

RESPIRATORY DISEASES IN CHILDREN AFTER THE ADMINISTRATION OF 10 – VALENT PNEUMOCOCCAL CONJUGATE VACCINE

DOENÇAS RESPIRATÓRIAS EM CRIANÇAS APÓS A VACINA PNEUMOCÓCICA 10 – VALENTE

ENFERMEDADES RESPIRATORIAS EN LOS NIÑOS DESPUÉS DE LA VACUNA NEUMOCÓCICA 10 – VALENTE

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ABSTRACT

Infancy is characterized by a series of changes. Physiologic maturation of the respiratory system as well as internal and external factors makes children under two years of age more susceptible to respiratory diseases. The objective of this study was to identify the occurrence of respiratory diseases after the administration of pneumococcal 10-valent conjugate vaccine in that age group and compare results with clinical and socio-demographic variables. The research was conducted with 90 children that had received at least three dosages of vaccine at Basic Health Units in the city of Imperatriz. Quantitative variables were expressed as frequency and percentage. To test the normality of the variables, the researchers used the chi-square test. The majority of the children aged over 1 year (52.2%); 71.1% were termed by parents/legal guardians as being of a light-brown complexion; family income of 70.0% of the participants was above the minimum wage; legal guardians' schooling ranged from eight to twelve years of education (62.2%); 61.1% of the children lived with smokers; 63.3% had no history of hospitalization. Regarding the occurrence of disease after vaccination, 32.3% developed some respiratory disease (pneumonia, meningitis, otitis media and pharyngitis). The results revealed that the later the vaccination, the lower the vaccine effectiveness. The study results indicate the need to analyse economic, demographic and nutritional aspects that might predispose to respiratory diseases, not only associate the diseases to the effectiveness, duration or age of administration of the pneumococcal 10-valent conjugate vaccine.

Keywords: Respiratory Diseases; Vaccine; Child.

RESUMO

A infância é uma fase de mudanças. Principalmente maturação fisiológica do sistema respiratório e fatores internos e externos tornam as crianças menores de dois anos mais suscetíveis a desenvolver doenças respiratórias. O objetivo do presente estudo foi identificar a ocorrência de doenças respiratórias após a administração da vacina pneumocócica 10-valente em crianças menores de dois anos e correlacionar com as variáveis clínicas e sociodemográficas. A pesquisa foi realizada com 90 crianças menores de dois anos que já tinham recebido pelo menos três doses da vacina, atendidas em Unidades Básicas de Saúde no município de Imperatriz-MA. As variáveis quantitativas foram apresentadas em frequência e porcentagem. Para testar a associação das variáveis, foi utilizado o teste qui-quadrado. A maioria das crianças tinha mais de um ano de idade (52,2%), era de cor parda referida pelos responsáveis (71,1), com renda familiar acima de um salário mínimo (70,0%), escolaridade dos responsáveis entre 8 e 12 anos de estudo (62,2%), convive com fumantes (61,1%), não teve evento de internação hospitalar (63,3%). Quanto à ocorrência de doenças após a vacina, 32,3% desenvolveram algumas doenças respiratórias (pneumonia, meningite, otite e faringite). De acordo com os resultados encontrados, observa-se que quanto mais tarde foi iniciado o esquema vacinal, menos eficácia a vacina teve. Os resultados deste estudo evidenciam que há necessidade de avaliar outros aspectos que predisõem ao acometimento por doenças respiratórias, tais como as condições econômicas, sociodemográficas e nutricionais, e não somente relacionar as doenças à efetividade, duração ou idade de administração da vacina pneumocócica 10-valente.

Palavras-chave: Doenças Respiratórias; Vacinas; Criança.

