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## Maternal immunization in Argentina: A storyline from the prospective of a middle income country



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### ABSTRACT

The importance of vaccination during pregnancy lies not only in directly protecting vaccinated women, but also by indirectly protecting small infants during the first few months of life. Vaccination against the flu and whooping cough is a priority within the comprehensive care strategy for pregnant women and small infants in Argentina, in the context of transitioning from child vaccination to family vaccination.

In 2011, the flu vaccine was included in the National Immunization Schedule (NIS) as mandatory and free of charge, with the aim of decreasing complications and death due to influenza in the at-risk population in Argentina. The national vaccination coverage attained in pregnant women in the past 4 years (2011–2014) has been satisfactory; 88% coverage was attained in the year this program was introduced to the schedule. In the following years, coverage was maintained at greater than 95%. In February 2012, Argentina became the first country in Latin America to have universal vaccination strategy for pregnant women against whooping cough. This recommendation was implemented throughout the country by vaccination with the diphtheria toxoid, tetanus toxoid, and acellular pertussis (Tdap) vaccine starting at 20 weeks of pregnancy, with the aim of decreasing morbimortality due to whooping cough in infants under 6 months of age. The vaccine was incorporated into the NIS in 2014. More than 1,200,000 doses were applied in this period. Both vaccines showed a suitable safety profile and no serious events were reported.

Argentina is an example of a middle-income country that has been able to implement a successful strategy for primary prevention through vaccines, making it a health policy.

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### 1. Introduction

The Republic of Argentina is part of the Region of the Americas. Located at the southeastern part of the American continent, its continental surface is around 2,780,000 km<sup>2</sup> and it extends 3800 km from north to south and 1425 km from east to west. The territory is quite diverse, including mountainous regions, plateaus, and plains, with extensive climatic and cultural diversity. Organized as a republican, representative, and federal system, it is composed of 24 jurisdictions: 23 provinces and one autonomous city. There are more than 40 million inhabitants [1] and more than 750,000 births are reported each year [2].

Argentina is a middle-income country in which the primary prevention strategy, by way of vaccines, was established as a priority in public health, comprising a policy of state in the last decade.

The health system is composed of three subsectors: public, private, and social security. Nevertheless, all inhabitants in the country are guaranteed universal and free access to health by means of the public system and through the national government. The system guarantees all vaccines included in the NIS, as overseen by the Argentinean State at the more than 8000 public vaccination centers located throughout the country.

The evolution and growth of the NIS in this period has made it one of the most modern and comprehensive in the region [3], with 19 free and mandatory vaccines available universally for all stages of life and in all sectors of the population. It is therefore a robust indicator of social equity and inclusion.

This vision of public health prioritizes the strategy for primary prevention through vaccines, which is reflected by the incorporation of 13 of the 19 vaccines as part of the schedule, and an over

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17-fold increase in the national budget earmarked for vaccination in the last decade.

One of the most important challenges in this period has been the transition from child vaccination to family vaccination, in which the vaccination of pregnant women is a cornerstone. Part of the challenge was the inclusion of the obstetricians and health personnel who take care of pregnant women and the newborns as a part of the strategy. The epidemiological circumstances faced before the start of the strategy of maternal immunization, reflected in the mortality of pregnant women with influenza during 2009–2010 and young infants during the outbreak of pertussis in 2011, aware health personnel and general population, attaching high strategy adherence. This allowed turning a potential threat into an opportunity for reaching satisfactory vaccine coverages.

As pregnancy vaccination takes place at primary care facilities which belong to the Expanded Program on Immunization, and not at the obstetrician office, it is offered to all women even if they did not achieve the obstetrician recommendation.

The importance of vaccination during pregnancy lies not only in directly protecting vaccinated women, but also by indirectly protecting small infants during the first few months of life. This is based on passive immunization generated by the transplacental transfer of maternal antibodies to infants who cannot be vaccinated due to their chronological age. Therefore, flu and whooping cough vaccination is a priority within the comprehensive care strategy of pregnant women and small infants in Argentina.

