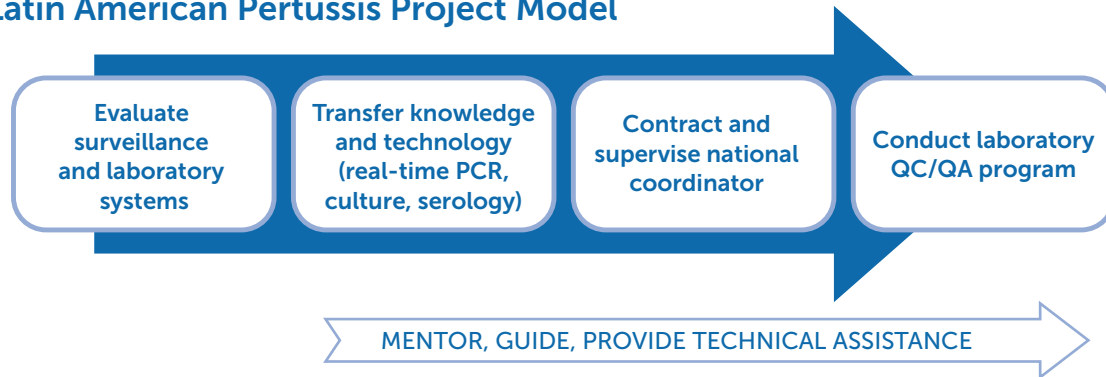


Figure 1: Latin American Pertussis Project model to strengthen pertussis surveillance. Currently in use in six countries in Latin America.²

Source: Pinell-Mcnamara VA, Acosta AM, Pedreira MC, Carvalho AF, Pawloski L, Tondella ML, et al. Expanding pertussis epidemiology in 6 Latin America countries through the Latin American Pertussis Project. *Emerg Infect Dis.* 2017 Dec; 23(Suppl 1):S94–S100.

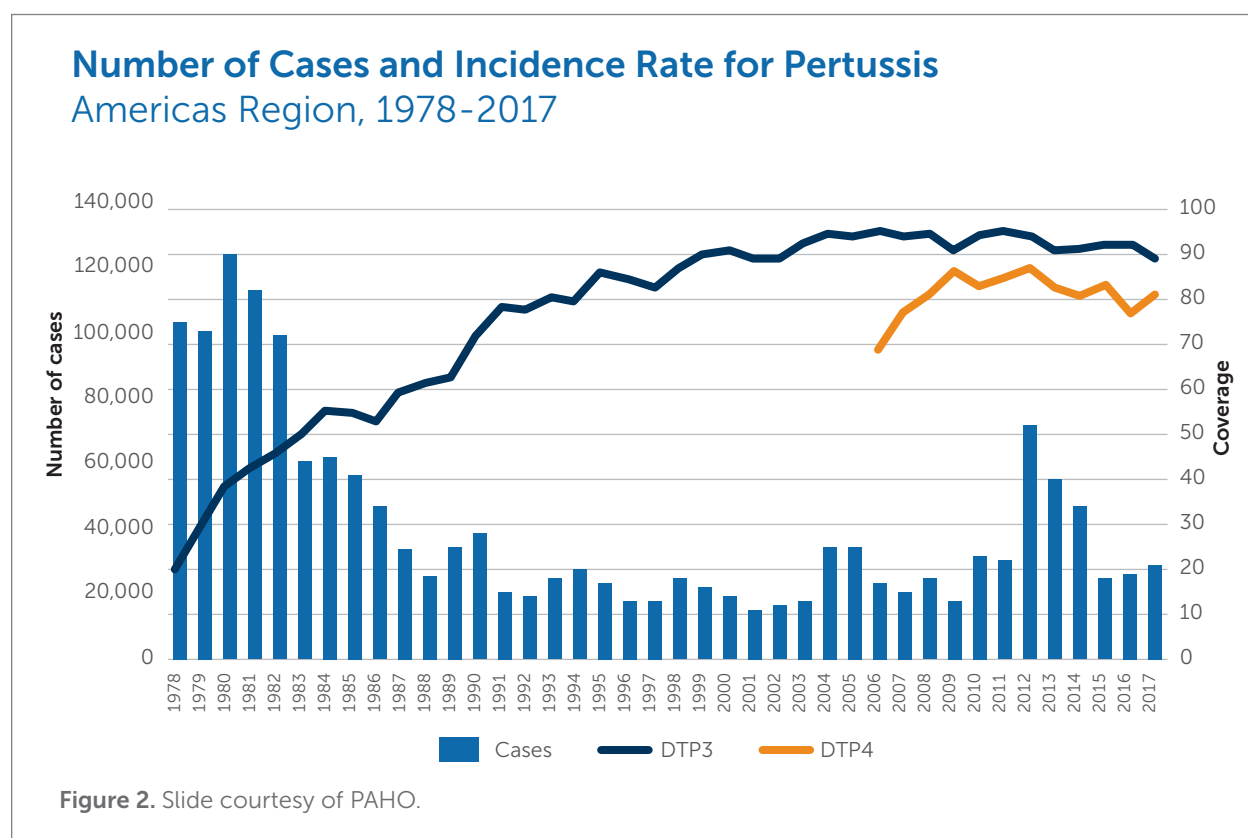
Countries were selected for inclusion in LAPP on the basis of reported pertussis disease burden, potential for integrating and sustaining new laboratory capacities and country-level requests to PAHO and CDC for technical support.² LAPP began in 2009 with Argentina, Mexico and Panama, and expanded to include Chile and Colombia in 2013 and Brazil in 2015.

At this capstone workshop, representatives of LAPP countries described current pertussis surveillance results and prevention and control initiatives within their borders. They reflected on the project's impact on epidemiologic and laboratory surveillance practices for pertussis in their countries, and on the ways in which surveillance evidence influenced national decisions on vaccination and control strategies. Along with LAPP advisors from PAHO and CDC, LAPP country representatives shared knowledge and lessons learned from the initiative. Workshop participants also looked forward, identifying challenges to address, policies to consider and research questions to pursue that could further the goals of LAPP and extend its impact beyond the six partner countries.

Certain themes that permeated workshop presentations and discussions provide an interpretive frame for the following proceedings. Participants stressed the necessity of raising awareness of pertussis, and the importance of surveillance to demonstrate the pertussis burden of disease. They affirmed that effective surveillance, which integrates epidemiologic and laboratory evidence, informs vaccination strategies that improve coverage and reduce illness and death. As exemplified by the LAPP experience, they concluded that developing and sustaining strong pertussis surveillance programs requires sustained training of in-country personnel, reinforced by information exchange on regional and global scales and among initiatives targeting other vaccine-preventable diseases.