RESUMEN

La infancia es una época de cambios. La madurez fisiológica del sistema respiratorio y factores internos y externos hacen que los niños menores de 2 años sean más propensos a las enfermedades respiratorias. El objetivo de este estudio fue identificar la incidencia de enfermedades respiratorias después de la vacuna 10-valente neumocócica en niños menores de dos años y su correlación con las variables clínicas y sociodemográficas. La investigación se realizó con 90 niños menores de 2 años que habían recibido al menos 3 dosis de la vacuna y estaban siendo atendidos en Unidades

Básicas de Salud de la ciudad de Imperatriz, Estado de Maranhão. Las variables cuantitativas se presentan como frecuencias y porcentajes. Para comprobar la asociación entre las variables se realizó la prueba chi cuadrado. La mayoría de los niños tenía más de 1 año (52,2%), tez mate según sus responsables (71,1), ingreso familiar superior al sueldo mínimo (70,0%), instrucción de los responsables entre 8 y 12 años de educación (62,2%) convivía con fumadores (61,1%) nunca había sido internado (63,3%). Acerca de la incidencia de la enfermedad después de la vacunación: el 32,3% tuvo algunas enfermedades respiratorias (neumonía, meningitis, otitis media y faringitis). Los resultados indican que cuánto más tarde se comience con la vacunación, menos eficaz será la vacuna. Los resultados también señalan que deben considerarse otros factores que predisponen a los niños a las enfermedades respiratorias tales como la situación económica, las condiciones sociodemográficas y nutricionales y que no hay que vincular estas enfermedades solamente a la eficacia de las vacunas, su duración o edad en que le dieron la antineumocócica 10 valente.

Palabras clave: Enfermedades Respiratorias; Vacuna; Niño.

INTRODUCTION

Respiratory diseases contribute to high child morbidity and mortality rates worldwide. It is estimated that 25-33% of deaths in the first five years of life are caused by acute respiratory infections and their complications. Currently, respiratory diseases account for 5 to 8% of all deaths in developing and developed countries, respectively.¹

In Brazil, childhood respiratory diseases are a major cause of morbidity and mortality in children under five years and are, consequently, a serious public health problem. Some studies reveal that in the last decades the incidence of acute respiratory tract infections and their complications has grown in several developing countries.²⁻⁴

Respiratory diseases account for 20 to 40% of medical consultations and for 20 to 35% of hospitalizations of children under five years; some are life threatening and affect children of all social classes regularly.⁵⁻⁷

According to data of the Brazilian Mortality Information System, respiratory diseases accounted for 9.9% of deaths in children aged less than five years in the early nineties. In 2000, such diseases accounted for 5.8% of deaths and, in 2001, for 41.5% of the main causes of hospitalizations and deaths in the Unified Health System (SUS).^{2,7}

Among other factors, inadequate environmental conditions – crowded housing and passive smoking – contribute to the occurrence of respiratory diseases in children, especially infants less than one year of age.⁵⁻⁷

Many pathogens are involved in the clinical manifestations of respiratory diseases affecting children of different ages and especially those under two years. Bacteria such as *Streptococcus pneumoniae* cause major respiratory viral infections and pose a serious and alarming threat to a child's recovery.⁸

Respiratory diseases caused by *Streptococcus pneumoniae* is a major cause of morbidity and mortality in children worldwide. As a preventive measure the Brazilian government included, since March 2010, 10-valent pneumococcal conjugate vaccine in the immunization schedule of children under two years. The goal is to reduce hospitalizations and deaths from pneumonia and other diseases caused by pneumococcus. This was a major breakthrough for public health in the country,

since it would protect children under the age of two against invasive diseases and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.^{1,7,9}

The duration of the protection against the disease has not been ascertained. Therefore, the present study aims at identifying the occurrence of respiratory diseases in that age group after the administration of 10-valent pneumococcal vaccine and at gathering data in order to estimate the length of protection afforded against those diseases.

THEORETICAL FRAMEWORK

A 10-valent pneumococcal conjugate vaccine consists of ten pneumococcal serotypes conjugated to protein D from the *Haemophilus influenzae*. The vaccine's excipient is sodium chloride, aluminium phosphate and water for injection; it contains no preservatives. The vaccine presentation is a glass vial with a 0.5 mL dose. It is intramuscularly administered in the vastus lateralis muscle starting from the second month of life. Vaccination schedule consists of three doses with at least one-month interval. A booster dose is recommended six months after the third dose. The most common adverse reactions are redness at the injection site and irritability.⁹

A recent study by the World Health Organization recommends evaluating the potential efficacy of the vaccine against invasive pneumococcal diseases (including sepsis, meningitis, bacterial pneumonia and bacteraemia). It was based on a comparison of immune responses to the seven serotypes common to 10-valent pneumococcal conjugate vaccine and 7-valent pneumococcal conjugate vaccine.^{9,10}

