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#### REFERÊNCIA

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## Impact of 10-valent pneumococcal conjugate vaccine on pneumococcal meningitis in children up to two years of age in Brazil

Impacto da vacina pneumocócica conjugada 10-valente na meningite pneumocócica em crianças com até dois anos de idade no Brasil

Impacto de la vacuna neumocócica conjugada 10-valente en la meningitis neumocócica en niños de hasta dos años de edad en Brasil

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### Abstract

*The objective of this study was to analyze the impact of vaccination against Streptococcus pneumoniae on the morbidity and mortality from pneumococcal meningitis in children ≤ 2 years in Brazil, from 2007 to 2012. This is a descriptive study and ecological analysis using data from the Information System on Notifiable Diseases. Pre-vaccination (2007-2009) and post-vaccination (2011-2012) periods were defined to compare incidence rates and mortality. A total of 1,311 cases and 430 deaths were reported during the study period. Incidence decreased from 3.70/100,000 in 2007 to 1.84/100,000 in 2012, and mortality decreased from 1.30/100,000 to 0.40/100,000, or 50% and 69% respectively, with the greatest impact in the 6-11 month age group. This decrease in Pneumococcal meningitis morbidity and mortality rates two years after introduction of the 10-valent pneumococcal conjugate vaccine suggests its effectiveness.*

Streptococcus pneumoniae; Meningitis; Vaccines

### Resumo

*O objetivo deste trabalho foi analisar o impacto da vacinação contra o Streptococcus pneumoniae na morbidade e mortalidade por meningite pneumocócica em crianças ≤ 2 anos, no Brasil, entre 2007-2012. Este é um estudo descritivo com análise ecológica, utilizando dados do Sistema de Informação de Agravos de Notificação. Foram definidos os períodos pré-vacinal (2007-2009) e pós-vacinal (2011-2012) para comparar as taxas de incidência e mortalidade. Foram identificados 1.311 casos e 430 óbitos no período do estudo. A taxa de incidência diminuiu de 3,70/100.000 no ano de 2007 para 1,84/100.000 em 2012, e a mortalidade reduziu de 1,30/100.000 para 0,40/100.000, o que significa uma redução de 50% e 69%, respectivamente, com maior impacto identificado na faixa etária de 6 a 11 meses. Os resultados indicam uma diminuição nos indicadores de morbidade e mortalidade de meningite pneumocócica, observados dois anos após a introdução da vacina pneumocócica conjugada 10-valente, sugerindo sua efetividade.*

Streptococcus pneumoniae; Meningite; Vacinas

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## Introduction

*Streptococcus pneumoniae* (pneumococcus) is one of the main etiological agents of bacterial pneumonia, septicemia, and meningitis in children worldwide, accounting for approximately 800 thousand deaths year in children younger than 5 years<sup>1,2,3</sup>. In Brazil, pneumococcal meningitis is the second leading cause of bacterial meningitis<sup>4</sup>, especially in infants younger than 1 year<sup>5</sup>. According to data from the SINAN database (Information System on Notifiable Diseases), the mean annual incidence rates in 2001 and 2010 in children younger than 5 years and younger than 1 year were 1.09 and 8.62 cases/100,000 inhabitants, and the mean case-fatality rates were 33.6% and 31.3%, respectively. Bacterial meningitis has been a disease of compulsory notification in Brazil since 1975.

Advances in the immunogenicity and efficacy of anti-pneumococcal vaccines introduced since 1983 have highlighted their importance in the control and prevention of pneumococcal diseases as the leading cause of vaccine-preventable deaths<sup>6</sup>. Global performance against invasive pneumococcal disease were considered satisfactory using the first pneumococcal conjugate vaccine, including seven serotypes (PCV7), demonstrating 80% efficacy against invasive pneumococcal disease caused by the seven vaccine serotypes worldwide<sup>7</sup>. In Australia, Europe, and North America, the impact of PCV7 on invasive pneumococcal disease was a reduction that varied from 17% in Spain<sup>8</sup> to 80% in the United States<sup>9</sup>, with a mean decline of 45%<sup>10</sup>. Reductions in invasive pneumococcal disease caused by the seven serotypes in all age groups and associated with childhood vaccination varied from 1% in the Netherlands<sup>11</sup> to 94% in the United States<sup>12</sup>, with a mean reduction of 65.5%<sup>10</sup>.

