

Claudia Regina Cachulo Lopes¹

Eitan N Berezin^{II}

Risk and protective factors of acute respiratory infections in infants

ABSTRACT

OBJECTIVE: To analyze the effectiveness of maternal pneumococcal polysaccharide vaccine and the risk and protective factors for acute respiratory infections in infants.

METHODS: Nested cross-sectional study of a clinical trial evaluating children of 139 women selected in a public prenatal care unit in the municipality of São Paulo, Southeastern Brazil, from 2005 to 2006. Subjects were randomly assigned to three groups: non-immunized (n=46); immunized with pneumococcal polysaccharide vaccine in the last trimester of pregnancy (n=42); and immunized with the vaccine immediately after childbirth (n=45). Infants were followed up for infections presumably caused by pneumococcus at the age of three and six months and nasopharyngeal samples were collected. Risk factors such as smokers living in the same household, siblings and exclusive maternal breastfeeding were investigated.

RESULTS: The pneumococcal polysaccharide vaccine did not provide protection against pneumococcus infections. However, exclusive maternal breastfeeding until the age of six months protected infants against respiratory infections (OR= 7.331). Pneumococcal nasopharyngeal colonization at the age of three or six months increased the likelihood of occurrence of respiratory infections (OR= 2.792).

CONCLUSIONS: Exclusive breastfeeding for six months protects infants against presumably pneumococcal infections regardless of pneumococcal vaccination.

DESCRIPTORS: Pneumococcal Vaccines, administration & dosage. Vaccination. Pregnant Women. Prenatal Care. Immunity, Maternally-Acquired. Infant Welfare. Pneumococcal Infections, prevention & control. Cross-Sectional Studies.

¹ Programa de Pós-graduação em Pediatria. Santa Casa de Misericórdia de São Paulo. São Paulo, SP, Brasil

^{II} Departamento de Pediatria. Faculdade de Ciências Médicas. Santa Casa de Misericórdia de São Paulo. São Paulo, SP, Brasil

Correspondence:

Claudia Regina Cachulo Lopes
Hospital São Luiz Gonzaga
R. Michel Ouchana, 94- Jacanã
02276-140 São Paulo, SP, Brasil
E-mail: claudiarcachulo@terra.com.br

INTRODUCTION

Acute respiratory infections are a major cause of morbidity in children especially in infants younger than six months. Nasopharyngeal colonization with *Streptococcus pneumoniae* can lead to invasive respiratory infections.⁴ The main pathogenic bacteria of acute respiratory infections is pneumococcus.

In developing countries it is estimated that pneumococcus causes more than 1 million death a year in children under five, mostly due to pneumonia,^{11,15,16,22} at a rate of two children dying per hour in Latin America. In 2007, pneumococcal disease killed 8,000 children in Brazil.^a

The main predisposing factors for respiratory infections are: attendance of child day care centers, passive smoking, children of mothers with low schooling, overcrowding, and early termination of breastfeeding. Infants with these factors are more likely to develop respiratory infections, particularly *S. pneumoniae* infections.⁴

In Brazil, 30% of children under two are colonized with *S. pneumoniae*.^{1,4,10,21} The rate of pneumococcal nasopharyngeal colonization (PNC) in infants attending child day care centers is about 60%.¹⁷ A recent study showed that children exposed to smoking were more likely to have their nasopharynx colonized with acute middle ear infection pathogens (*Moraxella catarrhalis*, *Haemophilus influenzae*, and pneumococcus).²⁰

Immunization of children against *S. pneumoniae* with conjugated vaccines proved effective against PNC. However, these are still costly vaccines for widespread use in health services. Immunization of pregnant woman against *S. pneumoniae* aimed to increase antibodies in infants may be an effective approach to protect these children during the first months of life.^{13,16}

The objective of the present study was to analyze the effectiveness of maternal pneumococcal polysaccharide vaccine and to assess risk and protective factors for acute respiratory infections in infants.