Pertussis in Latin America

Persistent challenges



Pertussis, an endemic disease that flares in sporadic outbreaks worldwide, presents persistent challenges despite the widespread availability of vaccine and an estimated global vaccination coverage of 85 percent.^{8 9} The World Health Organization (WHO) recommends a primary series of 3 doses of diphtheria-tetanus-pertussis vaccine, beginning as early as 6 weeks of age and ending by 6 months of age with at least 4 weeks between doses, a booster dose for children aged 1–6 years.¹⁰ This schedule, at a minimum, is followed among the six LAPP countries, but individual countries vary widely in the timing of booster doses. Two forms of the vaccine are used: whole-cell (wP) vaccine (DTP) is relatively inexpensive and confers longer-lasting immunity, but is associated with adverse reactions that increase with age and limits number of injections recommended; acellular (aP) vaccine (DTaP) contains purified, inactivated *B. pertussis* toxin either alone or in combination with other antigenic components, such as pertactin.^{10 11} In addition, vaccination of pregnant women with Tdap, considered to be a cost-effective, complementary strategy to prevent pertussis-associated infant mortality¹², has been adopted in every LAPP country. However, neither WHO nor PAHO currently recommend the routine immunization of pregnant women against pertussis, except in areas affected by outbreaks.

Pertussis is considered to be far more contagious than polio, smallpox, rubella, mumps or diphtheria.⁹ *B. pertussis* spreads efficiently via airborne droplets and frequently causes severe disease in infants, especially those too young to have received their first vaccine dose. Protection provided by vaccination against pertussis occurs within a limited period. Immunity is established after three shots, typically administered at 2, 4 and 6 months, after which it gradually wanes; thus, in childhood, and in some cases during adolescence, booster doses are administered, including in the six LAPP countries. Waning immunity to both aP and wP vaccines challenges pertussis control, even where coverage rates for infant and childhood immunization are high.¹³ Accumulating evidence indicates that wP vaccines, typically given only to infants, offer longer-lasting protection against pertussis than aP vaccines^{13 14 15 16}, and that adolescents who received wP vaccines in childhood were better protected during a pertussis outbreak than were those who received aP vaccines alone.¹⁷

Current immunization strategies seek to reduce pertussis transmission from adolescents and adults to vulnerable neonates and infants.^{9 18} However, in settings where aP vaccines are used exclusively, recent studies suggest that children are a likely source of neonatal infection.^{16 19 20 21 22} Thus, the optimal timing of booster dosing to protect infants from pertussis may vary according to setting, and this remains an important area of investigation, alongside efforts to improve the potency of pertussis vaccines.^{13 14}

Recognition of pertussis disease is challenging, as its symptoms typically vary with age.⁹ Among infants and children, pertussis symptoms range from mild upper respiratory distress to severe, persistent and progressive coughing that can last for months. The classic symptom of pertussis—originally known as “whooping cough”—is violent and rapid coughing, during which rapid expulsion of air from the lungs forces subsequent inhalation, producing a loud “whoop.” In infants and young children, pertussis progresses through three consecutive and distinct symptomatic stages, some of which resemble those of common viral infections. Adolescents and adults generally experience milder—and sometimes undetectable—versions of symptoms present in infants and children.

The accuracy of laboratory diagnosis of pertussis depends upon the timing and quality of specimen collection.^{2 23} As shown in Figure 3, no single pertussis diagnostic assay optimally detects infection at all stages of disease. Multiple diagnostics for pertussis are not used or available through much of Latin America², but personnel in all six LAPP countries were trained in polymerase chain reaction (PCR), culture and serology, according to Veronica Pinell-McNamara, of CDC. Most LAPP countries are now implementing PCR, some employ culture and a few have serology capacity, Pinell-McNamara reported.

Optimal Timing for Diagnostic Testing for Pertussis, in Weeks

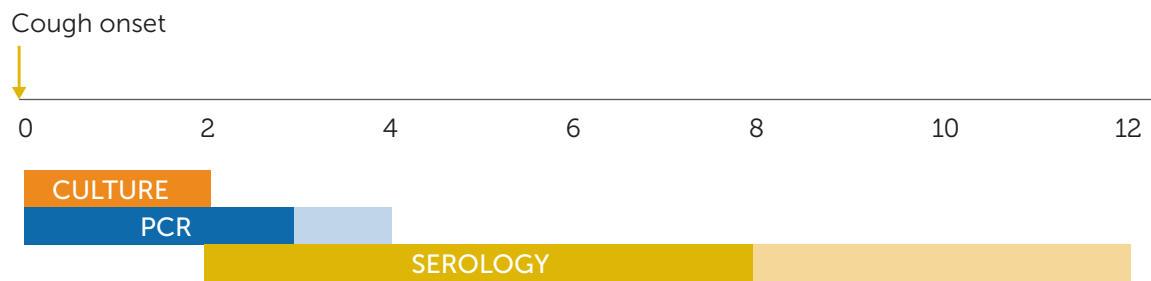


Figure 3: Optimal timing for diagnostic testing for pertussis, in weeks. Darker colors indicate optimal timing window; lighter colors indicate that tests may provide accurate results during these periods.²⁴

Source: CDC. Optimal timing for diagnostic testing for pertussis (weeks) [Internet]. Available from: <https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html>