In Brazil, 10-valent pneumococcal conjugate vaccine (PCV10) was introduced into the childhood vaccination schedule of the National Immunization Program, Ministry of Health (PNI/MS) in 2010, with the recommendation of three doses, at two, four, and six months of age, with a booster between 12 and 15 months<sup>13</sup>. The approval of PCV10 was initially based on studies of PCV7, as recommended by the World Health Organization (WHO)<sup>14</sup>. Even with the declining trend in pneumococcal meningitis in recent years in Brazil<sup>15</sup>, the introduction of PCV10 raises further prospects for controlling pneumococcal disease, with Brazil as the forerunner in implementing this vaccine in its Public Health System.

In this scenario, performance analyses of PCV10 are essential for assessing the intervention's impact. The current study's objectives were

to describe cases of pneumococcal meningitis in children up to 2 years of age and to compare the incidence and mortality rates in the pre- and post-implementation periods for the PCV10 vaccine in Brazil, thus contributing knowledge to support meningitis surveillance and strengthen the country's public health policies.

## Method

A descriptive study of cases of pneumococcal meningitis was performed, in addition to an ecological analysis of incidence and mortality rates for the disease in the immediate pre- and post-implementation periods for PCV10. Cases of pneumococcal meningitis included in the study were in children 2 years or younger, recorded in the SINAN database and confirmed by a specific laboratory criterion, which included isolation of *S. pneumoniae* in culture, latex agglutination reaction, or polymerase chain reaction (PCR).

The introduction of PCV10 vaccine varied between the States of Brazil in 2010, so that year was excluded from the statistical analyses. Thus, the pre-vaccination period was defined as the three years prior to introduction of the vaccine (2007-2009), and the post-vaccination period included the years 2011 and 2012.

Calculation of the incidence and mortality rates from pneumococcal meningitis used population estimates reported by the Brazilian Institute of Geography and Statistics (IBGE – <http://www.sidra.ibge.gov.br/bda/tabela/listabl.asp?c=1552&z=cdo=7>, accessed on 22/Jan/2014; <http://www.ibge.gov.br/home/estatistica/populacao/trabalhoerendimento/pnad2012/microdados.shtm>, accessed on 22/Jan/2014). Stratification of the population of infants under 1 year (reported by IBGE) into two groups (younger and older than six months) used the proportion of infants under six months according to the database of the Information System on Live Births (SINASC) for each year included in the study ([http://tabnet.datasus.gov.br/cgi/sinasc/dados/nov\\_indice.htm](http://tabnet.datasus.gov.br/cgi/sinasc/dados/nov_indice.htm), accessed on 22/Jan/2014).

Cases of pneumococcal meningitis were described by age group, gender, signs and symptoms, confirmation criterion, evolution, and State and geographic region of residence, as recorded on the notification form. Data on vaccine status were not included, since they showed unsatisfactory completeness.

The study was approved by the Ethics Research Committee of the School of Health Sciences, University of Brasília (CEP/FS-UNB, review n. 171/711).

## Results

The study included 1,311 cases of pneumococcal meningitis in children up to 2 years of age and reported in the SINAN database from 2007 to 2012. Seventy-nine cases (5%) were excluded due to lack of specific laboratory confirmation. The 269 cases (16%) reported in 2010 were also excluded from the analysis since PCV10 was introduced that year.

Of the 1,311 cases of pneumococcal meningitis, 60% (n = 785) were in boys. The age group younger than one year accounted for the highest proportion of cases, concentrated in infants younger than six months in the post-vaccination period (Table 1).

The signs and symptoms described in all the study years were fever, vomiting, and seizures. As for confirmation, 69% (n = 906) of the cases were confirmed by culture, 27% (n = 357) by latex agglutination, and 4% (n = 48) by PCR. Culture was the principal confirmation criterion in all the

study years, and there was an increase in cases confirmed by latex and PCR in the post-vaccination period (Table 1).

Approximately 30% of cases evolved to death each year during the study period, but in the second year of the post-vaccination period this proportion decreased to 22% (Table 1).

The highest proportions of cases in the entire study period were in the Southeast and South regions of Brazil, with 59% and 16%, respectively. The highest incidence rates were also seen in these regions. Meanwhile, the largest reductions in these rates when comparing 2012 to 2007 were in the States of Minas Gerais and Santa Catarina, both with a decrease of 65% (Table 2).