Safety monitoring in vaccines is also a paramount objective in Argentina. The notification of adverse events following immunization (AEFI) is performed passively. This implies that cases must be spontaneously reported by health effectors. The final evaluation and classification of serious AEFI is performed by the Comisión Nacional de Seguridad en Vacunas (CoNaSeVa) [National Commission for Safety in Vaccines]. It is composed of external consultants who belong to national scientific societies such as the Argentine Society of Pediatrics, the Argentine Society of Infectious Diseases, the Argentine Society for Pediatric Infectious Diseases, the national regulatory agency – Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) – [National Administration of Drugs, Food and Medical Technology], the Pan American Health Organization (PAHO), and representatives of the Dirección Nacional de Control de Enfermedades Inmunoprevenibles (DiNACEI) [National Immunization Program].

## 2. Development

### 2.1. Influenza

Pregnant women infected by the influenza virus present a greater risk of serious progression, hospitalization, and death compared to the rest of the healthy adult population. The product of conception can also be affected, generating intrauterine growth restriction, premature birth, fetal and/or neonatal death [4–7].

Flu vaccination in pregnant women has been shown to be safe and effective in providing protection not only to the woman, but also to the fetus and infant [8,9], through the passive transfer of antibodies through the placenta [10,11].

The available scientific evidence sustains the safety of flu vaccination [12,13] as a preventative measure during pregnancy and shows the cost-effectiveness of the strategy [14] in terms of flu prevention and its complications, both in pregnancy and in the product of conception. The PAHO establishes pregnant women as a priority group among the population in whom flu vaccination is aimed.

#### 2.1.1. Experience in Argentina

The analysis of 332 total deaths occurring in Argentina during the influenza A (H1N1) pandemic in 2009 evidenced that 6%

(20/332) of the deaths occurred in pregnant women and women in the immediate postpartum. Of these, only 47% presented a comorbidity that would determine a greater risk of complications due to the flu, unlike 70% of the non-pregnant women who died [15]; this highlights the vulnerability generated by the condition of being pregnant itself in infection by the flu virus.

The high number of pregnant and post-partum women who died is consistent with international reports that identify pregnancy as an independent risk factor for serious disease and death due to influenza [7,15,16]. The increased vulnerability of this population, demonstrated nationally and internationally [6,15], led to the subsequent definition of a sustained preventative strategy, through the implementation of a free and mandatory flu vaccine for at-risk groups, including pregnant women.

In 2010, the largest national flu vaccination campaign in the history of our country was carried out, with the objective of decreasing mortality due to the influenza A (H1N1) virus; it included 12 million adjuvant monovalent vaccine doses. This strategy was aimed at pregnant women in any trimester of pregnancy, postpartum women, health personnel, children 6–59 months of age and people aged 5–64 years with risk factors (heart, kidney and chronic respiratory diseases, immunocompromised, diabetes, morbid obesity, etc.), and people over 65 years of age [17]. Vaccination coverage in pregnant women that year reached 98.1% (total number of doses applied: 444,397), with an average national coverage for all risk groups of 93.4%. Eighty-five percent (85%) of the target population was vaccinated at least 14 days prior to the start of the winter season. In 2010, there were no cases of death due to confirmed flu based on real time or conventional chain polymerase reaction (CPR), reported in patients belonging to the aforementioned risk groups.

In 2011, under the framework of a comprehensive prevention strategy in respiratory diseases, Argentina incorporated the flu vaccine into the NIS, as free and mandatory for all vulnerable groups (children aged 6–24 months, postpartum women, health personnel, people aged 2–64 years of age with risk factors, and people over the age of 65), including pregnant women in any trimester of pregnancy, with the objective of decreasing complications, hospitalizations, and deaths due to the influenza virus [3,18].