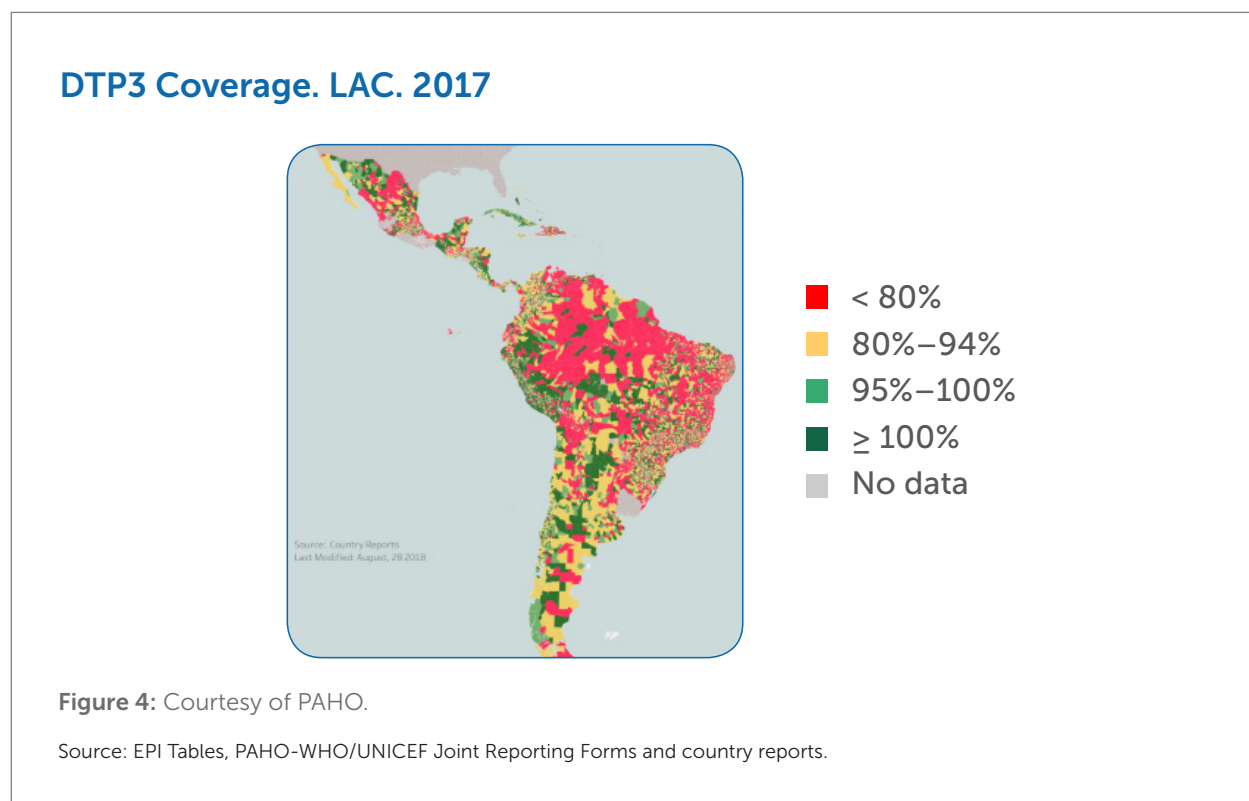
Diagnostic inconsistency, as well as age-based variation in clinical signs and symptoms of the disease, complicate case definition for pertussis, as noted in a recent systematic review of pertussis epidemiology in Latin America and the Caribbean.²³ Some workshop participants advocated for the development of an age-specific standardized pertussis case definition.

Reported pertussis incidence and case fatality rates vary widely among countries in Latin America. This situation is due at least in part to a lack of high homogeneous vaccination coverage, as well as differences in case management, surveillance infrastructure and case identification by healthcare providers.^{5 23} As a result of the previously noted challenges pertussis poses to surveillance (e.g., lack of awareness of the disease, particularly among adolescents and adults; lack of a regional standard case definition; and limited laboratory capacity), reporting in Latin America tends to focus on cases among hospitalized infants or young children, which are often confirmed solely by clinical criteria. These factors may lead to underestimation or overestimation of disease prevalence.

Pertussis in adolescents and adults is likely underreported, because adults and adolescents less often seek medical attention for their presumably milder symptoms, and because those symptoms frequently go unrecognized as pertussis. Adoption of a common, age-specific case definition for pertussis could provide better estimates of disease burden in adolescents and adults, in turn supporting the creation of more effective age-dependent vaccination strategies.

Current strategies and next steps

In her overview of pertussis epidemiology and control in Latin America, Ana Elena Chévez, of PAHO, noted that three-dose DTP coverage (DTP3) across the Americas increased from about 20 percent in 1978 to 90 percent by 2000, with a majority receiving four doses (DTP4) after 2006, and with 80 percent DTP4 coverage in 2017.²⁵ However, as shown in Figure 4, DTP3 coverage is patchy throughout Latin America and the Caribbean, with many areas falling well below the 80 percent target, and other areas, such as southern Mexico, failing to report.



While both the number of pertussis cases and the rate of disease incidence have declined overall across the Americas since 1978, this period was punctuated by periodic outbreaks, most recently between 2012 and 2014, Chévez reported. During these years, pertussis cases in children and adolescents, as well as in infants, increased markedly.²⁵ Recent recommendations by the PAHO Technical Advisory Group on vaccine-preventable diseases, summarized in Box 1, coincide with LAPP's goal of strengthening epidemiological surveillance in order to guide and improve outbreak response.

BOX 1: RECOMMENDATIONS AND CONSIDERATIONS OF THE PAHO TECHNICAL ADVISORY GROUP ON VACCINE-PREVENTABLE DISEASES, 2009-2018

1. Countries that employ wP vaccines should continue that strategy.
2. Vaccination schedules for diphtheria, tetanus and pertussis vaccinations should be harmonized.
3. Immunization coverage DTP3 and DTP4 should be monitored.
4. The pertussis surveillance system should be strengthened to improve epidemiological monitoring and accuracy of data on incidence, lethality, distribution by age group, proportion of confirmed cases and effectiveness of the vaccine.
5. Outbreaks should be thoroughly investigated to improve understanding of the current epidemiology of the disease in Latin America and the Caribbean. In areas affected by outbreaks, efforts should be made to vaccinate pregnant women, as well as infants starting at 6 weeks of age.*

*Chávez AE. Overview of pertussis in Latin America. Buenos Aires, Argentina; 2019.

Certain Latin American countries, including Argentina, Brazil, Chile, Colombia, Mexico and Panama, have introduced Tdap for pregnant women²³, although PAHO and WHO have yet to recommend routine maternal pertussis vaccination except during outbreaks. Chávez noted that maternal coverage estimates for Latin America are inadequate. To better understand the impact of current vaccination strategies in Latin America and the Caribbean and improve their coordination, PAHO convened a group of experts from the PAHO/WHO Immunization Unit, Emory University School of Public Health and Argentina's Institute of Clinical and Healthcare Effectiveness. These efforts produced the *Maternal and Neonatal Immunization Field Guide for Latin America and the Caribbean*.²⁶

Global surveillance standards for pertussis issued by WHO are structured according to three different objectives: defining the burden of disease, supporting immunization policy and responding to outbreaks.²⁷ A field guide specific to pertussis surveillance in Latin America and the Caribbean is currently being updated in an effort led by PAHO, as Chávez described; it will be published following review in July 2019 by the PAHO Technical Advisory Group on Vaccine-preventable Diseases. In 2020, Chávez reported, the objective is to commence in-country training and implementation of information systems for data aggregation and outbreak documentation as specified in the field guide.

