

## Epidemiological situation of pertussis and strategies to control it. Argentina, 2002-2011

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### ABSTRACT

**Introduction.** Pertussis is a challenge for public health. Objectives: To describe pertussis-related morbidity and mortality and immunization coverage for the 2002-2011 period, profile of cases for 2011, and control strategies implemented by the Ministry of Health (MoH) of Argentina. **Methods.** Descriptive, epidemiological surveillance study. Morbidity data were obtained from the National Health Surveillance System, while mortality data were obtained from the MoH's Health Statistics and Information Department and official jurisdictional reports. Administrative immunization coverage was used based on the data provided by the MoH's jurisdictions. The Epi-Info software, version 7.1.2, was used for analysis.

**Results.** The number of reported cases of pertussis increased between 2002 and 2011, reaching its peak in 2011: an incidence of 16 x 100 000 inhabitants, and 76 deaths. Most deaths occurred in infants younger than 1 year old. Immunization coverage achieved at a national level with the third dose and the dose administered at the time of starting primary education was >90%, while the coverage achieved with the first booster dose was 80%-90%. In 2011, 2821 confirmed cases were reported (incidence of 7 x 100 000 inhabitants): 84% in infants <1 year old; 76 deaths: 97% in infants <1 year old (60.5% in infants <2 months old). Among the strategies that were deployed, a total of 906 clinical nodes and 405 laboratory nodes were consolidated; the use of the polymerase chain reaction as a diagnostic method and the differential classification of cases were implemented, and additional vaccine doses were administered.

### Conclusions

- The number of pertussis cases increased between 2002 and 2011; the highest morbidity and mortality occurred in infants younger than 1 year old; immunization coverage reached 80%-90%.
- The highest number of pertussis-related deaths was recorded in 2011.
- The MoH strengthened the epidemiological surveillance and set guidelines for control measures.

**Key words:** pertussis, epidemiological surveillance, pertussis immunization.

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### INTRODUCTION

Pertussis is a highly contagious acute respiratory disease caused by a bacterium called *Bordetella pertussis*. Universal immunization with the pertussis vaccine in children younger than 7 years old is critical for the control of this disease.<sup>1</sup>

Pertussis is, however, a challenge for public health, even in countries with high immunization coverage. Huge efforts have been made worldwide to achieve advances in reporting, diagnosing and preventing this condition. Most cases are described in infants younger than 6 months old, who have the highest rate of hospitalization, morbidity and mortality.<sup>1-4</sup> This is an endemic/epidemic disease, with outbreaks every 3-5 years. As per the World Health Organization's estimates, in 2008 there were 16 million cases of pertussis worldwide (95% in developing countries) and 195 000 deaths were recorded.<sup>5</sup>

The objectives of this study were to describe the evolution of pertussis morbidity and mortality and immunization coverage in the 2002-2011 period, to characterize the epidemiological profile of cases for 2011, and to describe control strategies implemented by the Ministry of Health (MoH) of Argentina during this period.

### METHODS

Descriptive, observational, and epidemiological surveillance study.

Data on morbidity: these were obtained from the National Health Surveillance System in Argentina (*Sistema Nacional de Vigilancia de la Salud de Argentina*, SNVS), agency

that receives reports of notifiable diseases (Law 15465), including pertussis. The SNVS is a network that links the different providers located across the 24 jurisdictions of Argentina (23 provinces plus the Autonomous City of Buenos Aires) in a timely manner so that they can share and exchange information. Internet is the communication support system, and data are hosted in central servers. The SNVS software was developed in modules. For pertussis reporting, there are two modules: the clinical module (C2) and the laboratory module (SIVILA). Both modules collect information from different sources: C2 from the medical practice (outpatient visits, ER Department or hospitalization), while SIVILA collects data from laboratories where samples are obtained, referred to or analyzed. The study population consisted of cases reported to the SNVS from January 1<sup>st</sup>, 2002 to December 31<sup>st</sup>, 2011. Morbidity was analyzed for the 2002-2011 period using cases reported to the C2 module, whereas cases confirmed in 2011 were reviewed by combining C2 and SIVILA modules using the algorithm recommended by the MoH.<sup>6-8</sup>