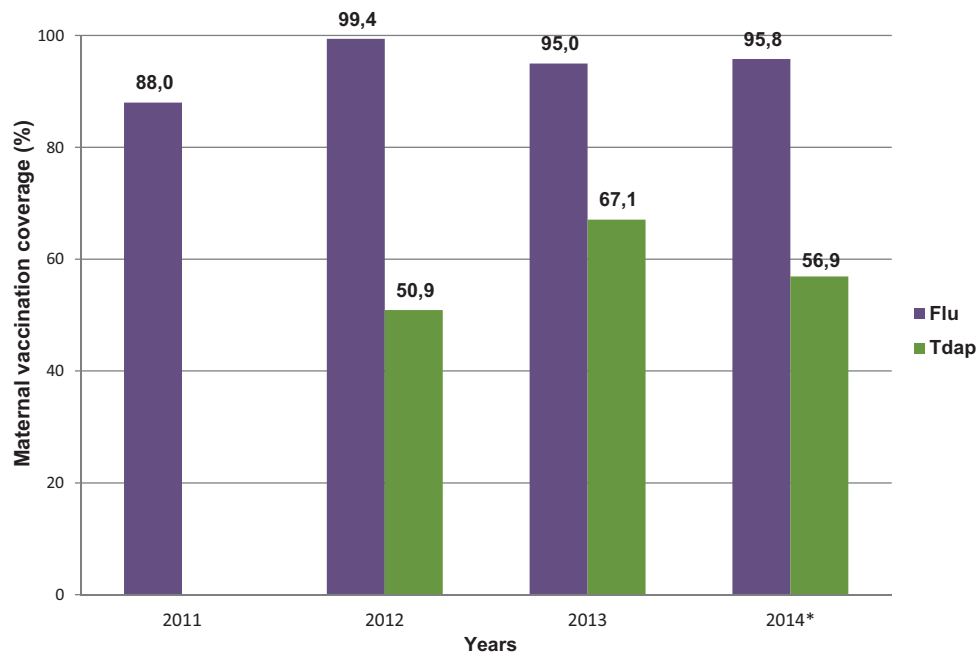
Since its incorporation as part of the NIS in 2011 and through 2014, 1,422,059 flu vaccine doses have been given to pregnant women. The flu vaccines, overseen by the national Ministry of Health in this time period and used in this population, were Agrippal® S1 (in 2011 and 2012) and Viraflu® (in 2013 and 2014); both are inactivated, trivalent vaccines without adjuvants.

The national vaccination coverage attained in this group in the past 4 years (2011–2014) has been satisfactory. Eighty-eight percent (88%) coverage was achieved in the year this program was introduced to the schedule and in the following years, coverage was maintained at greater than 95% [19] (Graph 1). National Immunization Program estimates flu vaccination coverages in pregnant women based on a 50% cohort of live newborns as denominator.

During the 2011–2014 period, 10 AEFI were reported (rate: 0.7/100,000 doses applied [d.a.]), of which 4 were mild events associated with the vaccine (rate: 0.28/100,000 d.a.) and 5 were program errors (rate: 0.35/100,000 d.a.). One case of ascending acute flaccid paralysis was reported and classified as non-conclusive due to the lack of complementary studies. No deaths were recorded due to influenza in promptly vaccinated pregnant women, nor were there any serious adverse events reported in relation to vaccination (Table 1).

#### 2.2. Whooping Cough

Whooping cough is an acute contagious and infectious disease that is vaccine-preventable; it essentially compromises the



**Graph 1.** Flu and Tdap vaccination coverage in pregnant women. Years 2011–2014. Argentina. Source: DiNaCEI [National Immunization Program], National Ministry of Health, Argentina.

respiratory airways. Although it affects all age groups, infants and small children have been shown to be the groups with the greatest morbidity and mortality, which in turn generate high health costs [20].

Even when the disease tends to be not serious in adolescents and young adults, the epidemiological implications are relevant as they may constitute the main source or reservoir of infection, especially for infants under 6 months of age in whom the disease may develop with greater severity [21–23].

In this context, in the last 40 years, several vaccination strategies have been tested, developed, and implemented in Argentina and around the world, with an aim to decrease the incidence of whooping cough in the pediatric population, thus decreasing its morbimortality in the most vulnerable population, defined as infants under one year of age.

These strategies have included direct vaccination of the pediatric population (primary series in infants, with successive reinforcements until school-age), reinforcement doses for adolescents [24], vaccination of postpartum women and cocoon strategy [25,26], and vaccination of health personnel assisting children under 12 months, and those living with neonates that weigh under 1500 g at birth [25,27]. Despite the efforts undertaken, none of these strategies have been able to substantially impact the infant population under 6 months of age, who are unprotected as they are not old enough to receive the primary three-dose series.