Table 3 shows that proportionally, the largest share of cases of pneumococcal meningitis occurred in the year 2007, with 30% of the cases from the study period, a proportion that remained relatively stable in 2008 and 2009. The two years of the post-vaccination period showed the lowest proportion of cases, with a decrease

Table 1

Characteristics of cases of pneumococcal meningitis in the pre-vaccination period (2007-2009) and post-vaccination period (2011-2012) for PCV10. Brazil, 2007-2012.

Variables	2007		2008		2009		2011		2012	
	n	%	n	%	n	%	n	%	n	%
Gender										
Male	222	61.7	200	62.7	177	61.5	106	55.2	80	52.6
Female	138	38.3	119	37.3	111	38.5	86	44.8	72	47.4
Age group										
< 1 year										
< 6 months	136	37.8	98	30.7	98	34.0	111	57.8	78	51.3
≥ 6 months	124	34.4	120	37.6	109	37.8	39	20.3	29	19.1
1 year	74	20.6	75	23.5	53	18.4	21	10.9	26	17.1
2 years	26	7.2	26	8.2	28	9.7	21	10.9	19	12.5
Signs and symptoms										
Fever	336	93.3	314	98.4	266	92.4	174	90.6	136	89.5
Vomiting	235	65.3	227	71.2	180	62.5	116	60.4	89	58.6
Seizures	164	45.6	154	48.3	119	41.3	76	39.6	61	40.1
Neck stiffness	138	38.3	137	42.9	117	40.6	58	30.2	52	34.2
Bulging fontanelle	116	32.2	89	27.9	82	28.5	58	30.2	50	32.9
Confirmatory criterion										
Culture	277	76.9	222	69.6	205	71.2	114	59.4	88	57.9
Latex	80	22.2	87	27.3	73	25.3	68	35.4	49	32.2
PCR	3	0.8	10	3.1	10	3.5	10	5.2	15	9.9
Evolution										
Cure	204	56.7	175	54.9	166	57.6	112	58.3	97	63.8
Death	127	35.3	106	33.2	97	33.7	65	33.9	33	21.7

Source: Information System on Notifiable Diseases (SINAN).

Table 2

Distribution of incidence rates (IR) \* and mortality rates (MR) \*\* from pneumococcal meningitis in the Southeast and South regions and States of Brazil, 2007-2012.

Region/State	2007		2008		2009		2011		2012	
	IR	MR	IR	MR	IR	MR	IR	MR	IR	MR
Southeast	5.65	2.08	4.88	1.73	4.78	1.84	3.93	1.42	2.99	0.69
MG	3.74	1.66	3.70	1.59	2.91	1.18	2.99	1.04	1.29	0.52
ES	5.53	1.66	1.72	1.15	4.06	1.16	3.37	1.35	2.67	1.34
RJ	5.86	3.15	4.83	1.96	5.44	3.68	5.81	2.66	3.62	0.82
SP	6.55	1.94	5.83	1.78	5.62	1.61	3.73	1.16	3.58	0.67
South	5.00	1.52	4.93	1.16	4.55	0.93	2.33	0.65	2.59	0.37
PR	5.73	2.55	5.77	1.77	4.36	0.69	2.29	0.23	3.64	0.91
SC	5.72	1.14	4.81	0.40	4.56	2.07	2.01	0.80	1.99	0.00
RS	3.80	0.67	4.09	0.96	4.76	0.50	2.58	1.03	1.80	0.00
Brazil	3.70	1.30	3.38	1.12	3.12	1.06	2.29	0.79	1.80	0.39

ES: Espírito Santo; MG: Minas Gerais; PR: Paraná; RJ: Rio de Janeiro; RS: Rio Grande do Sul; SC: Santa Catarina; SP: São Paulo.

\* Cases/100,000 inhabitants;

\*\* Deaths/100,000 inhabitants.

of 14.6% in 2011 and 11.6% in 2012, accounting for a 58% reduction in the absolute number of cases when comparing 2012 to 2007. The highest incidence and mortality rates were in infants younger than one year throughout the study period (Table 3).

The study showed a 50% reduction in the incidence rate and 69% in the mortality rate from pneumococcal meningitis, comparing 2012 to 2007. Children six months to one year of age showed the highest reductions in rates: 73% in incidence and 85% in mortality (Table 3).