Respiratory infections caused by bacteria comprise 10-20% of cases of upper respiratory tract infections in children. Brazil is among the 15 countries with the highest incidence of pneumonia: 0.11(of) cases per child per year in under-fives, totalling 1.8 million cases per year.^{3,11}

The main childhood respiratory infections are pharyngitis, purulent tonsillitis, adenoiditis, otitis media, sinusitis, pneumonia, rhino pharyngitis and mastoiditis. These infections have bacterial aetiology and account on average for 10% of consultations related to bacterial infections.^{11,12}

Children have a vulnerable immune system since only from the second month of life their immune system begins to produce antibodies. Despite having an immature immune system, the infant receives protection against various infectious diseases through maternal antibodies acquired during intra-uterine life and also through breast feeding. Besides their immunological fragility their respiratory system structures are immature and susceptible to infections.^{4,13,14}

METHOD

This is a quantitative cross-sectional study carried out from December 2011 to March 2012 at Basic Health Units (UBS) in the of city Imperatriz, state of Maranhão. According to information provided by the local Health Department, there are 30 UBSs in the area and 2,253 children registered in the municipality's Family Health Strategy (FHS) program in the age group relevant for this research (<2 years).

The research environment consisted of three UBSs randomly selected since such units focus on family health as main primary health care strategy, ideal for actions on child health promotion.

The study sample comprised 90 children. Previously defined inclusion criteria were as follows: children less than two years of age with complete vaccination schedule of 10-valent pneumococcal vaccine (3 doses); children registered at the Family Health Strategy (ESF) program. Exclusion criterion was failure to participate in one of the stages of the study. Data collection was initiated after legal guardians' signing of the Statement of Informed Consent.

A data collection instrument was tested in the pilot study. It consisted of a structured questionnaire containing biological (clinical history, history of personal and familial diseases), socio-economic and demographic variables. The questionnaire was completed by the children's mothers or legal guardians. Clinical information and dates of doses of pneumococcal 10-valent vaccine administered were obtained through the child's medical records and the Handbook of Child Health of the Brazilian Department of Health.

Data collected was entered and stored in Excel 7.0 software and processed in Epi-info 3.5.3 Statistical Program. Quantitative variables were recorded as frequency and percentage. Chi-square test was used to test the association of the variables.

The study was approved by the Ethics Committee on Human Research of the University Hospital of the Federal University of Maranhão (protocol No 318/11).

RESULTS AND DISCUSSION

Ninety children aged between 0 and 23 months and 29 days were assessed. The number of female and male participants was equivalent. As for skin colour, 71.1% of parents/

guardians declared them light-brown skinned; 26.7% white; and 2.2% black. Family income ranged between one and three minimum wages (Table 1).

Table 1 - Distribution of children immunised with 10-valent pneumococcal conjugate vaccine according to demographic and economic data. Imperatriz- MA, 2012

Variables	Freq.	(%)
Age group		
0 – 12 months	43	47,8%
12 – 23 months and 29 days	47	52,2%
Gender		
Male	45	50,0%
Female	45	50,0%
Skin colour		
White	24	26,7%
Light-brown	64	71,1%
Black	02	2,2%
Family income		
< 1 minimum wage	23	25,6%
1 to 3 minimum wages	63	70,0%
>3 minimum wages	04	4,4%

Elaborated by the authors.

Most of the guardians were between 20 and 30 years old (63.3%) and had eight to twelve years of schooling (62.2%). Average schooling and parental age are protective factors against respiratory disease. The study demonstrated that having more than eight years of schooling and being within adult age group contributes to a better understanding of the factors that trigger diseases and consequently favours a greater attentiveness to the child's health.

Such results differ from those found in similar studies, in which guardians' low education level and their being under 20 years of age are clearly associated with respiratory diseases. However, the present study confirms that higher parent education level acts as a protective factor against disease.^{4,9,15}

Social conditions, expressed by socio demographic and economic variables are essential when investigating the occurrence of respiratory morbidity in children under two years. From a social and economic point of view, respiratory diseases generate costs which the caregiver cannot usually provide immediately.