In 2011, the US Center for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended the implementation of a vaccination strategy with the Tdap vaccine in pregnant women after the twentieth week of pregnancy, based on scientific evidence that it sustains protection transferred to small infants through the transplacental transfer of antibodies [25].

### 2.2.1. Experience in Argentina

The pediatric vaccination schedule for whooping cough in Argentina includes three doses (2, 4, and 6 months). The first reinforcing dose (15–18 months) [3] was started in the year 1978; a second reinforcing dose (school-age) was added in 1985 using a vaccine entirely composed of whole-cell pertussis [28]. This has resulted in a decrease in the disease, as has also been observed in other parts of the world [29].

While Argentinean national immunization program use whole cell pertussis for children immunization, private subsector which represents less than 5% of population provides both, cellular and acellular pertussis vaccines.

Nevertheless, epidemiological monitoring of whooping cough in Argentina has shown a growing trend in case reports in recent years, which is consistent with reports by other countries with high levels of vaccination coverage against pertussis [30–36] (Graph 2). The reasons for this increase are multifactorial: the high incidence probably made the epidemiological monitoring system more

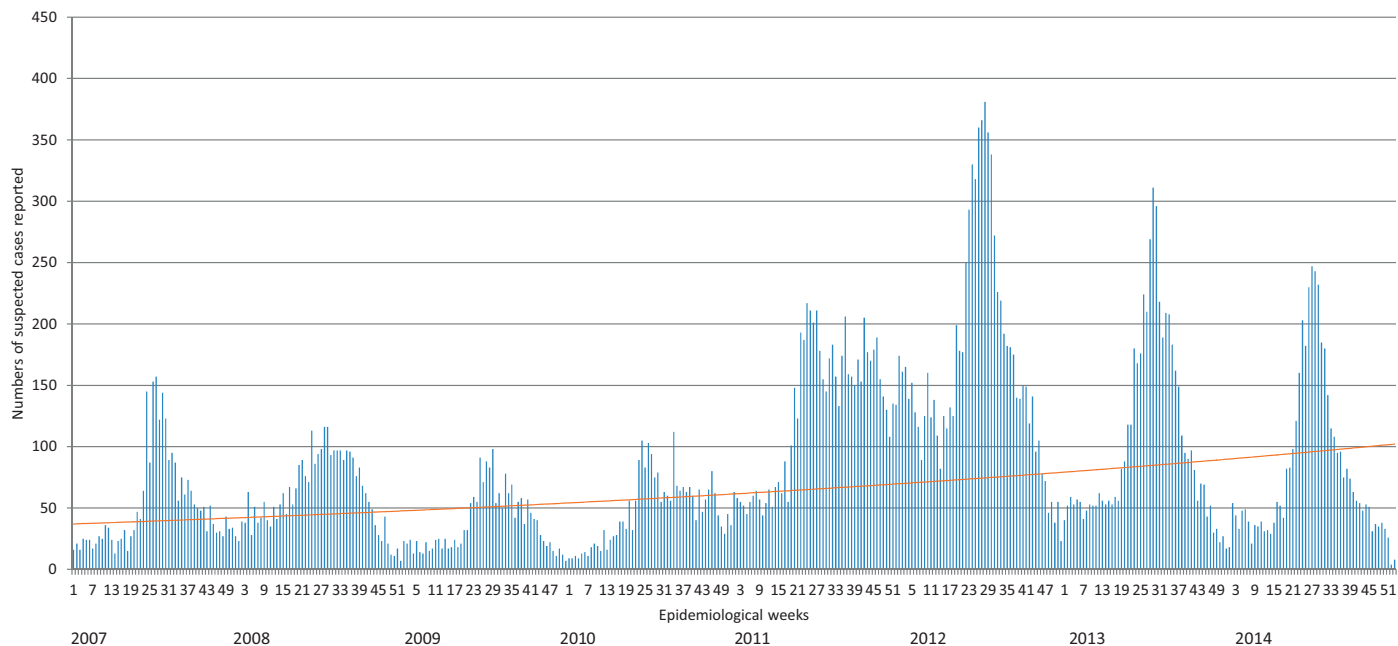
**Table 1**  
Flu and Tdap vaccination coverage in pregnant women. Years 2011–2014. Argentina.

