

# Preventing Pertussis in the Early Infant: Development and Results of a Prenatal Vaccination Program

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## Article Information

Received: 25 Jan 16

Accepted: 28 Feb 2016

Plagiarism software: Turnitin

## Keywords:

Pertussis disease,  
*Bordetella pertussis*,  
Vaccination in pregnancy,  
Whooping cough,  
Tdap vaccine,  
Early infants,  
Cocoon strategy



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## INTRODUCTION

Incidence of Pertussis has increased in Spain in the last 20 years with an important outbreak in 2011.<sup>1</sup> Non vaccinated infants (usually under 3 months of age) are at special risk of serious complications. Actually, 39 of 40 related deaths due to pertussis in Spain (2000-2014) were in infants younger than 3 months.<sup>2</sup> This susceptibility is due to low levels of immunity against *Bordetella pertussis* in pregnant women even when they have been correctly vaccinated in their childhood.<sup>3</sup>

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530/ami.2016.2.17	

## ABSTRACT

**Introduction:** Cases of Pertussis increase every year with special morbidity and mortality in early infants. The objective was to evaluate results of a program of vaccination of pregnant women launched in our center in 2013.

**Methods:** This is an observational retrospective study. We reviewed all cases of Pertussis disease in our center (2011-2015) and compared clinical data between two groups of age: Early infants (<3 months of age) and Other Groups (>3 months). We also compared perinatal events in vaccinated versus non vaccinated pregnant women.

**Results:** During the period 2011-2015, 63 cases (9 in Early Infants; 54 Other Groups) were treated. All cases in Early Infants required hospitalization (100% vs. 3,70%;  $p < 0,05$ ) with more days of hospitalization (10,2 days vs. 0,36 days;  $p < 0,05$ ) and need of oxygen (66,67% vs. 3,70%;  $p < 0,05$ ). No differences were seen in response to Azithromycin (87,5% vs. 97,91%;  $p > 0,05$ ) nor in incidence in close relatives (44,44% vs. 27,45%;  $p > 0,05$ ). No differences were observed in Perinatal events in vaccinated vs. non vaccinated in terms of duration of pregnancy (279 days vs. 278 days;  $p > 0,05$ ), weight at birth (3290gr vs. 3220gr;  $p > 0,05$ ), admission at NICU (1,58% vs. 1,87%;  $p > 0,05$ ) and Apgar test score <7 at 5 minutes (0,27% vs. 0%;  $p > 0,05$ ). Proportion in early infants affected lowered from 40% in 2011 to 3,85% in 2015.

**Conclusions:** Maternal immunization with Tdap vaccine seems to be a good strategy to reduce incidence of pertussis in the offspring. Additional measures such as vaccinating relatives should be considered.

Due to the rise of cases of whooping cough, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practice (ACIP) recommended in 2008 immunization in immediate postpartum for every mothers and close contacts. In 2012, updated guidelines recommended to vaccinate every pregnant women during pregnancy.<sup>4</sup> The objective was to stimulate production of antibodies against pertussis and to transfer them through the placenta to the fetus in order to protect him the early months of life until he would receive first dose of Tdap vaccine.

Our Hospital is a private institution serving more than 2500 deliveries per year located in the nearby of Barcelona which is the most important city in the north of Spain. Guidelines for Pertussis vaccination in pregnant women were approved

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in our Department in 2013 following international recommendations. In 2014, the Regional Ministry of Health endorsed the ACIP guidelines and vaccination was offered to all pregnant women in the region.

In this paper we review incidence of pertussis disease in Early infants and Other Groups of age in our Hospital before and after the Protocol was approved, focusing on morbidity and clinical aspects of early infants. We describe also the development of the program of vaccination in the population we serve.

## METHODS

This was a retrospective observational study conducted in Hospital General de Catalonia reviewing all cases of whooping cough recorded from year 2011 to 2015. From October 2013, a booster of Tdap was offered to all women between 27 and 36 weeks of pregnancy. Pertussis is a notifiable disease in Spain; we collected all cases of pertussis declared from our Hospital in this period of time. Cases were stratified by age in two groups: Early infants (defined as younger than 3 months) and Other groups (any patient not included in the first group). Outcomes of interest were: hospitalization, days at hospital, need for oxygen, response to single regime of antibiotic, diagnosed cases among patients relatives and death.