Data on mortality: these data were obtained from the MoH's Health Statistics and Information Department (*Dirección de Estadística e Información en Salud*, DEIS); and in 2011, official reports from provinces were also used.<sup>9</sup>

Cases were defined and classified as per the MoH's recommendations (see *Annex*).<sup>6,10-12</sup>

Rate estimates were calculated based on population data from the 2001 and 2010 censuses, conducted by the National Statistics and Censuses Institute of Argentina, as applicable. Immunization coverage estimates were calculated based on the administrative coverage (ratio between the number of doses administered and the number of individuals to be vaccinated over 100), according to data provided by jurisdictions participating in the MoH's National Program for the Control of Vaccine-Preventable Diseases (*Programa Nacional de Control de Enfermedades Inmunoprevenibles*, ProNaCEI).

For laboratory detection of *Bordetella pertussis* infections, microbiological (culture) and molecular techniques were used based on the polymerase chain reaction (PCR) performed on nasopharyngeal aspirates (specimens of choice) or nasopharyngeal swabs at the laboratories located across the different jurisdictions of Argentina. The working algorithm was that recommended by the two national reference laboratories (NRLs): the VacSal, corresponding to the School of Exact

Sciences of Universidad Nacional de La Plata, and the National Infectious Disease Institute (*Instituto Nacional de Enfermedades Infecciosas*, INEI) - ANLIS "Dr. Carlos G. Malbrán," as per the recommendations made by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC). Serological assays are performed at the INEI-ANLIS "Dr. Carlos G. Malbrán."

Regan Lowe and Bordet Gengou media supplemented with horse or sheep blood (10%-15% v/v) and plates with and without cephalexin at 40 ug/mL were used for cultures. Plates were seeded with patients' secretions and visually inspected up to 10 days following incubation before being considered negative.<sup>13</sup> End-point PCR (conventional PCR) and/or real-time PCR were used for molecular diagnosis. *Bordetella pertussis* DNA by end-point PCR was detected using the IS481 insertion sequence and the pertussis toxin (ptx) promoter as target sequences.<sup>14,15</sup> For real-time PCR, multiplex and singleplex assays were performed using the CDC's platform.<sup>16</sup>

For serological diagnosis, anti-*Bordetella spp.* antibody titers were assessed using ELISA (with serum samples collected at a 21-day interval), and a difference of two or more titers between both serum samples was considered positive.

Data were analyzed using the Epi Info 7.1.2 software.

## RESULTS

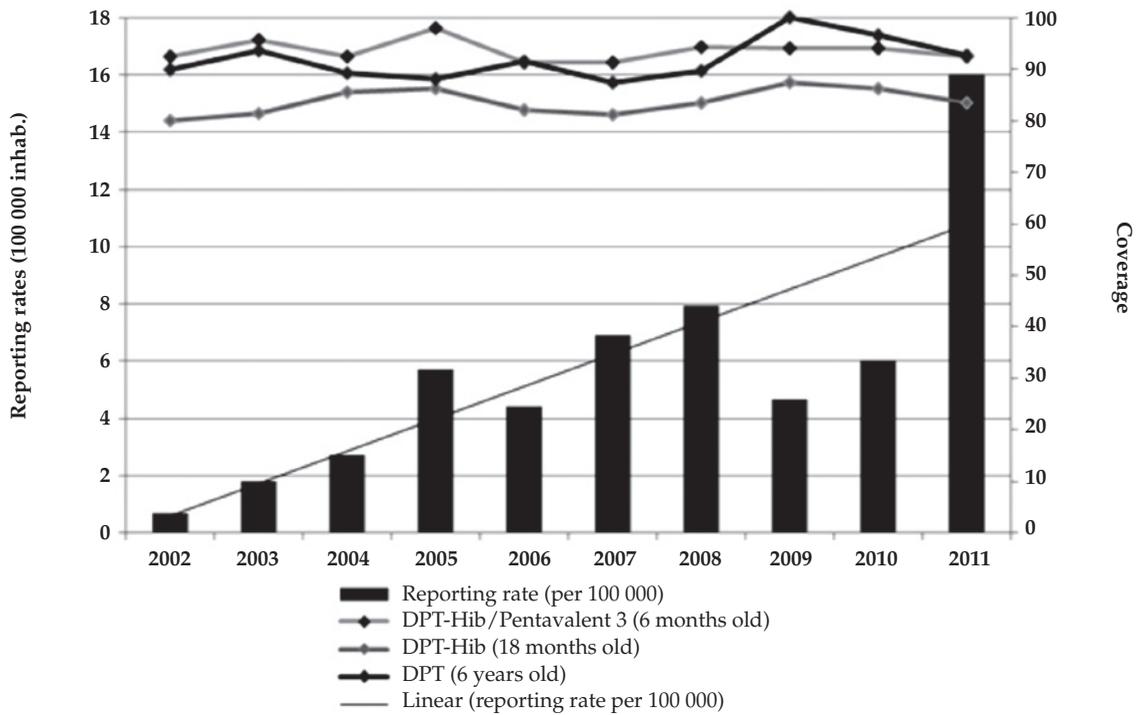
### Epidemiological data for the 2002-2011 period