LAPP's Impact

Improving and integrating epidemiologic and laboratory surveillance

The six countries selected for inclusion in LAPP had in common a significant pertussis disease burden as well as the potential to integrate and sustain new laboratory capacities that could ultimately improve vaccination strategies and disease control.² At the same time, each country faced unique challenges in improving epidemiologic and laboratory surveillance. Accordingly, each country received an initial assessment of its pertussis surveillance system and relevant laboratory capacity by a technical team comprised of CDC epidemiology and laboratory staff and PAHO advisors, whose findings informed subsequent on-site laboratory and epidemiologic training, guidance and technical assistance to improve surveillance.

Each LAPP country also participated in a laboratory quality control and quality assurance (QC/QA) program in cooperation with CDC.² All countries received laboratory training in pertussis culture and multitarget RT-PCR; five received training on serologic assays. LAPP supported with training reagents and materials, and in some cases, RT-PCR instruments and reagents for ongoing testing. Training was reinforced and extended through ongoing communication, including quarterly teleconferences on a range of topics and follow-up visits by technical teams. National surveillance coordinators, who were co-managed by LAPP and the MOHs of Argentina, Panama and Brazil, received supplemental training and technical support. LAPP advisors also worked with national-level MOH staff to improve case reporting procedures and monitor and analyze surveillance data for pertussis.

At the workshop, representatives from each LAPP country presented brief updates on epidemiologic findings and discussed the impact of LAPP-informed surveillance recommendations on pertussis vaccination and control strategies. Key points from these presentations, summarized below, reveal country-specific challenges addressed by LAPP capacity-building, training and research. This section also summarizes a workshop presentation on diagnostic advances in Peru—which, while not a LAPP-supported country, engaged in LAPP-sponsored information exchanges, including participation in this workshop.

Argentina

When a pertussis outbreak swept the country in 2011–2012, quick decisions needed to be made in order to address high mortality in infants²⁸, noted Maria del Valle Juárez, of Argentina’s MOH. Valle Juárez described how surveillance assistance provided through LAPP, in the form of staffing and workshop-based training, informed strategies to protect this vulnerable population, including maternal Tdap vaccination from 20 weeks of pregnancy.²⁹ In 2012, Argentina became the first country in Latin America to adopt this measure; subsequent analysis of national surveillance data³⁰ and a study comparing hospitalization and mortality rates among confirmed cases³¹ provide evidence that this strategy reduced illness and death in infants younger than 1 year.

LAPP also aided Argentina’s efforts to adopt molecular diagnostic methods for pertussis using real-time polymerase chain reaction (RT-PCR) at its two NRLs, stated Claudia Lara, of the National Institute of Infectious Diseases, National Laboratories and Health Institutes Administration (ANLIS-INEI) “Dr. Carlos G. Malbrán.” The NRLs incorporated a PCR diagnostic protocol and open-system platform developed by CDC, which also provided DNA extraction reagents and primers. Information from LAPP-supported training workshops on diagnostic methodologies eventually reached hundreds of clinics and laboratories throughout the country, which are connected through Argentina’s national surveillance system.²⁸ The resulting integration of epidemiological and laboratory surveillance for pertussis increased system sensitivity and precision.



Brazil

As in Argentina, the pertussis epidemic beginning in 2011 spurred efforts in Brazil to reduce illness and death among infants. Before joining LAPP in 2015, Brazil had introduced Tdap for pregnant women in 2014, revised its case definition for pertussis and introduced new treatment schemes. Daniela Leite, of Brazil's National Reference Center for Pertussis at the Adolfo Lutz Institute, São Paulo, described how these initiatives were strengthened through various LAPP activities:

- Technical visits, which recommended actions to improve surveillance protocols and improved performance of diagnostic testing;
- Data analysis training, which enabled identification of appropriate performance indicators to monitor surveillance;
- Provision of reagents to detect additional *Bordetella* species by PCR;
- Provision of reagents and training of staff on detection of pertactin-deficient isolates for a special study;
- Implementation of external quality control for laboratory diagnostics; and
- Provision of financial and technical resources for evaluating the immunologic impact of maternal vaccination, including:
 - Supply of IgG anti-PT ELISA reagents
 - Training and testing of ~900 maternal/cord blood specimens with a microsphere-based multiplex antibody capture assay (MMACA)
 - Manuscript preparation

Chile

While recognizing the benefits of such LAPP activities as identifying and improving gaps in the epidemiological surveillance of pertussis, Iván Ríos Orellana, of Chile's MOH, emphasized advancements in laboratory surveillance, and specifically the implementation of diagnostic RT-PCR in five regional laboratories throughout the country. Completed in 2015, this initiative aimed to increase the number of PCR-confirmed cases, involving training and technology transfer by CDC to five public and three private laboratories. External quality control for laboratory diagnostics, also supported by CDC, is currently underway as a pilot program.

Ríos Orellana also stressed the importance of opportunities afforded by participation in LAPP for sharing knowledge and experience with regional public health professionals. Such exchanges, he argued, are key to tackling ongoing challenges presented by pertussis through the refinement of case definitions, and by improving chemoprophylaxis, surveillance indicators and diagnostic protocols.

Colombia

LAPP's influence in Colombia was broad, spanning research support, technology transfer and supply, epidemiological surveillance, training, and quality control, according to Adriana Ulloa Virgüez, of Colombia's National Institute of Health. For example, in Colombia, as well as in Argentina, Brazil and Panama, LAPP organized trainings of more than 300 public health workers on Epi-Info™, a public domain suite of interoperable software tools developed and offered by CDC (<https://www.cdc.gov/epiinfo/index.html>), Veronica Pinell-McNamara noted. These trainings, along with subsequent support in the use of this tool, enabled the linking of epidemiological surveillance and laboratory data, data analysis, and mapping activities, Pinell-McNamara reported.

Leading up to a 2018 resolution encouraging Colombia's public health labs to implement PCR confirmation of pertussis cases and reporting to the NRL, LAPP-sponsored training and technology transfer in RT-PCR led to increased PCR use among district laboratories, Ulloa Virgüez reported. PCR-based pertussis diagnosis is not yet decentralized in Colombia, as it is in Argentina and Chile, but capacity has been extended to a majority of Colombia's district laboratories. Sustaining and expanding these gains will be challenging due to the expense of equipping laboratories to conduct RT-PCR, Ulloa Virgüez noted. Reagents available through CDC's International Reagent Resource (IRR; <https://www.internationalreagentresource.org/>) defray some of these costs.

LAPP-supported research conducted in Colombia aimed to improve both laboratory diagnosis and epidemiological intelligence related to pertussis. Among such projects, Ulloa Virgüez highlighted a comparison of immunofluorescence detection (IFD), serology and PCR diagnostic methodologies; a survey of healthy carriers of *B. pertussis* in high- and low-incidence populations; and work on the molecular characterization of *B. pertussis*. LAPP also supported the training of medical professionals to recognize pertussis in children older than 1 year, and in adolescents and adults, in order to improve understanding of pertussis incidence and previously undetected sources of infection.