METHODS

Nested cross-sectional study of a clinical trial evaluating children of 139 women selected in a public prenatal care unit in São Paulo, Southeastern Brazil, from May 2005 to January 2006. Pregnant women were consecutively interviewed as they arrived at the clinic and included in the study after they agreed to participate.

There were examined data from a larger study^b conducted with pregnant women and children to assess the effectiveness of a 23-valent pneumococcal polysaccharide vaccine (PPV) offered during pregnancy. Pregnant women after week 28 of pregnancy without any major obstetrical conditions were randomly assigned to three groups during a routine low-risk prenatal care visit. Of 150 pregnant women recruited, 139 infants were followed up at the age of three months. There were excluded from the analysis six women as they did not complete all infant visits at six months of age and 133 mother-infant pairs remained in the study. Of these, 87 mothers had been immunized with PPV either during pregnancy or puerperium and 46 had not been immunized. During the initial interview, information on risk factors for pneumococcal infection, number of people and children (under five) living in the same household, presence of smokers and attendance of a child day care center was collected.

Infants were underwent monthly evaluations during the first six months of life. During a routine pediatric visit they were checked for diseases such as acute middle ear infection (MEI), broncopneumonia (BCP) or any other invasive disease caused by *S. pneumoniae*. Diagnosis of MEI was clinically made by a physician in the emergency room. Diagnosis of BCP was clinically made but required radiological confirmation showing lobar, segmental or interstitial images of pneumonia. The principal investigator monitored most diagnoses and clinical follow-up of infants.

During the visits the mothers were asked about their infant's feeding, especially regarding exclusive breastfeeding and attendance of a day care center, which are both known risk and protective factors for pneumococcal disease, respectively.^{14,18} In addition to these variables, antibiotic use was assessed, even when there was no definite diagnosis.

The association between risk and/or protective factors and pneumococcal disease (BCP/MEI) or nasopharyngeal colonization was assessed using the chi-square test or Fisher's exact test. A 5% significance level was set. A multiple logistic regression analysis was performed to assess the combined effect of risk factors on disease occurrence. Variables with $p < 0.20$ in the bivariate analysis were included in the multivariate model. The backward maximum likelihood method was used for selecting variables that might be better predictors of the outcome. Odds ratios (OR) and their related 95% confidence intervals were estimated in the final model.

^a Andrus J. Sabin Vaccine Institute. Proceedings of the Second Regional Pneumococcal Symposium; 2006 Dec 12-14; São Paulo, BR. São Paulo: Sabin Vaccine Institute; 2006.

^b The study "Avaliação da vacina pneumocócica polissacarídica em gestantes" was developed at the Department of Pediatrics, School of Medical Sciences of Santa Casa de São Paulo, and funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Epi Info 3.1 and SPSS 13.0 were used in the statistical analyses.

The study was approved by the Research Ethics Committee of Santa Casa de São Paulo. All subjects signed a free informed consent form.

RESULTS

No difference of disease prevalence was found between immunized and non-immunized women (Table 1).

The rate of PNC in infants at the age of three and six months was 17.2% (24/139), and 16.5% (22/133), respectively. The prevalence of PNC in at least one time point at three or six months was 27% (36/133). The rate of penicillin resistance was 25% (6/24) and 40.9% (9/22) at three and six months of age, respectively.

The association between nasopharyngeal colonization at three months and disease (MEI/BCP) was not statistically significant ($p=0.34$). At six months of age, 23 infants had disease, of which 34.8% (8) were colonized while 12.7% of those did not have disease were colonized ($p=0.015$). No infant developed invasive disease.

Table 1 shows the distribution of children with and without disease (MEI/BCP), by risk and protective factors, during the first six months of life.

The associations between disease and the following risk or protective factors were significant: smokers and children under five living in the household; nasopharyngeal

colonization by a resistant strain at the age of three or six months; and no exclusive breastfeeding by the age of three or six months.

In the multivariate analysis, the variable "living with other children under five" ($p<0.20$) was added. For adjusting the logistic regression model the variable "disease (MEI/BCP) by the age of six month" was selected.