The number of suspected cases reported showed an increasing trend, reaching the highest rate in 2011: 16 x 100 000 inhabitants (*Figure 1*). The highest number of pertussis-related deaths was recorded in 2011, and all deaths occurred in the group of infants younger than 1 year old, except for five cases in the following age groups: 1-4 years old (3), 25-34 years old (1), and older than 75 years old (1) (*Figure 2*).

### National pertussis immunization coverage for the 2002-2011 period

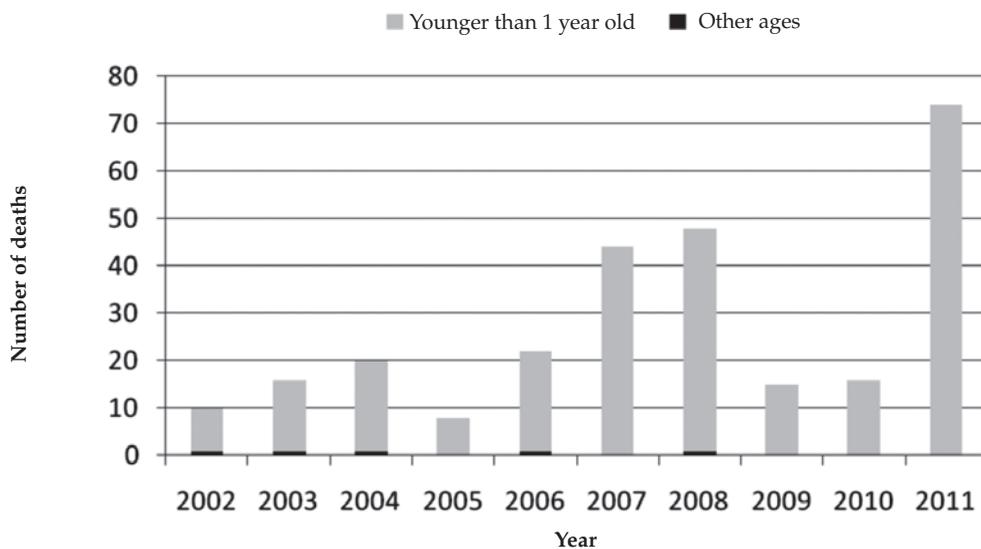
Coverage achieved with the third dose and with the dose administered at the time of starting primary education was over 90%, while the 18-month booster dose achieved 80%-90% coverage (*Figure 1*). The booster dose at 11 years old, introduced in the immunization schedule since 2009, achieved a 54.6% and a 72.8% coverage in 2010 and 2011, respectively.

FIGURE 1. Reporting of pertussis cases and selected immunization coverage. Argentina, 2002-2011



Source: C2-SNVS and National Program for the Control of Vaccine-Preventable Diseases. Ministry of Health of Argentina.

FIGURE 2. Pertussis-related deaths. Argentina, 2002-2011



Source: Health Statistics and Information Department (Dirección de Estadística e Información en Salud, DEIS). Ministry of Health of Argentina.

