



The effectiveness of maternal pertussis vaccination in protecting newborn infants in Brazil: A case-control study



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ARTICLE INFO

Article history:

Received 6 December 2018

Received in revised form 6 March 2019

Accepted 21 March 2019

Available online 1 April 2019

Keywords:

Bordetella pertussis
Maternal immunization
Pertussis vaccine
Case-control study
Brazil

ABSTRACT

Introduction: In 2014, the Brazilian Ministry of Health (MoH) recommended Tdap to pregnant women in response to a significant increase in the incidence of pertussis among infants. The present study assessed the effectiveness of maternal immunization in preventing pertussis in infants.

Methods: An unmatched case-control study was undertaken in São Paulo State, Brazil from February 2015 to July 2016. Cases were infants aged <8 weeks at onset of pertussis reported to the Surveillance System and confirmed by real-time polymerase chain reaction or culture. Four to six healthy infants were selected as controls per case from birth certificates in the Information System on Live Births database. General characteristics and mother's vaccination status were compared between cases and controls. The vaccine effectiveness (VE) was calculated as 1 – odds ratio (OR). For the adjusted VE, the OR was calculated using logistic regression analysis.

Results: Forty-two cases and 248 controls were enrolled in the study. Mothers of 8 cases (19.1%) and 143 controls (57.4%) were vaccinated during pregnancy, resulting in an unadjusted VE of 82.6% (95% confidence interval [CI], 60.8–92.3%). The VE was unchanged after adjusting for maternal age and monthly household income.

Conclusion: Maternal pertussis vaccination during pregnancy was effective in protecting infants aged <8 weeks from pertussis.

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Abbreviations: CI, confidence interval; DTaP, diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine; DTwP, diphtheria toxoid, tetanus toxoid, and whole cells pertussis vaccine; DTwP, Hib-HBV – diphtheria tetanus-whole-cell pertussis + Haemophilus influenzae b + hepatitis B vaccine; MoH, Brazilian Ministry of Health; OR, odds ratio; SINAN, National Notifiable Diseases Information System database (Sistema de Informação de Agravos de Notificação); SINASC, Information System on Live Births database (Sistema de Informação sobre Nascidos Vivos); Tdap, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis; VE, vaccine effectiveness.

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1. Introduction

Pertussis is a highly contagious respiratory disease caused by *Bordetella pertussis* (1, 2). The disease most commonly affects infants and young children and can induce uncontrollable violent coughing for long periods [1,2]. Globally, the childhood vaccination with pertussis-containing vaccines has reduced the incidence of the disease [2,3].

In Brazil, the current routine childhood vaccination schedule includes three doses of the diphtheria-tetanus-whole-cell pertussis + *Haemophilus influenzae* b + hepatitis B (DTwP-Hib-HBV)

pentavalent vaccine, given at 2, 4 and 6 months of age, followed by two booster doses of DTwP at 15 months and 4 years of age [4,5]. DTwP vaccine coverage reached the national goal of 95% during the 1990s, resulting in a great decrease of the number of pertussis cases. However, a significant increase in pertussis incidence rates was observed in this country from 2011 to 2014 [4,5]. As a result, the Brazilian Ministry of Health (MoH) recommended Tdap be given to women between the 27th and 36th week of pregnancy, in 2014 [4,5]. In 2017, the MoH extended the recommendation to the 20th week of pregnancy [4].

Considering the limited data available concerning effectiveness of maternal pertussis vaccination when vaccination during pregnancy was introduced into the national vaccination schedule, the Immunization Program of São Paulo State, Brazil, developed studies of the effectiveness and immunogenicity of Tdap in pregnant women for post implementation evaluation.

The present study is an unmatched case-control evaluation aimed to assess the effectiveness of maternal Tdap vaccination during pregnancy in preventing pertussis in infants younger than 2 months of age in São Paulo State, Brazil.

2. Methods

2.1. Settings and study population

São Paulo State has a population of 45.5 million accounting one-fifth of Brazilian population. This is the wealthiest state of Brazil and responsible for one-third of national gross domestic product. The study included under-2-months of age cases and controls from the metropolitan areas of São Paulo, Sorocaba and Campinas. These metropolitan regions together have a population of 33.4 million inhabitants (74.2% of the State population) [6].