Mexico

Marco Antonio Gonzáles Garcia, of Mexico's MOH, described the National Epidemiological Surveillance System (SINAVE) as a sensitive and robust system for pertussis surveillance based on its performance across indicators such as timeliness of case notification, classification, sample collection and processing. LAPP supported the introduction of PCR diagnosis for pertussis in 2012, and it has since become the primary method for case confirmation by SINAVE, Gonzáles Garcia reported.

Laboratory surveillance of pertussis in Mexico proceeds from sentinel hospitals; specimens are sent to state laboratories, which isolate and characterize *B. pertussis*, then report their results to the NRL (known as InDRE), according to Luis Ángel Sapián López, of Mexico's MOH. He noted that InDRE gained particular benefit from participating in the LAPP-supported QA/QC program extended to all LAPP countries, which utilize CDC as an external laboratory of reference. Program evaluation provided through LAPP improved coordination within Mexico's public laboratory network, Sapián López added.

Supported by LAPP-sponsored technical training and technology transfer, InDRE introduced RT-PCR in 2011 and gained capacity to detect three additional *Bordetella* species and *B. pertussis-parapertussis* dual infections. For both sentinel laboratories and InDRE, LAPP provided technical evaluation; training in RT-PCR, ELISA and culturing techniques; and external quality control.

Peru

Participation in this workshop by Peru, a non-partner country, exemplified the regional exchange of knowledge and experience that LAPP intended to support. Faviola Valdivia Guerrero, of Peru's National Institute of Health and NRL for severe respiratory infections, reviewed case definitions for pertussis, the establishment of a maternal vaccination program, and the introduction of RT-PCR diagnosis for pertussis, and described how surveillance informs strategic goals for disease control in Peru.

Prior to 2012, IFD was the predominant method for the laboratory confirmation of pertussis in Peru. After a validation study demonstrated the superiority of RT-PCR, it was implemented at the NRL, which receives samples from 24 regional reference laboratories. Sample collection and transport were initially problematic; thus, a program of training for regional lab staff was undertaken. At the same time, the identification of criteria associated with lab-positive cases enabled more efficient sampling. Peru is now regionalizing laboratory diagnosis in order to better monitor pertussis in high-incidence areas, and is also researching rapid PCR diagnosis to reduce the number of samples that require transportation, Guerrero reported.



Research mentoring and communication

Among the lessons learned during the first several years of LAPP, Pinell-McNamara and co-authors² observe that while mentoring supported the successful adoption of new technologies, sustaining those innovations required a regional commitment to materially support them. Not surprisingly, these points were raised in the open discussion after the LAPP-country presentations, during which several participants noted both the diagnostic power afforded by RT-PCR and the difficulty of obtaining reagents and supplies necessary for its routine use in pertussis surveillance. Some characterized this dilemma as a forward cycle, in which it is necessary to demonstrate that new technologies improve surveillance in order to secure funding for their use. LAPP has, to some extent, propelled this cycle, but participants recognized that they will need to advocate effectively to sustain improvements realized through their participation in LAPP. At the same time, participants credited LAPP with strengthening regional connections among professionals involved in pertussis epidemiology and control, in ways that validate their work and raise awareness of the disease burden associated with pertussis.

LAPP mentoring supported evaluative studies on pertussis control strategies, such as maternal immunization (discussed in detail in the next section of this summary). More broadly, LAPP teleconferences, meetings and workshops promoted the exchange of ideas and experiences among leaders, technical experts and key stakeholders from the Latin American region. This workshop, for example, included a session on the molecular characterization and phenotypic analysis of *Bordetella* species (see sidebar, “Pertussis at the Molecular Level”).

Several workshop participants remarked that information and experiences shared through LAPP meetings and communications had contributed to their improved understanding of surveillance and vaccination strategies in the region.

PERTUSSIS AT THE MOLECULAR LEVEL

Three workshop presentations explored genetic variation in *B. pertussis* that could affect the susceptibility of circulating strains to immunity from pertussis vaccines. *B. pertussis* strains that differ in their production of antigenic proteins from vaccine-producing strains could contribute to the resurgence of pertussis, even in countries where vaccine coverage is high.

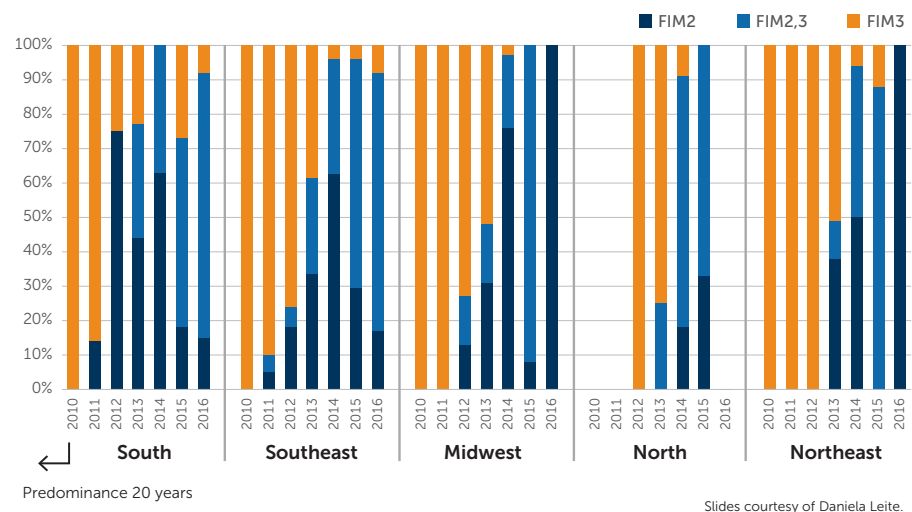
Lucia Pawloski, of CDC, discussed losses and changes in the antigenic proteins produced by *B. pertussis* strains circulating in the U.S. A retrospective screening of CDC's isolate collection revealed widespread deficiency in pertactin, which previously had been associated with the use of the aP vaccine, beginning in 2010.^{1,2} More than 16 different mutations responsible for pertactin deficiencies were identified, and although pertactin deficiency did not reduce vaccine effectiveness, Pawloski stressed the importance of continued surveillance of circulating *B. pertussis* strains in countries that use wP as well as aP vaccines.^{1,3}

Daniela Leite, of the Adolfo Lutz Institute in Brazil, described a survey of 555 samples of *B. pertussis* collected between 2010 and 2016 from five geographical regions of Brazil, which continue to use wP vaccine. In contrast to the U.S., as described by Pawloski, Brazilian researchers found only three pertactin-deficient isolates. However, they discovered that another antigenic protein, known as Fim, had undergone significant genetic shifts from year to year that remain unexplained. Molecular typing of the isolates revealed 110 distinct profiles, among which the proportions of the six predominant types also varied widely across the survey period.