### Epidemiological data for cases confirmed in 2011

A total of 10 395 suspected cases were reported; of these, 2821 (27%) were classified as confirmed; 1928 had positive lab tests, and 893 were confirmed with the clinical module. Confirmed cases were recorded in all weeks of the year, increasing as of epidemiological week (EW) 36. The minimum number of cases (17) was recorded in EW 19, while the maximum (107) was recorded in EW 44 and 45. The median number of cases reported by week was 46. Ninety-nine percent (2784) of cases included data on age: 84% were infants younger than 1 year old, 54% were younger than 4 months old and 21% were younger than 2 months old (Figure 3). The incidence rate was  $7 \times 100\,000$  inhabitants, while that corresponding to infants younger than 1 year old was  $344 \times 100\,000$  inhabitants (Table 1). Sex distribution was similar: 51% were girls.

Confirmed cases were recorded in all provinces, except in La Rioja. Distribution by province was asymmetrical: the highest incidence rates were recorded in Neuquén, Chaco, Buenos Aires and Santa Fe; in the younger than 1 year old group, the highest incidence was recorded in Chaco, Santa Fe and Buenos Aires (Table 1).

Four provinces had incidence rates higher than the national rate; three of them (Chaco, Buenos Aires and Neuquén) issued outbreak alerts or reported them nationwide.

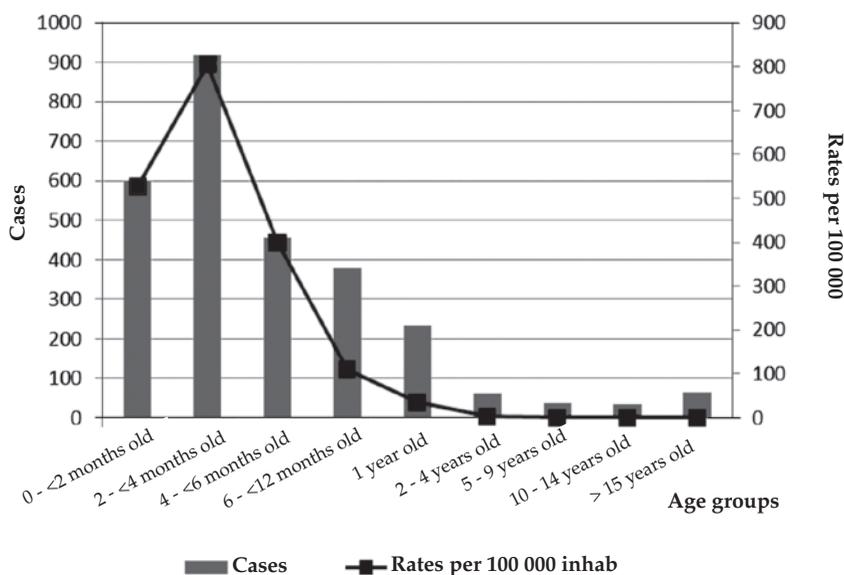
According to data collected by SIVILA, 1181/1928 had immunization information: 426/1181 were younger than 2 months old and had no indication for vaccination as per our national immunization schedule; 290/1181 had been fully vaccinated for their age; and 465/1181 had not completed their immunization schedule for their age.

According to the DEIS, 74 deaths occurred in 2011, all were infants younger than 1 year old. According to the jurisdictional data reported to the ProNaCEI, 76 deaths occurred in 2011: 74 in infants younger than 1 year old, and 2 in 1 year old infants. The case fatality rate was 2.69% of the total number of confirmed cases, and 3.14% among infants younger than 1 year old. Of all deaths, 89.5% (68/76) occurred in infants younger than 4 months old, while 60.5% (46/76) in infants younger than 2 months old. No immunization data was recorded in 15.8% (12/76) of cases; 15.8% (12/76) had an incomplete immunization schedule, while 7.9% (6/76) had completed their immunization schedule (5 infants had received 1 dose, and 1 infant had received 3 doses).