The following variables were selected through the backward method: nasopharyngeal colonization at three or six months of age; living with other children under five; and no exclusive breastfeeding.

Children who were not on exclusive breastfeeding by six months of age were found to be seven times more likely to develop disease (Table 2). Nasopharyngeal colonization with *S. pneumoniae* at three or six months of age increased the risk of disease (MEI/BCP) by about three folds. Living with other children under five in the same household also increased the likelihood of disease (OR= 2.69, 95% CI: 1.00;7.27).

The model was sensitive as it correctly detected 97.3% (107/110) of children who did not develop disease. However, it was not specific as only 13% (3/23) of those children who developed disease were correctly identified.

No statistically significant association was seen between antibiotic use by the age of three months and colonization with resistant *S. pneumoniae* by the age of three ($p=0.59$) or six months ($p=0.13$).

Table 1. Distribution of children with and without disease at 6 months of age, by risk or protective factors and diagnosis of acute middle ear infection and pneumonia. São Paulo, Southeastern Brazil, 2005–2006.

Risk or protective factors	Disease by the age of 6 months (n=23)		No disease by the age of 6 months (n=110)		p
	%	n	%	n	
Smokers in the household (55/133)	60.9	14	37.3	41	0.032
Children attending a day care center and living in the household (16/133)	13	3	11.8	13	0.550
Children under 5 living in the household (47/133)	52.2	12	31.8	35	0.054
More than 5 people living in the household (39/133)	34.8	8	28.2	31	0.344
Attendance of a day care center by the age of 6 months (17/133)	8.7	2	13.6	15	0.403
Maternal illiteracy (5/133)	4.3	1	3.6	4	0.509
Nasopharyngeal colonization by the age of 3 or 6 months (36/133)	43.5	10	23.6	26	0.048
Nasopharyngeal colonization with a resistant strain by the age 3 or 6 months (13/133)	21.7	5	7.3	8	0.049
Exclusive breastfeeding for 3 months (89/133)	43.5	10	71.8	79	0.014
Exclusive breastfeeding for 6 months (65/133)	17.4	4	55.5	61	0.001
PSV23 vaccine during pregnancy (42/133)	16.7	7	83.3	35	0.990
PSV23 vaccine during puerperium (45/133)	17.8	8	82.2	37	0.990
No immunization (46/133)	17.4	8	82.6	38	0.990

Table 2. Odds ratio and confidence intervals of explanatory variables in the multiple logistic regression model among children diagnosed with acute middle ear infection and pneumonia. São Paulo, Southeastern Brazil, 2005–2006.

Variable	OR	95% IC
Children under 5 living in the household	2.69	1.00; 7.27
Nasopharyngeal colonization by the age of 3 or 6 months	2.79	1.00; 7.76
No exclusive breastfeeding for 6 months	7.33	2.19; 24.51

DISCUSSION

Among strategies to reduce pneumococcal disease during childhood, the single proven effective measure is the administration of a conjugated vaccine against *S. pneumoniae*.^{2,3,6,8,9,19}

Exclusive breastfeeding for six months was the single factor that contributed most to prevent pneumococcal disease leading to a 7-fold reduction in the risk of respiratory disease. Nasopharyngeal colonization with *S. pneumoniae* was a predisposing factor for disease development. It occurs before disease and interventions that can reduce nasopharyngeal colonization might reduce the likelihood of disease. However, a study conducted in Pittsburg (US) reported that exclusive breastfeeding did not have an effect on PNC.¹⁴

Maternal immunization during pregnancy might be a prevention strategy. However, consistent with other studies,^{5,7,12,16} our study did not find vaccination of pregnant women effective to protect against colonization or infection.

Penicillin resistance of *S. pneumoniae* has increased worldwide and its main predisposing factor is antibiotic use. We did not find any statistically significant association between antibiotic use by the age of three months and nasopharyngeal colonization with resistant pneumococcus at three or six months of age.

Exclusive breastfeeding proved to be a major factor for reducing colonization and thus reducing pneumococcal disease during the first six months of life.

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