Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effect of maternal immunization against pertussis in Medellin and the metropolitan area, Colombia, 2016–2017

Doracelly Hincapié-Palacio [a,*], María Cristina Hoyos [a], Jesus Ochoa [a], Nilton Montoya [a], Diego García [b], Elkin Osorio [b], Pertussis Working Group [1]

[a] University of Antioquia, National School of Public Health "Héctor Abad Gómez", Theoretical Epidemiology, Epidemiology Group, Medellín, Colombia
[b] Ministry of Health and Social Protection, Bogotá D.C, Colombia

ARTICLE INFO

Article history:
Received 12 December 2017
Received in revised form 11 April 2018
Accepted 4 May 2018
Available online xxxx

Keywords:
Seroepidemiological study
Vaccination
Pregnant
Whooping cough
Colombia
Latin America

ABSTRACT

Background: In 2013, pertussis immunization (Tdap) for pregnant women was implemented in Colombia to protect newborns in response to increased pertussis incidence.
Objective: To assess the effect of Tdap maternal immunization on the concentration of mother/umbilical cord antibodies and the occurrence of pertussis in infants during their first six months of life.
Methods: A cohort study in eight randomly selected hospitals in Medellin and metropolitan area of Antioquia, Colombia was conducted in 2015–2016. IgG PT antibody levels in paired maternal and umbilical cord sera were measured from 805 mothers immunized recruited during labor and 200 mothers recruited during the prenatal care before immunization and followed until delivery. Antibodies were analyzed by commercial ELISA kits. 896 infants were followed to detect acute respiratory infections and paroxysms of coughing, inspiratory whoop, apnea, cyanosis or post-tussive vomiting. For laboratory confirmation, *B. pertussis*- specific real time PCR was performed.
Results: We observed a high prevalence of titers >100 IU/mL (mother: 18.40% [95% CI 16–21%]; umbilical cord: 23.1% [95% CI 19.2–27.4%]), positive correlation of umbilical cord and maternal antibodies, higher antibody concentration in vaccinated than in non-vaccinated mothers and significant difference in antibody levels before and after vaccination (Wilcoxon test p = 0.000). The trans placental transport ratio was higher if the mother was vaccinated between 26 and 30 weeks of pregnancy and maximum eight weeks before delivery. Two cases of pertussis were confirmed in infants (incidence of 1.99 per 1000).
Conclusion: The expected effect of Tdap maternal vaccination against pertussis was observed.

1. Introduction

Pertussis is a transmissible respiratory disease caused by *B. pertussis* and occasionally by *B. parapertussis, B. holmesii or B. bronchyséptica* [1].

Worldwide, pertussis is an important cause of morbidity and mortality with 294,000 deaths estimated each year in young children, mainly among unvaccinated infants [2]. In recent years, an increase in incidence has been reported in developed and developing countries despite high vaccination coverage [3,4].

In Colombia, pertussis is cyclical with increases in incidence every two to three years. The highest incidence rate in the last 20 years was observed in 2012 (8.5 cases per 100,000 inhabitants), with cases reported primarily among adolescents and adults [5].

Preventing pertussis has been a target of routine vaccination programs in many countries since the 1940 s. In Colombia, the triple whole-cell bacterial (DTwP) vaccine was introduced in 1980 and in 2001 the pentavalent vaccine was included in the Colombian vaccination program. The current schedule includes three doses of the pentavalent vaccine at 2, 4 and 6 months of age and two DTwP boosters at 18 months and 5 years of age. In response to the national outbreak, in 2013 the Colombian Advisory Committee on Immunization Practice recommended a tetanus toxoide-diphteria toxoid – acellular pertussis (Tdap) vaccine for pregnant women after 21st weeks gestation but later expanded this recommendation after the 26th weeks gestation [5,6]. This strategy seeks

* Corresponding author at: Street 62 Num 52-59, Medellín, Colombia.
E-mail address: doracelly.hincapie@udea.edu.co (D. Hincapié-Palacio).
[1] Pertussis Working group "Salvacuna: a project for the prevention of pertussis" http://www.epiteorica.com: University of Antioquia: Marcela Acevedo Zapata, Catalina González Vélez, Paula Andrea Pérez Estrada, Adriana Molina Giraldo. Sectional Secretary of Health and Social Protection of Antioquia: Blanca Isabel Restrepo V. Marcela Arrubla Villa. Adriana Patricia Echeverri Ríos. Secretary of Health of Medellín: Rita E. Almanza, Denise González Ortiz, Eduardo Santacruz S, Norma Elena Orrego Zapata. "ESE" General Hospital of Medellín: Daniel Arango.

https://doi.org/10.1016/j.vaccine.2018.05.020
0264-410X/

to reduce the susceptibility of the infants especially in the first two months of life before the beginning of the regular vaccination schedule [4].

The purpose of this study was to determine the effect of this vaccination strategy on the concentration of mother/cord IgG PT antibodies, to establish the trans placental transport ratio of antibodies and to estimate whether antibody maternal could protect infants through the first six months of life.

2. Methods

A cohort study was designed to assess the prevalence of IgG PT antibodies of paired maternal delivery – umbilical cord samples. Infants of these mothers were followed from birth through their first six months of life to monitor for pertussis incidence.

A random representative sample of eight from 17 urban hospitals, that attended childbirths, were randomly selected from Medellín and nine municipalities in the metropolitan area (“Aburrá Valley” subregion). In order to enroll mothers across a wide array of hospitals, we stratified hospitals by number of delivery discharges in 2015, incidence of pertussis, vaccination coverage with Tdap, and the number of people with health insurance coverage.