Vaccine Year	Flu				Total	Tdap			
	2011	2012	2013	2014 <sup>a</sup>		2012	2013	2014 <sup>a</sup>	Total
Doses applied to pregnant women	329,697	367,081	381,658	343,623	<b>1,422,059</b>	372,242	470,352	416,129	<b>1,258,723</b>
AEFI reported in pregnant women	0	1	4	5	<b>10</b>	7	8	5	<b>20</b>
AEFI rate in pregnant women <sup>b</sup>	0	0.27	1.05	1.45	<b>0.7</b>	1.88	1.7	1.2	<b>1.59</b>
AEFI vaccine related	0	1	3	0	<b>4</b>	3	2	2	<b>7</b>
AEFI vaccine related rate <sup>b</sup>	0	0.27	0.78	0	<b>0.28</b>	0.81	0.43	0.48	<b>0.57</b>
Program errors	0	0	0	5	<b>5</b>	4	5	3	<b>12</b>
Program errors rate <sup>b</sup>	0	0	0	1.45	<b>0.35</b>	1.07	1.06	0.72	<b>0.95</b>

Source: DiNaCEI [National Immunization Program], National Ministry of Health, Argentina.

<sup>a</sup> 2014 Preliminary data as of 27 February 2015.

<sup>b</sup> Rates calculated for each 100,000 doses applied.



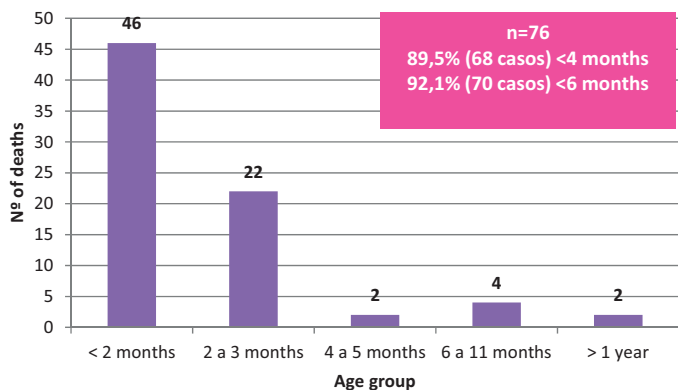
**Graph 2.** Reporting trend for suspected cases of whooping cough. Years 2007–2014. Argentina. Source: DiNaCEI [National Immunization Program], National Ministry of Health, Argentina.

sensitive, there have been advances in terms of the availability of new diagnostic methods, case definitions have been modified enabling stratification by age group (given the differential presentation of the disease in each group), etc.

This increase in case reports and deaths due to whooping cough has been recorded since 2002; by 2011, the largest number of deaths due to whooping cough had been recorded in recent decades. By specifically evaluating the deaths in 2011, a total of 76 cases were reported. Of these, 97.3% (74/76) were under one year of age and 60.5% of them were under 2 months of age [37]. This situation generated the need to propose a prevention strategy for those infants who are too young to be vaccinated (Graph 3).

In 2011, the DiNaCEI [National Immunization Program] of the national Ministry of Health assembled the Comisión Nacional de Inmunizaciones (CoNaIn) [National Commission for Immunizations], a technical advisory group on vaccines in Argentina [38], to agree upon a proposal given the emerging epidemiological situation in the country.

In this context, the need to establish a vaccination strategy against whooping cough in pregnant women was proposed based on the analysis of the national and international scientific evidence



**Graph 3.** Whooping cough, mortality by age group. Year 2011. Argentina. Source: DiNaCEI [National Immunization Program], National Ministry of Health, Argentina.