2.2. Case and control definitions

A case of pertussis was defined as clinically compatible cough illness (≥ 2 weeks of paroxysmal cough, inspiratory gasp, and/or post-tussive vomiting) in an infant aged < 8 weeks at disease onset, born between February 1st 2015 and May 31st 2016, with laboratory confirmation (culture or real time polymerase chain reaction) of pertussis. The upper age limit of eight weeks was chosen because this is the age at which primary immunizations are routinely offered. The cases were identified through the National Notifiable Diseases Information System database (*Sistema de Informação de Agravos de Notificação*, SINAN).

A list of possible controls born on February 1st 2015 or after was obtained from the Information System on Live Births database (*Sistema de Informação sobre Nascidos Vivos*, SINASC). This system gathers data from birth certificates throughout the country. For each enrolled infant case, 4 to 6 control infants were recruited from birth certificates of infants resident in the same city as the case. We selected controls who were born within one month before or after the reference case.

Cases and controls were eligible for enrollment if they were resident in São Paulo State, ≥ 37 weeks gestational age, and weight > 2500 g at birth. Exclusion criteria were: (1) having received immunosuppressive drugs or corticosteroids at a dose greater than 2 mg/kg /day for more than 15 days; (2) having a primary or acquired immunodeficiency; (3) having heart, neurological or renal disease; (4) having a chromosomal anomaly or serious congenital disease; or (5) having previously received transfusion of blood or blood products. Control infants were additionally considered ineligible if they had had a pertussis diagnosis before 2 months of age.

The mother or other the legal guardian for each case was contacted and a home visit was scheduled. The mother or other legal

guardian for each control was approached directly at the residences, because the registration of live births does not record telephone numbers. If a control could not be found, the field research team moved to the next control on the list.

The legal guardians of cases and controls were interviewed face-to-face using a standard form, with sociodemographic, clinical and epidemiological variables and the vaccination status of the mother and child. The immunization status of the mother was determined based on the prenatal report or vaccination card. The mother was considered vaccinated if she had received Tdap ≥ 21 days before delivery. Vaccination in pregnancy was coded as a binary variable of either having received vaccine or not having received vaccine. The number of completed weeks' gestation at the time of vaccination was also recorded. Cases and controls were excluded from the analysis if maternal pertussis vaccination was not known, to avoid possible misclassification of the exposure. An infant was considered enrolled when the maternal interview and the infant and maternal vaccine history were all completed.

2.3. Statistical analysis and sample-size estimation

This is an unmatched case-control study. General characteristics and the mother's vaccination status were compared between cases and controls. An unadjusted VE was calculated as $VE = 1 - OR$, where OR is the odds ratio for vaccination in pregnancy, between cases and controls. For the adjusted VE, the OR was calculated using logistic regression analysis. The multiple logistic regression model was performed based on variables statistically associated with the outcome, using a stepwise forward strategy. The variables that presented a $p \leq 0.2$ in the bivariate analysis were selected for inclusion in the multivariable model and those that had $p < 0.05$ were retained in the final multivariate model. Epi-info (version 3.5.3) and Stata13 software were used for this analysis.

The minimal sample-size estimation was 29 cases and 115 controls, considering a non-paired study, 50% of vaccinated mothers among controls, four controls for each case (4:1), significance level of 0.05, power of the 80%, odds ratio of 0.25 and two-tailed test.

2.4. Ethics

The study was approved by the Research Ethics Committee of Instituto Adolfo Lutz, license number 37581114.0.0000.0059. Participating mothers or legal guardians provided written informed consent.

3. Results

During the study period of February 1st 2015 to July 31st 2016, 53 (54.6%) of 97 pertussis cases aged < 2 months in São Paulo State were from the metropolitan areas of São Paulo, Sorocaba and Campinas. A total of 42 incident, laboratory-confirmed cases of pertussis was enrolled in the study. Among the 11 excluded cases, 9 were not found at the addresses registered in SINASC, 2 were < 37 weeks' gestational age or weight < 2500 g at birth, and one mother refused to participate in the study. As controls, 249 infants were enrolled.

Among the cases, 8 (19.0%) had a mother younger than 20 years of age; 26 (61.9%) had a mother who was non-white; 28 (66.7%) lived in a household with a monthly income $< R\$1.576$ and 9 (21.4%) had a mother with < 7 prenatal care visits (Table 1). Both cases and controls had a mean gestational age at birth of 39 weeks.