Studies identify the following as prevalent risk factors for morbidity and mortality from these diseases in childhood: poor socioeconomic conditions, low levels of parental schooling, poor health care system, malnutrition and the child's very young age. Biological immaturity explains the difficulty of the respiratory system in fighting respiratory diseases in such age

group, therefore specific preventive measures, like immunization, are necessary in this development stage.^{4,7,9,15,16}

In accordance with other findings in literature on the area, the present study highlights that a low family income influences the appearance of respiratory diseases since it is associated with household crowding. The number of people who share the bedroom with the children facilitates the cross-transmission of pathogens that cause respiratory diseases.^{4,15,17}

Among the participants, four (4.4%) were exclusively breastfed and eighty-six (95.6%) received complementary feeding. The study revealed also that fifty-five children (61.1%) lived with smokers and were consequently passive smokers; thirty-five (38.9%) did not live with smokers; 57.6% of the parents took their children to the health unit regularly, compared to 42.4% that did not; 92.2% of the parents took the children for medical consultations whenever they were sick, while 7.8% did not. (Table 2).

Table 2 - Distribution of children according to lifestyle, Imperatriz – MA, 2012

Variables	Freq.	(%)
Type of feeding		
Exclusive breastfeeding	04	4,4%
Complementary feeding	86	95,6%
Passive smoker		
Yes	55	61,1%
No	35	38,9%
Monthly childcare consultation		
Yes	19	57,6%
No	14	42,4%
Visits doctor/nurse when ill		
Yes	83	92,2%
No	07	7,8%

Elaborated by the authors.

The study was conducted with children aged between 0 and 23 months and 29 days. The authors stress that children should be exclusively breastfed until they are six months old because such milk's nutritional and immunogenic properties promote the infant's physical development. There is scientific evidence that the antibodies present in breast milk protect the child and contribute to reducing morbidity and mortality from respiratory diseases and diarrhoea. After the sixth month, breast milk no longer satisfies the growing infant's nutritional needs and they need complementary feeding, confirming thus the results of this study.¹⁸⁻²¹

Tobacco smoke is the main domestic pollutant associated with the appearance of respiratory diseases. It acts on the de-

fence mechanisms of the respiratory mucosa altering the mucociliary transport system and the role of the alveolar macrophages. A third of the women and nearly half of the men are smokers, consequently the rates of second-hand smoke are high (40-60%). These findings are consistent with those related in the present study.^{4,13,14}

In this research, 36.7% of the children had been hospitalized: 17.8% due to acute respiratory infection, 16.7% due to diarrhoea and 1.1% due to premature birth; 63.3% had no history of admission to hospital. In addition, 8.9% had chronic illnesses such as asthma and sickle-cell anaemia; 91.1% had no chronic illness; 64.4% had had three doses of the vaccine; and 35.6% had got three doses plus a booster dose.

After vaccination, thirty-five (38.9%) children had influenza, five (5.6%) caught pneumonia, one (1.1%) had meningitis, eight (8.9%) otitis, fifteen (16.7) pharyngitis, one (1.1%) allergic rhinitis and twenty (27.8%) did not become ill. The study revealed that 57.6% of the guardians took the child to paediatric check-ups and 92.2% sought the health services on illness periods. (Table 3)

Table 3 - Distribution of children according to clinical data. Imperatriz – MA, 2012

Variables	Freq.	(%)
Hospitalization		
Yes	33	36,7%
No	57	63,3%
Causes of hospitalization		
Acute respiratory infection	16	17,8%
Diarrhoea	15	16,7%
Prematurity	01	1,1%
Others	02	2,2%
Not hospitalized	56	62,2%
Chronic disease		
Yes	08	8,9%
No	82	91,1%
Vaccination		
3 doses	58	64,4%
3 doses + booster	32	35,6%
Respiratory diseases after vaccination		
Influenza	35	38,9%
Pneumonia	05	5,6%
Meningitis	01	1,1%
Otitis	08	8,9%
Pharyngitis	15	16,7%
Allergic rhinitis	01	1,1%
Not ill	25	27,8%

Elaborated by the authors.