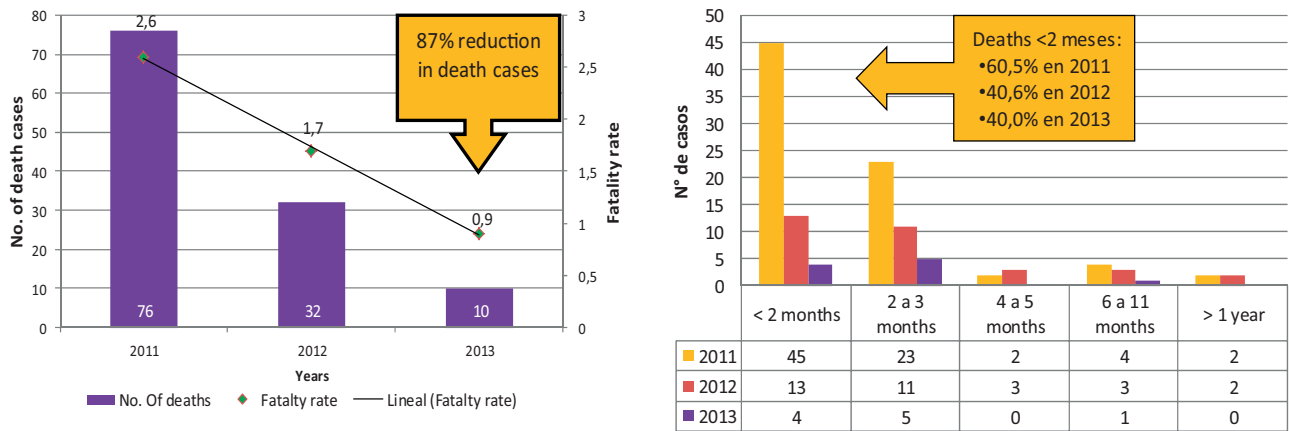
available at the time. This evidence showed low levels of anti-*Bordetella pertussis* antibodies in postpartum women who were not vaccinated during pregnancy as well as low umbilical cord levels [39]. Moreover, there was a greater possibility for transplacental transfer of antibodies to infants in those women who were vaccinated with Tdap during pregnancy. This hypothesis was sustained by demonstrating a significant increase in antibodies to pertussis toxin and fimbriae 2/3 in the children of mothers vaccinated with Tdap during pregnancy, thus providing passive protection to small infants [40–42].

In February 2012, Argentina became the first country in Latin America to have a universal vaccination strategy for pregnant women against whooping cough. This recommendation was implemented throughout the country by free vaccination starting at 20 weeks of pregnancy, with an objective to decrease morbimortality due to whooping cough in infants under 6 months of age.

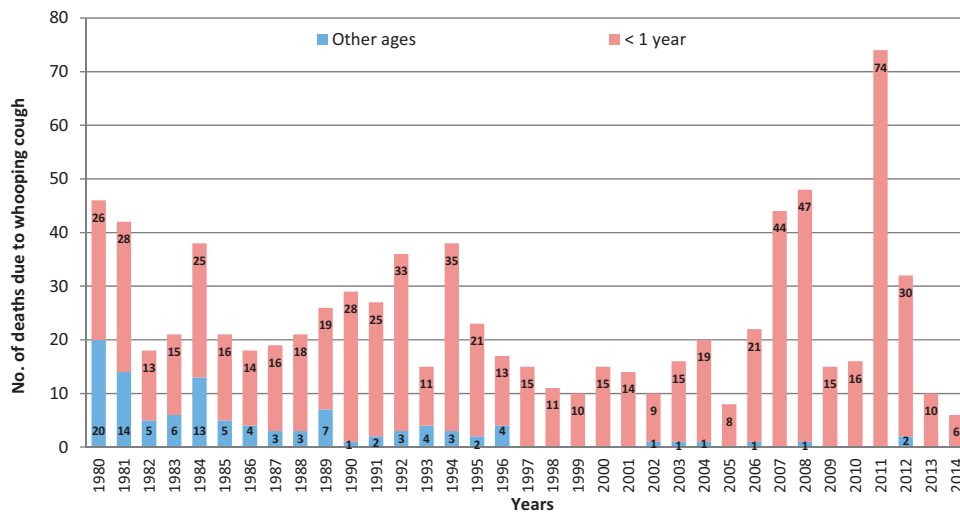
In the year this strategy was started, national coverage for Tdap vaccination in pregnant women reached 51%; by 2013, coverage was greater than 67% (total number of doses applied: 470,352). Preliminary data for vaccination coverage in 2014 show results that reach 56.9% (Graph 1). National Immunization Program estimates Tdap vaccination coverages in pregnant women based on a cohort of live newborns as denominator.