Of all vaccinated mothers of cases and controls (151), 91.7% had received the Tdap vaccine at ≥ 27 weeks gestation. The mean of gestation age at vaccination was 31.1 weeks (range 18.0–37.0)

Table 1
Characteristics of cases and controls.

Variables	Cases (N = 42)		Controls (N = 249)		Total (N = 291)		p
	n	%	n	%	n	%	
Male	18	42.9	126	50.6	144	49.5	0.353
Breastfeeding							
Exclusive	6	14.2	55	22.1	61	21.0	0.495
With complement	18	42.9	92	36.9	110	37.8	
No	18	42.9	102	41.0	120	41.2	
Maternal Tdap vaccination situation							
Vaccinated	8	19.1	143	57.4	151	51.9	<0.001
Unvaccinated	34	80.9	106	42.6	140	48.1	
Mother's age (years)							
<20	8	19.0	21	8.4	29	10.0	0.033
≥20	34	81.1	228	91.6	262	90.0	
Mother's race							
White	16	38.1	132	53.0	148	50.9	0.074
Non-white	26	61.9	117	47.0	143	49.1	
Maternal schooling							
<8 years	16	38.1	66	26.5	66	26.5	0.123
≥8 years	26	61.9	183	73.5	183	73.5	
Monthly household income							
<R\$ 1.576	28	66.7	98	39.7	126	43.6	0.001
≥R\$1.576	14	33.3	149	60.3	163	56.4	
Number of maternal prenatal visits							
<7	9	21.4	37	14.9	46	15.8	0.281
≥7	33	78.6	212	85.1	245	84.2	
Birth weight (g)							
2500–3000	14	33.4	62	24.9	76	26.1	0.368
3001–3500	19	45.2	111	44.6	130	44.7	
≥3501	9	21.4	76	30.5	85	29.2	

Table 2
Cases and controls distributed by maternal Tdap vaccination situation.

History of maternal pertussis vaccination	Cases (N = 42)		Controls (N = 249)		Unadjusted VE % (95% CI)	Adjusted VE % (95% CI) ^a
	n	%	n	%		
Vaccinated	8	19.1	143	57.4	82.6 (60.8–92.3)	80.7 (55.9–91.6)
Unvaccinated	34	80.9	106	42.6	1	1

^a Adjusted for maternal age (OR = 0.97; 95% CI = 0.92–1.02) and household income (OR = 0.38; 95% CI = 0.18–0.82).

for mothers of cases and 30.4 weeks (range 10.0–40.0) for mothers of controls ($p = 0.637$).

Of the 42 cases included in the analysis, 8 (19.1%) had a mother who received Tdap during pregnancy. Compared with 143 of 249 mothers of control (57.4%) (Table 2). The unadjusted OR for vaccination in pregnancy was 0.17 (95% CI, 0.08–0.39), giving an unadjusted VE of 82.6% (95% CI, 60.8%–92.3%). After adjustment for maternal age and household income, the VE was similar at 80.7% (95% CI, 55.9%–91.6%).

4. Discussion

We found a high level of effectiveness (83%) for maternal Tdap vaccination during pregnancy in preventing pertussis in infants before their first dose of DTwP, a result consistent with those of earlier studies. An assessment of the maternal vaccination program in England showed a vaccine effectiveness of 91% (95% CI, 84 to 95%) among infants <3 months of age [7], while another case-control in England estimated that maternal vaccination with Tdap had an effectiveness of 93% in protecting infants [8]. A case-control study in the US found an effectiveness of 77.7% for Tdap vaccination during the third trimester [9], while an study in the US found a VE of 91% in the first two months of life, also in addition to demonstrating that maternal Tdap vaccination confers a significant amount of protection against pertussis over the entire first year of life (69%), even after infants are immunized with DTaP [10].

A considerable increase in the incidence of pertussis was observed in Brazil between 2011 and 2014, in spite of high DTwP vaccine coverage among children. The national incidence of pertussis in 2010 and 2014 was 0.3 and 4.2 per 100,000, respectively. In São Paulo state, the overall incidence of pertussis was <0.8 per 100,000 in 2010, rising to 2.20 per 100,000 in 2011 and reaching 5.06 per 100,000 in 2014 [4]. The incidence of pertussis then dropped to a pre-epidemic levels in 2015 (1.5 and 1.3 in Brazil and São Paulo State, respectively) [4]. The vaccination of pregnant women with Tdap was introduced in November 2014, and vaccine coverage reached 61% in São Paulo State in 2015 [4]. The observed decrease in the incidence of pertussis in 2015 occurred among all age groups, including adolescents and adults [4], suggesting that the maternal vaccination program alone cannot explain the drop in the number of cases among all age groups, as it is not thought to provide herd protection [4]. However, a decrease in the proportion of reported cases among infants <2 months of age was observed in 2015, in comparison to a significant increase of the proportion of reported cases in infants aged 6 to 11 months, suggesting an impact of the maternal vaccination program on young infants [4].