Two cohorts of mothers were recruited from December 2015 to April 2016, in order to obtain a minimum of 500 vaccinated and 500 non-vaccinated mothers needed to estimate the prevalence and average of IgG PT antibodies from mothers and umbilical cord blood (minimum value of 2, maximum of 360, variance of 7569 to 8010, 95% confidence and potency of 80%) [7–9]. Cohort 1 consisted of mothers who had been hospitalized for delivery care at one of eight hospitals randomly selected. Cohort 2 was a convenience sample of mothers who attended prenatal care at two of these hospitals. They were recruited in the outpatient service before receiving the pertussis vaccination and subsequently were followed until delivery.

Mothers were eligible for inclusion in the study if the delivery occurred at $\geq$37 weeks gestation. Exclusion criteria were one or more of the following: the mother had documented having multiple gestations, the delivery occurred at <37 weeks gestation, having fever in the previous 72 h (chorioamnionitis, sepsis), having admission in an intensive care unit, or if the mother were at an advanced stage of labor.

Written informed consent was obtained from participants. A survey collected the following data: demographics (age, health insurance), medical data (obstetric gynecological history, previous maternal morbidity, use of steroid drugs), date of previous vaccine administration (Tdap or DTwP), adverse reactions to vaccination (if any), date of gestational Tdap administration, gestational age, date of delivery and any history of pertussis-like illness of mothers and relatives. Vaccination status was obtained by reviewing the individuals' vaccination records and verified with the centralized database of the Expanded Immunization Program (“PAIweb”).

The mothers of both cohorts were vaccinated as part of the routine vaccination program, independently from the research team.

IgG –PT antibodies were measured by the SERION ELISA for classic Bordetella pertussis Toxin IgG, Virion Serion (sensitivity of 89/78 and specificity of 70/85) [10] in paired maternal delivery – umbilical cord samples. The blood samples were processed at the Department of Public Health Laboratory – Sectional Secretary of Health and Social Protection of Antioquia. The procedures and cut-off point recommended by the manufacturer were used. Results >100 IU/mL were indicative of recent contact with *B. pertussis* and values below 40 IU/mL served to exclude the possibility of recent infection [10].

To estimate the incidence of pertussis, infants of both cohorts, were followed during their first six months of life. Home visits were conducted by trained nurses every two months (2–4–6 months of age). Additionally, parents were instructed to fill up use of symptoms diaries about occurrence of any respiratory symptoms and to inform it to the study nurse during their scheduled visit and during a monthly telephone survey.

The physician from the local pertussis surveillance team conducted a home visit to collect data and confirm each probable pertussis case. Pertussis cases were confirmed if they met the case definition and had a positive laboratory confirmation (PCR), were epidemiology linked to a laboratory-confirmed case, or were confirmed by clinical criteria as indicated in the national surveillance guidelines [5]. A *B. pertussis*-specific real time PCR was performed systematically on nasopharyngeal aspirates from all infants aged <6 months meeting the clinical case definition: all acute respiratory infections with at least one of the following symptoms: paroxysms of coughing, inspiratory whoop, apnea, cyanosis or post-tussive vomiting.

The primary outcome of interest was anti-IgG PT level. Serum IgG values to PT were reported as geometric mean concentrations (GMC) and prevalence with 95% confidence intervals. Demographic characteristics of included and not included mothers from the cohort 1 were compared to assess possible selection bias. The statistical significance of the difference between antibodies before and after vaccination of the cohort 2 was calculated with the Wilcoxon test. Spearman correlation was performed to analyze the relationship between IgG to PT from mother and umbilical cord blood. P-values of 0.05 were considered as statistically significant. The trans placental transport ratio of IgG PT pertussis antibodies was measured as the ratio of umbilical cord blood to maternal antibodies by age and the time between gestational Tdap administration and delivery. Pertussis incidence was estimated for infants of both cohorts and according to the pertussis vaccination status of all mothers.

The data were analyzed using SPSS ® version 23 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

Ethics approval for this study was obtained from The National School of Public Health “Héctor Abad Gómez” at the University of Antioquia ethics board (session 129-15 Oct. 2015) and the ethics/research boards in each hospital.

3. Results

A total of 1005 mothers, 805 in cohort 1 and 200 in cohort 2, were enrolled. Ninety-six percent of mothers in cohort 1 and 80% of cohort 2 were recruited at delivery. A total of 896 children (89.15%) were followed from birth through their first six months of life (Fig. 1).

Mothers included and not included in cohort 1 had similar demographic characteristics. There were no significant differences in the age or health insurance distribution (Supplementary Table).

Both cohorts were composed of mothers with similar characteristics to the population of origin. Most mothers were between 18 and 34 years of age (range 13–43). Ninety-five percent of mothers resided in the urban area.

No differences were found in the gyneco-obstetrics history and past maternal morbidity between the two cohorts. Less than 8.1% (81/1005) of the mothers had a diagnosis of past maternal morbidity, and 7.8% (78/1005) had obstetric comorbidities (p = 0.11).

The mean gestational age at delivery was 38.7 weeks (SD ± 1.2). Fourteen mothers of cohort 2 had delivery before 37 weeks. Of the total of mothers, 6% (n = 12) had three or more deliveries. The use of steroid drugs was reported among 14 (1.7%) mothers in cohort 1 and one mother in cohort 2.

3.1. Tdap vaccination

A total of 745 (74.13%) vaccinated and 260 (25.87%) non-vaccinated mothers were included in the study (Table 1).

Please cite this article in press as: Hincapié-Palacio D et al. Effect of maternal immunization against pertussis in Medellin and the metropolitan area, Colombia, 2016–2017. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.020