The epidemiological situation was analyzed after this strategy was implemented, finding an 87% decrease in absolute mortality. There was a 69.9% decrease in the overall fatality rate (95% confidence interval [CI] = 50.38–81.81%;  $p < 0.001$ ) and an 83.67% decrease in infants under 2 months of age (95% CI = 63.92–92.61%;  $p < 0.001$ ) between 2011 and 2013. Of the deaths during this period, 89.8% (106/118) were under 6 months of age; of the 104 children with anti-pertussis vaccination data, only 3 had completed three vaccine doses (complete basic schedule)[43] (Graph 4). In 2014, the lowest number of deaths due to whooping cough in the last 40 years ( $n = 6$ ) was registered, representing a 92% reduction compared to 2011 (Graph 5).

The evaluation of this strategy, 2 years after its recommendation and implementation (2012–2013), led it to be incorporated into the NIS in 2014 as free and mandatory for all pregnant residents in the country [3,44], having demonstrated a significant decrease



**Graph 4.** Whooping cough: mortality and fatality by age group. Years 2011–2013. Argentina. Source: DiNaCEI [National Immunization Program], National Ministry of Health, Argentina.



**Graph 5.** Cases of deaths due to whooping cough, 1980–2014. Argentina. Source: Office of Statics and Health Information and Jurisdiction Reports.

in mortality and fatality due to whooping cough in small infants in Argentina.

Since this strategy was started in 2012, 1,258,723 total doses of the Tdap vaccine have been administered to pregnant women. The Tdap vaccines provided by the Ministry of Health in this period and used for the pregnant population alternated between Boostrix® and Adacel®.

A total of 20 AEFI were reported in the 2012–2014 period (rate: 1.59/100,000 d.a.). Of these, 7 were mild and related to the vaccine (2 episodes of rash after vaccination and 5 local reactions with local pain, redness and swelling). Sixty percent (60%) corresponded to program errors ( $n=12$ ; rate: 0.95/100,000 d.a.). These were mainly episodes in which the vaccine was administered before the recommended gestational age (20 weeks pregnant) and pregnant women were revaccinated with Tdap (strategy not recommended in the country during the period analyzed). None of them presented subsequent complications. There were no serious or fatal events reported (Table 1).

### 3. Conclusions

Argentina is an example of a middle-income country that has been able to implement a successful strategy for primary prevention through vaccines, making it a health policy. To attain this

objective, a joint effort between health teams is key, from the operational level to the central level, as is the support of scientific societies and opinion leaders, the commitment of communication media, and community awareness in terms of requesting the right to vaccination.

Argentina was able to expedite a vaccination policy in pregnant women, attaining satisfactory coverage in the vaccines prioritized during this stage of life. Both vaccines are now included in the NIS, financed entirely by the national government.

In Argentina, vaccination in pregnant women is a sustained strategy, with high coverage. This is the first national study to show the data regarding the safety of the flu vaccine since it was incorporated into the NIS. To our knowledge, it is also the first report in the Region of the Americas with safety data for the Tdap vaccine administered to pregnant women. Both vaccines presented a suitable safety profile. No serious adverse effects have been reported since the strategy was implemented as free and mandatory.

Data obtained to date for the flu and Tdap vaccines are promising and are based on the continuity of a successful vaccination strategy during pregnancy in Argentina.

Our primary concern is to share the Argentina experience in order to encourage other countries with similar social, economic, and cultural characteristics to call upon all the necessary players to undertake the challenge of prioritizing vaccination during



pregnancy, given the high impact that primary prevention has through vaccines in two vulnerable populations such as pregnant women and small infants.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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