### Strategies implemented by the MoH

- 2003: The SNVS was developed as a network that uses Internet as communication support to be able to establish a timely connection among the different providers working in the health sector. Following its creation, the

FIGURE 3. Pertussis cases and incidence rates by age group. Argentina, 2011



Source: SNVS; National Ministry of Health of Argentina.

TABLE 1. Number of patients, pertussis incidence rates (overall and &lt;1 year old) and immunization coverage by province. Argentina, 2011

Province	Total number of patients*	Incidence rate x 100 000 inhab.*	Patients <1 year old*	Incidence rate <1 year old x 100 000*	DPT-Hib-HB 3 <sup>rd</sup> dose %**	DPT-Hib 4 <sup>th</sup> dose %**
Buenos Aires	1583	10	1329	500	90.3	76.1
Aut. City of Buenos Aires	139	5	118	331	88.5	88.4
Catamarca	23	6	22	340	99.6	81.5
Chaco	114	11	101	514	105.7	86.5
Chubut	16	3	15	161	93.3	82.7
Córdoba	169	5	148	280	89.7	91.9
Corrientes	38	4	37	202	93.7	92.3
Entre Ríos	56	5	43	213	82.4	76.6
Formosa	5	1	5	50	91.4	84.5
Jujuy	11	2	9	73	106.7	105.0
La Pampa	16	5	6	116	94.0	82.2
La Rioja	0	0	0	0	84.5	77.9
Mendoza	52	3	44	140	98.1	82.6
Misiones	39	4	33	136	96.8	95.7
Neuquén	65	12	30	290	102.2	94.8
Río Negro	10	2	9	82	101.1	94.2
Salta	60	5	50	194	96.8	90.1
San Juan	28	4	25	341	95.2	71.3
San Luis	1	0	1	18	99.2	94.1
Santa Cruz	11	4	9	69	97.0	98.7
Santa Fe	292	9	245	501	93.3	88.0
Sgo. del Estero	2	0	2	11	87.0	98.4
Tierra del Fuego	6	5	4	181	92.3	96.1
Tucumán	45	3	37	139	93.1	85.8
Unknown	40	*	33	*	*	*
<b>Total</b>	<b>2821</b>	<b>7</b>	<b>2355</b>	<b>344</b>	<b>92.5</b>	<b>83.6</b>

Source: \* SNVS, Ministry of Health of Argentina. \*\* National Program for the Control of Vaccine-Preventable Diseases.

distribution of participants progressively expanded to the 24 Argentine jurisdictions, reaching 906 clinical nodes and 405 laboratory nodes in 2011, all trained through workshops conducted in each province.

- 2005: PCR microbiological and molecular diagnostic methodologies were transferred from NRLs to the laboratories located in the different country jurisdictions.
- 2006: The C2 reporting mode and frequency were changed from a collective, weekly modality to an individual, immediate reporting.
- 2009: An adult triple bacterial acellular (dTpa) dose was introduced in the national immunization schedule at 11 years old and health workers who are in contact with infants younger than 1 year old.
- 2010: NRLs implemented the real-time PCR diagnostic methodologies transferred by the US Centers for Disease Control and Prevention (CDC), supported by the Latin American Pertussis Project.\*
- 2011: The final epidemiological classification of cases was introduced in C2: suspected, probable, confirmed and ruled-out (such classification had not been previously used in the C2 module).

\* The Latin American Pertussis Project is a collaborative project among the US Centers for Disease Control and Prevention (CDC), the Pan American Health Organization (PAHO), the Sabin Vaccine Institute, and the Latin American Ministries of Health selected to strengthen pertussis surveillance in Latin America.

- 2011: Vaccination was recommended to household members if they lived with newborn infants with a birth weight of less than 1500 grams. At the end of 2011, the ProNaCEI summoned the National Advisory Committee on Immunization in order to agree on a proposal given the epidemiological situation of pertussis in Argentina and it was decided to administer a dTpa dose to pregnant women as of 20 weeks of gestation.