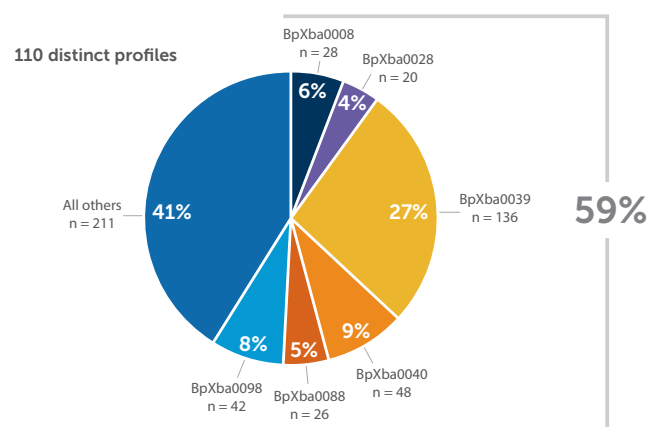
Daniela Hozbor, of the the National University of La Plata (UNLP) in Argentina, described the molecular characterization of 391 clinical isolates of *B. pertussis* collected in Argentina between 1997 and 2017. From the total characterized isolates, only two were detected as pertactin-negative isolates. Very low prevalence of pertactin deficient isolates was also detected in Brazil, another country with wP pertussis primary vaccination. Evidence of antigenic divergence between *B. pertussis* circulating bacteria and the strains used in vaccine production—particularly between lab-adapted strains and clinical isolates—was detected. Further study to determine the impact of this divergence on pertussis disease burden should be supported to better inform pertussis control in Latin America.

A fourth presentation, by Pam Cassiday, of CDC, discussed bacterial resistance to macrolides, the main class of antibiotics used to treat pertussis. While few macrolide-resistant *B. pertussis* isolates have been discovered, characterization of isolates collected in China and France revealed a common mutation that conferred resistance. Reports of macrolide-resistant isolates and specimens in China have increased, Cassiday observed, so continued monitoring for resistance is crucial.

Circulating Serotypes in Geographical Regions, Brazil, 2010-2016



Predominant Pulsotypes of 555 Isolates of *B. Pertussis*, Brazil, 2010-2016



¹Pawloski LC, Queenan AM, Cassiday PK, Lynch AS, Harrison MJ, Shang W, et al. Prevalence and molecular characterization of pertactin-deficient *Bordetella pertussis* in the United States. *Clin Vaccine Immunol.* 2014 Feb;21(2):119–125. doi:10.1128/CVI.00717-13

²Martin SW, Pawloski L, Williams M, Weening K, DeBolt C, Qin X, et al. Pertactin-negative *Bordetella pertussis* strains: evidence for a possible selective advantage. *Clin Infect Dis.* 2015 Jan 15;60(2):223-7. doi:10.1093/cid/ciu788

³Breakwell L, Kelso P, Finley K, Schoenfeld S, Goode B, Misegades LK, et al. Pertussis vaccine effectiveness in the setting of pertactin-deficient pertussis. *Pediatrics.* 2016 May;137(5). doi:10.1542/peds.2015-3973

Maternal Vaccination to Protect Infants

To a large extent, the burden of disease associated with pertussis arises from a combination of three factors: contagiousness, severe infant disease and waning immunity (after either vaccination or infection). Among several strategies proposed to reduce this burden, maternal vaccination has been most widely studied, implemented and accepted, according to speaker Helen Petousis-Harris, of the University of Auckland, New Zealand; however, she noted, further study and refinement are necessary to optimize its effectiveness. Several countries in Latin America and the Caribbean, including the six LAPP partner countries, vaccinate pregnant women against pertussis.

Maternal antibodies against pertussis have been demonstrated to offer short-lived protection against lethal disease during the first weeks of life, Petousis-Harris explained, and maternal Tdap vaccination programs in New Zealand, the United Kingdom and the U.S. have reduced case numbers, hospitalizations and deaths, particularly among newborns. A LAPP-supported study in Argentina—the first of its kind in Latin America—examined the effectiveness of maternal Tdap vaccination in preventing pertussis in infants younger than 2 months.³² Viviana Romanin, who coordinated the study, reported that it yielded evidence of the effectiveness of this measure in a middle-income country where wP (cellular) vaccines are used. Maternal vaccination during the third trimester was found to be slightly but not significantly more effective (83 percent) in preventing infant pertussis than during the second trimester (78 percent), Romanin stated. The researchers plan to conduct a similar analysis in infants aged 2–5 months. Looking more specifically at the immune response of maternal Tdap vaccination both in mothers and infants, another LAPP-supported study in Brazil indicated that IgG anti-pertussis toxin levels in infants born of vaccinated mothers were 5- to 6-fold higher as compared with their unvaccinated counterparts.³³

Determining optimal timing for an infant's initial dose of pertussis vaccine, in concert with maternal vaccination, will require further research, Petousis-Harris said. She noted that several studies in newborns following maternal Tdap vaccination found evidence of immune interference, but none had demonstrated that it resulted in clinical consequences.^{34 35 36}

Recommended Next Steps

The workshop's final panel discussion on the future of pertussis vaccine strategies and research in Latin America, and the open comment session afterward, served to reinforce and expand ideas expressed in previous sessions. Summarized here, these emergent themes offer guidance for the next stage of strategic advancement against pertussis in Latin America.

Continued and expanded integration of surveillance systems

Stacey Knobler, of Sabin, observed that integrating clinical and laboratory reporting and data collection systems not only supports effective vaccine strategy but also highlights areas where questions remain and data are needed to improve vaccination and health outcomes. Using these information systems to better inform priority-setting and resource allocation across the immunization ecosystem should be considered. Knobler additionally noted that while integrated surveillance is often touted as a model, it is not widely practiced, and she advised that its successful implementation, as described by several LAPP countries, should be highlighted and shared.



Stacey Knobler, Sabin Vaccine Institute, United States of America

Discussants also proposed that the practice of integration be expanded to incorporate private healthcare systems, individual healthcare providers and the professional societies who serve as their representatives. It was suggested that scientific societies be included in decision-making through the National Technical Advisory Groups pertaining to standardized case definitions for pertussis, and that physicians receive training to improve the accuracy and consistency of their reporting of suspected cases, including patients who do not require hospitalization.