From the preventive point of view, health professionals are responsible for assessing the factors that trigger respiratory diseases. Studies show the importance of child care prevention, which is essential for the promotion of optimal health in childhood, through the early detection of childhood diseases, professional guidance in the first years and vaccination against vaccine-preventable diseases as well as for avoiding successive consultations when the child is already ill.^{4,17}

Although this study detected a small number of hospitalizations, the main cause for the participants' admission to hospital was respiratory infection (17.8%).

Other studies demonstrated that, despite all prevention efforts, respiratory diseases are the leading causes of morbidity and mortality among under-fives in developing countries, accounting for more than four million deaths per year.^{20,21}

Among the children who had got three doses of the vaccine, 44.8% developed influenza later. However, there was no statistical significance in this finding. Comparatively, children who were given four doses of the vaccine had a lower prevalence of influenza but this was neither statistically significant ($p = 0.490$). (Table 4).

Table 4 - Association between frequency of vaccine doses and disease diagnosis. Imperatriz – MA, 2012

Respiratory Diseases	Doses				p
	3 doses		4 doses		
	Freq.	%	Freq.	%	
Influenza	26	44,8	9	28,1	0,490*
Pneumonia	4	6,9	1	3,1	
Meningitis	–	–	1	3,1	
Pharyngitis	4	6,9	4	12,5	
Otitis	8	13,8	7	21,9	
Allergic rhinitis	1	1,7	–	–	
Not ill	15	25,9	10	31,3	
Total	58	100%	32	100%	

Elaborated by the authors. * Chi-squared ($X^2 = 6.123$).

Despite negative results regarding the relationship between occurrences of diseases after the administration of 10-valent pneumococcal vaccine, the study found that the children's guardians related the onset of influenza symptoms to the vaccine administration.

According to existing literature on the theme, influenza is an infectious respiratory disease caused by the family *Orthomyxoviruses* and not by bacteria. 10-valent pneumococcal vaccine provides coverage against 88% of strains of pneumococcal bacteria, identified as the cause of pneumonia, meningitis, bacteraemia and acute otitis media in children. Immunity provided by the vaccine works when phagocytosis of pneumococci is fa-

cilitated by opsonized bacteria. Thus, the conjugation of capsular polysaccharide antigens with proteins can enhance vaccine immunogenicity in children less than two years old by enabling humoral immune response. This is due to the fact that children in that age group are less responsive to polysaccharide antigens and, therefore, present difficulty in opsonisation.²²⁻²⁴

Among the children who were given three doses of the vaccine, 6.9% had pneumonia (with no statistical significance). The percentage of hospitalizations for influenza was higher in those who got three doses of the vaccine (47.8%) compared to those who got four doses (15.6%); this finding has no statistical significance ($p = 0.296$). (Table 5)

Table 5 - Association between number of vaccine doses and cause of hospitalization. Imperatriz – MA, 2012

Causes of hospitalization	Doses				p
	3 doses		3 doses + booster		
	Freq.	%	Freq.	%	
Influenza	11	47,8	5	15,6	0,296*
Diarrhoea	11	47,8	4	12,5	
Prematurity	1	4,4	0	0,0	
Other	0	0,0	2	6,3	
Total	23	100%	11	100%	

Elaborated by the authors. * Chi-squared ($X^2 = 0.296$).

Direct comparison trials demonstrated that responses to 7-valent pneumococcal conjugated vaccine are not inferior to immunological responses to pneumococcal 10-valent conjugate vaccine. Respiratory diseases are the main cause of hospitalization in Brazil (40.3%), followed by parasitic and digestive tract diseases (27.1%), in children under four years old. Data show that hospitalizations for respiratory diseases and diarrhoea present a difference of only 3.1% among children who got four doses of the vaccine.^{9,11}

Among children who were administered three doses of the vaccine or three doses plus booster there was a higher prevalence of influenza and pharyngitis (47.8 and 21.7%, respectively). In these cases, the 6 to 12 months age group was the most affected. This finding was statistically significant ($p = 0.001$) (Table 6).