Safety aspects of the vaccines were observed in order to rule out possible perinatal adverse effects. Specifically, we compared duration of pregnancy, neonatal weight at birth, admission at Neonatal Intensive care Unit (NICU) and Apgar score <7 at 5 minutes in babies whose mothers have received immunization vs. those whose mothers had not received it. For the data analysis we used Wilcoxon test to compare quantitative variables and Fisher test for qualitative variables. Analysis was performed using R Commander free-software version 2.2-1 (Vienna, Austria). Statistical significance was set at  $p < 0.05$ .

## RESULTS

In the period of study 359 cases were declared. Only 63 (17,55%) of them resulted to be positive for *B. pertussis*. Infection occurred in young infants under 3 months in 9 cases (14,28%). All cases in the Early infants group required hospitalization vs. only two cases in the Other group (100% vs. 3,70%;  $p < 0,05$ ) with more days of hospitalization on average (10,2 days vs. 0,36 days;  $p < 0,05$ ). Five patients in the first group needed oxygen therapy vs. one patient in the second group (66,67% vs. 3,70%,  $p < 0,05$ ). One baby in the Early infants group was readmitted to Hospital because of persistent cough and cyanosis. One patient in Other Groups (37 year) had convulsions due to persistent cough. No statistical differences were seen in response to Azithromycin

(87,5% vs. 97,91%;  $p > 0,05$ ) nor in incidence in close relatives (44,44% vs. 27,45%;  $p > 0,05$ ) (Table 1).

Protocol for protection of newborns against pertussis was launched in October 2013. Since then, 1306 vaccines have been administrated in our institution: 868 (98,57%) to pregnant women in the third month of pregnancy and 19 (1,43%) to close relatives. In this period, proportion of cases of pertussis in the early infant has lowered from 40% in 2011 to 12,5% in 2014 and to 3,85% in 2015 (Table 2).

No differences were observed in terms of duration of pregnancy (279 days vs. 278 days;  $p > 0,05$ ), weight at birth (3290 vs. 3220;  $p > 0,05$ ), admission at NICU (1,58% vs. 1,87%;  $p > 0,05$ ) nor in Apgar test score <7 at 5 minutes (0,27% vs. 0%;  $p > 0,05$ ). No severe adverse maternal side effects were recorded (Table 3).

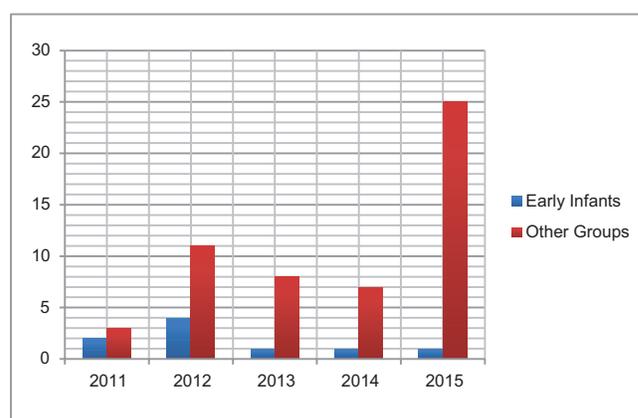


Figure 1: Evolution of cases by groups of age

Table 1: Morbidity of pertussis in early infants vs. other groups

	Infants ≤ 3 months	Other groups	p
Hospitalization	9/9	2/54	<0,05
Days in hospital	10	0,36	<0,05
Oxygen	6/9	2/54	<0,05
Response to single regime	7/9	49/54	ns
Affected relatives	4/9	14/54	ns

Table 2: Evolution of cases by groups of age

Year	2011	2012	2013	2014	2015
Early infants	2	4	1	1	1
Other groups	3	11	8	7	25
Total cases	5	15	9	8	23

Table 3: Perinatal events in vaccinated vs. non vaccinated

	Vaccinated	Non vaccinated	p
Duration	279	278	ns
Weight	3290	3320	ns
NICU (%)	1,58	1,87	ns
Apgar 5 minutes <7 (%)	0,27	0	ns

## DISCUSSION

The aim of this paper was to describe the evolution of the incidence of pertussis in young infant during the first months after the implementation of maternal Tdap immunization in our Hospital. Previous strategies recommending maternal postpartum vaccination had not demonstrated to be efficient<sup>5</sup> so in 2011ACIP modified guidelines including indication of Tdap between 27 and 36 weeks of pregnancy.<sup>4</sup>

Pertussis disease in the young infant causes more morbidity than in other ages. Different strategies have been proposed to reduce exposure of these babies to the infection.<sup>6</sup> Maternal immunization seems to have been the most effective one as it stimulates production of antibodies that will pass actively through the placenta protecting the offspring in the first weeks of life.