Decentralization of diagnostic centers

Lucia Tondella, of CDC, remarked that while LAPP technical training focused on NRLs, it is important to expand diagnostic expertise to regional labs. Collecting specimens and isolates from decentralized nodes is expensive and time-sensitive, she acknowledged, so streamlining transport is essential. "It's doable," she observed. "Brazil receives isolates across the entire country." Likewise, Argentina consolidated clinical and laboratory nodes over the course of a decade; laboratory surveillance has been decentralized there since 2011.

Evaluation of vaccination strategies

Angela Gentile, of Pediatric Hospital R. Gutierrez, in Argentina, advocated evidence-based priority setting, given limited resources for expanding vaccine coverage. She highlighted existing evidence from Argentina to support universal maternal vaccination. Similarly, an audience member from Paraguay suggested the need to better understand the cost-effectiveness of that country's policy of vaccinating adolescents and healthcare workers in order to sustain support for such strategies. It was highlighted that continued evaluation of current and future strategies will require sustained and systematic approaches to data generation and analysis to better inform decision-making.

Expansion of vaccine coverage

Consistent reporting and better monitoring of vaccine uptake are necessary to identify and explain geographic gaps in coverage, Chévez asserted. "We need to understand why people don't vaccinate," Gentile concurred, noting that experience on overcoming these barriers is relevant to all vaccine-preventable diseases. Similarly, it was observed that combining adolescent vaccination against pertussis with other needed immunizations could improve the economic feasibility of increasing vaccine coverage across several vaccine-preventable diseases. To pursue these strategies, pertussis experts were encouraged to engage with networks and programs that address other vaccine-preventable diseases. Public information campaigns, similar to those that have raised awareness of measles, were also recommended for pertussis.

Toward sustainability

Recognizing that the benefits of training provided by LAPP extended beyond national laboratories, Knobler suggested that these gains could be maintained and strengthened through sub-national and regional partnerships that offered training based on these established methods. Asserting that “institutions are less important than people,” a participant suggested that training more people to enable disseminated collection of epidemiologic data would improve surveillance. Along the same lines, Chévez advised each LAPP country to designate a pertussis liaison responsible for exchanging surveillance information throughout a regional pertussis intelligence network.

Many workshop participants remarked on the importance of information exchange in sustaining, as well as achieving, LAPP-associated gains in pertussis surveillance. Knowledge and experience from the six LAPP countries is now being disseminated throughout Latin America, observed Anna Acosta, of CDC. Her point was reinforced by an audience member from the Dominican Republic, who expressed his commitment to implement strategies discussed in the workshop—including lab confirmation of cases and maternal vaccination—to address a current pertussis outbreak in his country.

As previously noted, sustaining the LAPP-supported transition to culture-independent diagnostics for pertussis has already proven challenging in most LAPP partner countries. Demonstrating the impact of such technologies on disease burden provides the surest route to sustained in-country support, participants noted. Toward this goal, they advised participation in quality control programs to improve laboratory cost-effectiveness; training to optimize sample collection, handling and delivery; and persistent advocacy to gain the attention of government officials.

Developing standardized case definitions

Agreement on standard case definitions for pertussis in Latin America will help advance surveillance gains realized through LAPP by enabling accurate interpretation of epidemiologic information across the region and along the chain connecting patients, physicians, epidemiologists, diagnosticians and health policy-makers. Participants advised that pertussis case definitions be age-specific, inclusive and flexible, and that they should embody “agreement, not perfection,” in one speaker’s words.

PAHO is leading the development of standardized pertussis case definitions as part of its revised field guide for pertussis surveillance. Chévez, expressing hope that the guide will encourage further improvements in pertussis surveillance in Latin America, revealed a further ambition: to capture the attention of authorities and obtain more resources for pertussis surveillance. “A team of several countries can exert even more pressure,” she observed.

As the workshop drew to a close, Chévez considered the experience gained by LAPP partner countries over the past decade and anticipated the next stage of their progress against pertussis. Like growing children, she said, projects require different kinds of supports as they develop. Thus, Chévez concluded, as LAPP ends, efforts to understand and control pertussis in Latin America enter a new stage.



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Appendix A

Agenda: Latin American Pertussis Workshop

20 February, 2019

8:30-9:00 Registration

Session I – Latin American Pertussis Project (LAPP): Introductory remarks and partner perspectives

Moderated by Stacey Knobler, Sabin Vaccine Institute

9:00-9:10	Welcome remarks and Sabin Vaccine Institute partner perspective	Stacey Knobler, Sabin Vaccine Institute
9:10-9:20	Pan American Health Organization partner perspective	Ana Elena Chévez, Pan American Health Organization
9:20-9:30	U.S. Centers for Disease Control and Prevention partner perspective	M. Lucia Tondella, U.S. Centers for Disease Control and Prevention
9:30-9:45	Remarks from Ministry of Health, Argentina	

Session II – Panel discussion: Updates on LAPP-country epidemiology and impact of LAPP-informed surveillance recommendations

Moderated by Anna Acosta, U.S. Centers for Disease Control and Prevention

9:45-10:45	The impact of LAPP capacity-building, training, and research on pertussis vaccination and control strategies: 20-minute presentations from LAPP country representatives inclusive of case definitions, diagnostics/ QC, outbreak reports, mortality and age-related trends: Argentina, Brazil and Chile	
10:45-11:00	BREAK	
11:00-12:00	The impact of LAPP capacity-building, training, and research on pertussis vaccination and control strategies: 20-minute presentations from LAPP country representatives inclusive of case definitions, diagnostics/ QC, outbreak reports, mortality and age-related trends: Colombia, Mexico and Panama	
12:00-12:45	The impact of LAPP evidence and data generation on programmatic and policy decision-making	
12:45-13:45	LUNCH	

Session III – Pertussis epidemiology and impact of control strategies in Latin America and globally

Moderated by Ana Elena Chévez, Pan American Health Organization

13:45-14:05	Overview of pertussis in Latin America	Ana Elena Chévez, Pan American Health Organization
14:05-14:25	Epidemiology and Advances in the diagnosis of pertussis in Peru	Faviola Valdivia Guerrero, National Institute of Health
14:25-14:45	Maternal vaccination in Argentina: Tdap vaccine effectiveness during pregnancy	Viviana Romanin, Consultant
14:45-15:05	Maternal and infant pertussis vaccination: finding the sweet spot	Helen Petousis-Harris, University of Auckland
15:05-15:30	Discussion	
15:30-15:45	BREAK	

Session IV – Molecular characterization and phenotypic analysis of *Bordetella* species