## DISCUSSION

The increase observed in reporting as of 2002 is consistent with what has been reported in the past fifteen years in other countries with high levels of pertussis immunization (Australia, Canada, Italy, Japan, the Netherlands, Switzerland and the United States).<sup>4,17-21</sup> In the United States, outbreaks have been reported in California (2010)<sup>20</sup> and Washington (2012)<sup>21</sup>; while in our region, in Chile<sup>22</sup> and Uruguay<sup>23</sup> the number of reported cases of pertussis increased in 2011.

Most deaths in the 2002-2011 period occurred in infants younger than 1 year old, and this is the group with the highest rate of pertussis-related hospitalization, morbidity and mortality; the highest number of deaths was recorded in 2011.<sup>1-6,24</sup>

Although in the 2002-2011 period, national immunization coverage reached over 80%, it is worth noting that such coverage was administratively recorded which may pose certain errors: misrecording of administered doses (age, dose number, place of residence), estimation based on the doses shipped to the field instead of doses actually administered, or partial information regarding vaccines administered in the private sector.

In 2011, the recorded incidence rate was 7 per 100 000 inhabitants, similar to that reported in the United States (6 per 100 000 inhabitants).<sup>17</sup> Infants younger than 1 year old were the predominant group among confirmed cases (84%), with a specific incidence rate much higher than the overall rate, also consistent with the literature.<sup>1-5,17-23</sup> The low rates recorded for infants and children older than 1 year old may reflect the underdiagnosis of pertussis in other age groups, situation that should be modified to detect potential sources of transmission to infants and changes in the epidemiology of this condition. The epidemics in California (2010)<sup>20</sup> and Washington (2012)<sup>21</sup> resulted in high incidence rates in children aged 10 to 14 years old; as per 2011 United States reports, 38% were children aged 5 to 14 years old,

while 85% corresponded to infants and children older than 1 year old.<sup>17</sup>

In Argentina, pertussis surveillance has been strengthened: the data collection modality was changed from collective to individual data sheets, reporting increased and the system's sensitivity was improved through training workshops conducted in all provinces, new clinical and laboratory nodes were included in the providers' network, specificity on the access to *B. pertussis* diagnostic methods was optimized by NRLs where the implementation of molecular diagnosis in other Argentine laboratories was promoted. PCR was adopted as a confirmatory test given its swiftness and adequate specificity and sensitivity, as it happened in the United States (1996), France and Germany.<sup>4,25-27</sup> Since 2011, based on the diagnostic improvement, SNVS introduced "epidemiological classification" as a variable, and defined pertussis cases as confirmed, probable and ruled-out; as a result, it was possible to estimate pertussis incidence more accurately, which is the main indicator of the immunization impact and is useful to monitor trends.<sup>28</sup> For this reason, there are no historical data of confirmed cases for the 2002-2010 period, since this final classification was not present in the C2 module.

In October 2011, the Advisory Committee on Immunization Practices (ACIP) published a recommendation to administer the dTpa vaccine to pregnant women in the United States,<sup>29</sup> and several studies have demonstrated transplacental transfer of antibodies from mothers to babies.<sup>30</sup> At the end of 2011, the ProNaCEI summoned the National Advisory Committee on Immunization and studied this strategy. Argentina was the first Latin American country where the dTpa vaccine was recommended for pregnant women aiming at reducing mortality in infants younger than 1 year old.<sup>31</sup>

The strengthening of epidemiological surveillance and the implemented immunization strategies<sup>32,33</sup> contrast the increased number of cases, especially considering that immunization coverage in infants and at the time of starting primary education remained stable in the studied period, reaching over 80%. This situation may be the consequence of different factors:

1. The effectiveness of the vaccine to prevent the severe form of pertussis, following the third dose, is estimated to be 70% to 90%.<sup>3</sup>
2. Loss of immunity by the natural disease and induced by the vaccine; the latter may be significantly lost 5 to 8 years after the last

booster dose.<sup>34</sup> The duration of protection may vary depending on whether vaccines used are whole-cell or acellular.<sup>34</sup>

3. Greater specificity and sensitivity of the surveillance system for detecting and confirming cases.
4. Suboptimal immunization rates, with differences that are not reflected in the overall rate of the country.
5. Underestimation of pertussis incidence in adolescents and young adults, who have milder clinical forms of pertussis that act as reservoirs and sources of infection.
6. There are *B. pertussis* strains circulating in the population which are antigenically distinct from those included in the vaccines being administered.<sup>35</sup>

Weaknesses of our work include the lack of historical data regarding confirmed cases in the 2002-2010 period, and limitations in the information on immunization coverage collected through the administrative method; at present, a standardized national registry has been implemented to record administered doses.