A positive impact of maternal vaccination among infants aged <2 months of age represents a positive impact as pertussis mortality, as most pertussis' related deaths occur in this age group [2,5,11]. In Brazil, from 2007 to 2014, infants aged ≤2 months are 34.5% of all reported pertussis cases and 75% of all reported pertussis' related deaths [5].

Our sample size was not adequate to detect a difference in VE between doses administered in the third-trimester and doses administered earlier in pregnancy, once most Tdap-vaccinated mothers in our evaluation received vaccine during the recommended third trimester. There are recent evidences that transplacental transfer of maternal pertussis antibodies may be maximized by vaccination during the second or early third trimester. [12–14].

Our study has some limitations. First, the number of pertussis cases included was lower than expected, which did not allow us to compare the effectiveness of vaccination at different gestational ages. Second, we included only those controls whose mothers or legal guardians were found at home at the time of a household visit, resulting a loss of 30%. Third, the maternal immunization status of all cases and controls was checked using prenatal report or mothers' vaccination card, but error in the vaccination record could result in misclassification of vaccination status of cases and controls. Fourth, we did not assess severity of pertussis cases, as data were collected from interviews of mothers or other guardians. Finally, the study was conducted only in metropolitan areas of São Paulo State, which limits the extrapolation of the results the rest of Brazil or even to the entire state of São Paulo.

Our findings add to the growing body of evidence that vaccination during pregnancy is highly effective in protecting infants from pertussis and that it may have substantial impact on morbidity and mortality in infants too young to have been vaccinated.

Funding source

This work was supported by the Fundo Especial de Saúde para Imunização em Massa e Controle de Doenças (FESIMA), Instituto Adolfo Lutz, Coordenadoria de Controle de Doenças, Secretaria de Estado da Saúde de São Paulo – SP, and the São Paulo Research Foundation, FAPESP [2015/16157-1].

Contributors' statement

Drs Fernandes, Sato, Vaz-de-Lima, de Brito, Luna, Sato, and Dr de Castilho conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Sato, Rodrigues, Dr Carvalhanas, Ramos, and Leite selected possible cases and controls in the databases.

Dr Fernandes, Dr Sato, Dr Vaz-de-Lima, Rodrigues, Dr Carvalhanas, Dr Sato and Ramos designed the data collection instruments.

Dr Fernandes, Ramos, Leite, Dr Carvalhanas, and Dr Sato coordinated the fieldwork.

Drs Fernandes, Sato, de Brito, Luna, and de Castilho carried out the statistical analyses.

Rodrigues, Leite, Dr Carvalhanas, and Ramos reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgments

We would like to thank the Fundo Especial de Saúde para Imunização em Massa e Controle de Doenças (FESIMA), Instituto

Adolfo Lutz, Coordenadoria de Controle de Doenças, and the São Paulo Research Foundation, FAPESP [2015/16157-1] for supporting this study. The Maternal Pertussis Vaccine Working Group also consists of: Edna M. de Souza, Jane H. Atobe, Carmem A F Oliveira (*Centro de Imunologia, Instituto Adolfo Lutz*), José Cassio de Moraes (Faculdade de Ciências Médicas da Santa Casa de São Paulo), Jacqueline Correia Gaspar (Núcleo de Informação em Vigilância Epidemiológica, Centro de Vigilância Epidemiológica “Prof. Alexandre Vranjac”, Coordenadoria de Controle de Doenças da Secretaria de Estado da Saúde de São Paulo), and Sílvia Silva de Oliveira (Coordenadoria de Vigilância em Saúde, Secretaria Municipal de Saúde de São Paulo). The authors would like to thank Cátia Martinez and Carlos Alfredo Anzelotti Pereira Tavares (Centro de Informações Estratégicas em Saúde – CIVS, Coordenadoria de Controle de Doenças – CCD) for assisting in the selection of controls. The Authors thank Arthur L. Reingold for his valuable comments.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

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