According to this study, starting vaccination late decreases the effectiveness of the vaccine. Routine childhood vaccination should start as soon as the baby is two months old.^{25,26}

Pneumococcus is a major cause of infection in neonates and in children less than two years old. It accounts for 45% of community-acquired pneumonia. It causes also pneumonia, otitis, sinusitis, meningitis and bacteraemia – it is responsible for 27% of cases of pneumonia in children in developing countries and 70% of cases of invasive diseases.

Table 6 - Association between age at which the child became ill and disease. Imperatriz – MA, 2012

Diseases	Age						p
	0-6 months		6-12 months		12-24 months		
	Freq.	%	Freq.	%	Freq.	%	
Influenza	6	17,1	22	47,8	7	50	0,001*
Pneumonia	–	–	4	8,7	1	7,1	
Meningitis	–	–	1	2,2	–	–	
Pharyngitis	1	4,3	10	21,7	4	28,6	
Otitis	1	4,3	6	13,0	1	7,1	
Allergic rhinitis	–	–	1	2,2	–	–	
Not ill	15	65,2	2	4,3	1	7,1	
Total	23	100%	46	100%	13	100%	

Elaborated by the authors. * Chi-squared ($X^2= 38.2$).

Other studies report that 10-valent pneumococcal vaccine, administered to children aged 2 to 23 months, is conjugated to protein D of *Haemophilus influenzae* to tetanus and diphtheria toxoids. Conjugate vaccines are those in which bacterial antigens are bound to protein carriers, thus facilitating the processing by T lymphocytes. This type of vaccine induces a long-term antibody response even in young infants. Furthermore, its serotypes increase the spectrum of coverage against invasive pneumococcal diseases. Therefore, it protects against bacterial but not viral infections.^{24, 27}

Comparative studies performed with 7-valent pneumococcal vaccine revealed a marked decline in invasive pneumococcal diseases in the age group under two years respecting those not vaccinated.^{9,28}

In the group of those who received three doses as well as in the group who received three doses plus booster, the age group with the higher number of cases was between 6 and 12 months. However, such finding did not have statistical significance ($p = 0.206$). (Table 7)

Table 7 - Association between number of vaccine doses and age the child became ill. Imperatriz – MA, 2012

Diseases	Age						p
	0-6 months		6-12 months		12-24 months		
	Freq.	%	Freq.	%	Freq.	%	
3 doses	14	25,5	34	62,0	7	12,7	0,206*
3 doses + booster	9	32,1	12	38,0	7	25,0	
Total	13	57,6	46	100%	14	100%	

Elaborated by the authors. * Chi-squared ($X^2 = 3.6$)

In the stage of lactation (0 to 12 months) the infant has few antibodies and is more susceptible to diseases. In response to the administration of polysaccharide conjugate vaccine the

antibody level may decrease up to one year after vaccination. A decline in the number of cases of respiratory diseases has been observed in countries in which 7-valent pneumococcal vaccine was introduced into immunization programs. There are no studies on 10-valent pneumococcal vaccine.^{25,27,29}

Few studies bring consistent quantitative data regarding the duration of protection provided by 10-valent conjugate vaccine and its relationship to the age when vaccination schedule started.

CONCLUSION

Despite the significant contribution of vaccination programs to public health, the incidence of vaccine-preventable diseases among children is still high. The present study results demonstrate that other factors leading to the appearance of respiratory diseases such as social, demographic, economic and dietary conditions should also be evaluated. These diseases should not only be related to the effectiveness, duration or period of administration of 10-valent pneumococcal conjugate vaccine.

10-valent pneumococcal vaccine was introduced in Brazil in 2009. In the state of Maranhão the vaccine was only available in the second half of 2010. There are not enough quantitative studies that prove the efficacy of this vaccine in the prevention of respiratory diseases caused by pneumococcus. The lack of such knowledge was the main limitation of the present study.

Therefore, the authors recommend further studies (preferably longitudinal ones using more representative samples) on the relationship between the duration of immunization by 10-valent pneumococcal vaccine and the reduction or absence of respiratory diseases caused by *Streptococcus pneumoniae* in children under two years old.

The study made a significant contribution to the improvement of public health services by providing a better understanding of pneumococcal diseases and of 10 valent pneumococcal conjugate vaccine.

It also subsidised the implementation of specific action plans for the control of respiratory diseases.

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