Some of the strengths of this study are that it includes an analysis of a 10-year historical series of national data, an epidemiological profile of confirmed cases in 2011, and details on the advances made in pertussis surveillance.

The challenges presented by pertussis are closely related to the complexity of its control. A more effective vaccine conferring long-lasting immunity, should become available. Vaccination of pregnant women was implemented as a strategy to protect younger infants; its effectiveness and safety should be monitored. Meanwhile, existing control measures should not be neglected.

## CONCLUSIONS

- In the 2002-2011 period, reporting of cases of pertussis increased, most deaths occurred in infants younger than 1 year old, and the level of immunization coverage in infants and children at the time of starting primary education reached 80% and 90%.
- In 2011, the distribution of cases in Argentina was heterogeneous, greater morbidity and mortality were observed in infants younger than 4 months old, and more than half of deceased infants were not old enough to have started their primary immunization schedule.
- In the studied period, the MoH strengthened the epidemiological surveillance of pertussis and introduced additional doses of pertussis vaccines. ■

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## ANNEX

### Definitions of pertussis cases used in the 2002-2011 period:

2002-2007 period<sup>10</sup> (weekly numerical reporting modality):

**Suspected case:** Individual with paroxysmal cough for, at least, 2 weeks, no fever, and one of the following symptoms: paroxysmal cough, inspiratory stridor, coughs with vomiting and coughing up spinnable mucus, with no other apparent cause.

**Confirmed case:** Suspected case with isolation of *Bordetella pertussis* on respiratory secretion (specimen) or an epidemiological link with a laboratory confirmed case.

2007-2011 period<sup>6</sup> (individual-immediate reporting modality):

**Suspected case:** Patient with cough for, at least, 14 days, no fever and one of the following symptoms: paroxysmal cough, inspiratory stridor, coughs with vomiting and coughing up spinnable mucus, with no other apparent cause.

In infants younger than 6 months old, paroxysms may not be present, but they may present with apnea and cyanosis. When there is an outbreak, the definition of case should be adjusted.

**Confirmed case:** Suspected case with isolation of *Bordetella pertussis* on respiratory secretion (specimen) or positive PCR or seroconversion between two serum samples collected during the acute phase and during the recovery period, or an epidemiological link with a laboratory confirmed case.

2011<sup>11</sup> (individual-immediate reporting modality):

**Suspected case:** Infants younger than 6 months old. Any acute respiratory tract infection with at least one of the following symptoms: apnea, cyanosis, inspiratory stridor, coughs with vomiting, or paroxysmal cough.

Children older than 6 months old and younger than 11 years old. Cough for 14 or more days accompanied with one or more of the following symptoms: paroxysmal cough, inspiratory stridor, or coughs with vomiting, with no other apparent cause.

Children older than 11 years old. Persistent cough for 14 or more days with no other symptoms.

**Confirmed case:** Patient with respiratory infection and cough of any duration, and positive culture for the causative agent.

Patient with clinical symptoms compatible with pertussis and positive lab results using specific PCR assays.

Patient with clinical symptoms compatible with pertussis and positive lab results (seroconversion) using a specific serological assay.

Patient with clinical symptoms compatible with pertussis and an epidemiological link with a laboratory confirmed case.

**Probable case:** Patient with clinical symptoms compatible with pertussis and no laboratory confirmation (not studied or inconclusive lab results), and no epidemiological link with a laboratory confirmed case.

Patient with incomplete clinical symptoms or insufficient data and a positive PCR or seroconversion result.

**Ruled-out case:** Incomplete clinical symptoms or insufficient data, negative lab result and no epidemiological link with a laboratory confirmed case.