Moderated by Daniela Hozbor, National University of La Plata

15:45-16:05	Vaccine immunogen deficiency in the United States	Lucia Pawloski, U.S. Centers for Disease Control and Prevention
16:05-16:25	Research and genetic characterization of the circulating strains of <i>Bordetella pertussis</i> in Brazil. Are there any new variants in the country?	Daniela Leite, Adolfo Lutz Institute
16:25-16:50	Pertactin-negative <i>Bordetella pertussis</i> strains are rarely detected in Argentina a country that use whole cell vaccine for primary doses	Daniela Hozbor, National University of La Plata
16:50-17:10	Antibiotic susceptibility	Pam Cassiday, U.S. Centers for Disease Control and Prevention
17:10-17:30	Discussion	
17:30-18:30	WELCOME RECEPTION	

21 February, 2019

Session V – Welcome

9:00-9:15	Recap of first day	Stacey Knobler, Sabin Vaccine Institute
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Session VI – Panel discussion: the future of pertussis vaccine strategies and research in Latin America

Moderated by Angela Gentile, Pediatric Hospital R. Gutiérrez

	Discussion topics:	
9:15-11:15	<ul style="list-style-type: none">• Strategies and new developments to control pertussis: wP-aP boosting, maternal immunization, vaccine reformulation & novel vaccines• Application and capacity for culture-independent genomics• Needs/efforts to improve disease surveillance	
11:15-11:30	Summary and closing remarks for open sessions	
11:30-13:00	LUNCH	

This workshop and meeting report were partially supported by an educational grant from Sanofi Pasteur, which has had no influence or involvement in content, organization or preparation of any activities.

Appendix B

Participants: Latin American Pertussis Workshop

1. Aarón Agüero, Ministry of Health, Costa Rica
2. Adriana Paola Ulloa, National Institute of Health, Colombia
3. Aida Delgado, District Health Office N09D02, Ecuador
4. Aida Lucia Vargas Rosario, Ministry of Health, Dominican Republic
5. Alejandro Lepetic, GSK Vaccines, Argentina
6. Alison Mack, Consultant Writer, United States of America
7. Ana Barquero Uriarte, Ministry of Health, Costa Rica
8. Ana Elena Chévez, PAHO, United States of America
9. Andrea Verónica Müller, INPB ANLIS "Dr. Carlos G. Malbrán," Argentina
10. Andrés Montilla, National Institute of Health, Colombia
11. Ángela Gentile, Pediatric Hospital R. Gutierrez, Argentina
12. Anna Acosta, CDC, United States of America
13. Beatriz Graciela Lopez, INEI-ANLIS "Dr. Carlos G. Malbrán," Argentina
14. Carmen Lucía Contreras, University of Guatemala, Guatemala
15. Cecilia González, MINSAL, Chile
16. Claudia Lara, INEI-ANLIS "Dr. Carlos G. Malbrán," Argentina
17. Claudia Perandones, ANLIS "Dr. Carlos G. Malbrán," Argentina
18. Cristina Mariño, Central Military Hospital, Colombia
19. Cristina Pedreira, Immunization Advisor, Consultant, Brazil
20. Daniel Curcio, Pfizer, Argentina
21. Daniel Ibáñez, Public Health Institute of Chile, Chile
22. Daniela Hozbor, UNLP, Argentina
23. Daniela Leite, Adolfo Lutz Institute, Brazil
24. Darío Di Biase, INPB-ANLIS "Dr. Carlos G. Malbrán," Argentina
25. Dilcia Araceli Castellanos Ardón, Ministry of Health, Honduras
26. Dulcelina Concepción Urbina Ruíz, Ministry of Health, Honduras
27. Eitan Berezin, Santa Casa University Hospital, Brazil
28. Faviola Valdivia, National Institute of Health, Peru
29. Gabriela Aguilar Carrada, Ministry of Health, Mexico
30. Gabriela García Gabarrot, Ministry of Health, Uruguay
31. Gloria Rey, PAHO, United States of America
32. Gloriela de Villarreal, Gorgas Institute, Panama
33. Grettel Chanto, INCIENSA, Costa Rica
34. Guadalupe Viveros Terrazas, Ministry of Health, Mexico
35. Gustavo Gagliano, Ministry of Health, Uruguay
36. Helen Petousis-Harris, University of Auckland, New Zealand

37. Hugo Dibarboure, Sanofi, Uruguay
38. Ileana Moya, Ministry of Health, Honduras
39. Iván Ríos, MINSAL, Chile
40. Jonathan Zintgraff, INEI-ANLIS "Dr. Carlos G. Malbrán," Argentina
41. Karen Virginia Ovalles Olivares, Ministry of Health, Dominican Republic
42. Lucia Pawloski, CDC, United States of America
43. Lucila Torres, Ministry of Health, El Salvador
44. Luis Ángel Sapián López, Ministry of Health, Mexico
45. Luisa Osiela González Blandón, Ministry of Health, Nicaragua
46. Marco Antonio Gonzáles García, Ministry of Health, Mexico
47. María Andrea Uboldi, Ministry of Health of Santa Fe, Argentina
48. María del Valle Juárez, National Ministry of Health and Social Development, Argentina
49. María Laura Bello, Pfizer, Argentina
50. Maria Lucia Tondella, CDC, United States of America
51. María Seoane, GSK, Argentina
52. Mariano Tristán, INEI-ANLIS "Dr. Carlos G. Malbrán," Argentina
53. Marina Kosacoff, Sanofi, Argentina
54. Martha Ligia Orozco Solórzano, Ministry of Health, Nicaragua
55. Mayra Fredesvinda Canario Céspedes, Ministry of Health, Dominican Republic
56. Mirta Lescano, ANLIS "Dr. Carlos G. Malbrán," Argentina
57. Nathalia Katz, Ministry of Health, Argentina
58. Noelia Speranza, Ministry of Health, Uruguay
59. Pablo Bianculli, Sanofi, Argentina
60. Pamela Cassiday, CDC, United States of America
61. Reynaldo Javier Hernández Mendoza, Ministry of Health, Nicaragua
62. Ricardo Saldaña, Gorgas Institute, Panama
63. Roque López, Secretary of Health, Honduras
64. Rubén Ramóns, Gorgas Institute, Panama
65. Sandra Besada-Lombana, Sanofi Pasteur, Colombia
66. Silvina Neyro, National Ministry of Health, Argentina
67. Sonia Arza, Ministry of Health, Paraguay
68. Stacey Knobler, Sabin Vaccine Institute, United States of America
69. Susan Hariri, CDC, United States of America
70. Veronica Pinell-McNamara, CDC, United States of America
71. Viviana Romanin, Consultant, Argentina
72. Wendy Castillo, Gorgas Institute, Panama