In our series, we have observed a continuous global increase in cases of pertussis in the last years (Figure 1). Several reasons have been exposed in the literature to explain this trend.<sup>7</sup> Although vaccination against pertussis in childhood has achieved high coverage in our country, protection provided by Tdap is not permanent.

Existing evidence demonstrates that mothers correctly immunized in their childhood have low levels of antibodies in the moment of delivery. Although these antibodies are transported to the fetal circulation, they don't reach a protective level.<sup>8,3</sup>

Vaccination during pregnancy boosts production of IgG against *Bordetella pertussis*.<sup>9</sup> These immunoglobulins should confer protection during the first weeks of infant's life until the first dose of the vaccine is received (at six weeks in the Catalan vaccination official calendar).

Other concerning issue about pertussis vaccination in pregnancy is the possibility of harmful effects on perinatal results. Our data don't show any differences in duration of pregnancy, weight at birth and admission at NICU. Our findings are similar to previous publications where safety of vaccination against pertussis in pregnancy is also confirmed.<sup>10-11</sup>

Our study shows a stable trend of observed number of cases in the Early infants group since 2013 (1 case per year). Percentage of cases in early infants has therefore decreased from 40% in 2011 to 3,85% in 2015. We are not sure whether this stabilization may only be attributed to our pregnant women's vaccination program but we can argue that number of cases in the Other group has continued increasing every year. Awareness about the importance of the infection

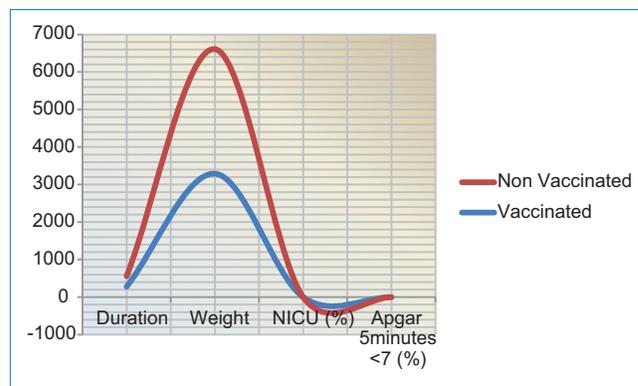


Figure 2: Perinatal events

probably has improved other preventive measures such as correct vaccination, early treatment and prophylaxis of adults with suspicious symptoms and isolation of babies from possible contacts in their environment.

To our knowledge, this is the first publication reporting results of maternal vaccination in our region. However, our study has some weak points. The target population was limited to our hospital, so conclusions can't be applied to the general population but provisional results published by the Regional Department of Health (Catalonia endorsed ACIP recommendations in January 2014) are very similar in terms of decrease in number of early infants affected. Although number in vaccines administrated increased every month, very few of them (1,43%) were given to close relatives as proposed by the cocoon vaccination strategy.<sup>12-13</sup>

## CONCLUSION

In 2013, we launched a program of maternal pertussis vaccination achieving a high coverage rate among women delivering in our Hospital. The vaccine administration demonstrated to be safe (no differences in adverse perinatal events nor maternal effects were observed) and efficient for the prevention of new cases in early infants despite the rise in cases in the other groups of age. We think that maternal vaccination before delivery is one of the most important strategies to develop but not the only. Immunization of people who are very close to the offspring (cocooning strategy) should be the next objective in order to reduce exposure to *Bordetella pertussis*.

## RECOMMENDATIONS

Future prospective studies should be conducted in order to verify these findings in general population and to control the safety of vaccination program in pregnant women and their newborns.

## ACKNOWLEDGMENT

Eva Borrás, from the Department of Health of Catalonia, helped with some epidemiological data.

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**How to cite this article:** Acosta J, Benages C, Díaz MA, Xiberta M, Muñoz F. Preventing pertussis in the early infant: development and results of a prenatal vaccination program. *Acta Medica International.* 2016;3(2):78-81.

**Source of Support:** Nil, **Conflict of Interest:** None declared.