The reductions in rates identified in this study two years after introduction of the PCV10 were associated with vaccination coverage rates of 73% in 2011 and 89% in 2012, according to data from the PNI.

## Discussion

After introduction of the 10-valent pneumococcal conjugate vaccine in Brazil, there was a reduction in the number of cases and in the incidence of pneumococcal meningitis in children younger than 2 years in 2012. There was an important reduction in the incidence rate for pneumococcal meningitis, especially in the second year post-vaccination when compared to the year 2007. The findings are similar to those in North America and Australia, where the incidence of invasive pneumococcal disease, includ-

ing meningitis, declined by 56%-69% in children younger than 2 years, following introduction of PCV7<sup>16,17,18,19,20,21,22,23</sup>. In Europe, in the same age group, the reduction was 82% after the introduction of PCV7<sup>24</sup>.

In Brazil, the highest incidence of pneumococcal meningitis affects children younger than 2 years<sup>15</sup>. The largest decrease in the incidence rate for pneumococcal meningitis was in the 6-11 month group. This corroborates a population-based study in Brazil in 2012, relating invasive pneumococcal disease to pneumonias<sup>25</sup>. Another finding was the reduction in the incidence of pneumococcal meningitis in the second year post-vaccination in infants younger than six months, similar to a study in the United States in 2006, showing a 40% decrease in IPD in infants from birth to 90 days of age<sup>21,25</sup>.

This study's results suggest the benefit of PCV10 in reducing the incidence of pneumococcal meningitis, since the current literature refers to the impact of PCV7 used in other countries, with differences in the composition compared to PCV10, the latter with the addition of three more serotypes: 1, 5, and 7F. In Finland, results of a randomized clinical trial showed 92% and 100% efficacy rates for PCV10 using vaccination schemes of 2+1 and 3+1 doses, respectively<sup>26</sup>. In Quebec, PCV7 was replaced by PCV10 five years after the former was introduced, and the data show lower incidence of invasive pneumococcal disease in children vaccinated with PCV10

Table 3

Characteristics of cases, annual proportions, incidence rates (IR) \* and mortality rates, (MR) \*\* by age bracket for pneumococcal meningitis in the pre-vaccination period (2007-2009) and post-vaccination period (2011-2012) for PCV10. Brazil, 2007-2012.

Incidence/Age group	Pre-vaccination									Post-vaccination						Total n
	2007			2008			2009			2011			2012			
	n	%	IR	N	%	IR	n	%	IR	n	%	IR	n	%	IR	
< 1 year																
< 6 months	136	26.1	8.92	98	18.8	6.47	98	18.8	6.71	111	21.3	8.46	78	15.0	5.88	521
≥ 6 months	124	29.5	7.46	120	28.5	7.65	109	25.9	7.02	39	9.3	2.74	29	6.9	2.02	421
1 year	74	29.7	2.28	75	30.1	2.39	53	21.3	1.73	21	8.4	0.77	26	10.4	0.95	249
2 years	26	21.7	0.79	26	21.7	0.81	28	23.3	0.89	21	17.5	0.76	19	15.8	0.68	120
<b>Total</b>	<b>360</b>	<b>27.5</b>	<b>3.70</b>	<b>319</b>	<b>24.3</b>	<b>3.38</b>	<b>288</b>	<b>22.0</b>	<b>3.12</b>	<b>192</b>	<b>14.6</b>	<b>2.34</b>	<b>152</b>	<b>11.6</b>	<b>1.84</b>	<b>1311</b>

  

Mortality/Age group	Pre-vaccination									Post-vaccination						Total n
	2007			2008			2009			2011			2012			
	n	%	MR	N	%	MR	n	%	MR	n	%	MR	n	%	MR	
< 1 year																
< 6 months	40	16.5	2.62	111	45.7	1.31	36	14.8	2.46	39	16.0	2.97	17	7.0	1.28	243
≥ 6 months	54	35.1	3.25	39	25.3	0.36	42	27.3	2.71	12	7.8	0.84	7	4.5	0.49	154
1 year	25	33.3	0.77	21	28.0	0.32	14	18.7	0.46	9	12.0	0.33	6	8.0	0.22	75
2 years	8	18.2	0.24	21	47.7	0.94	6	13.6	0.19	6	13.6	0.22	3	6.8	0.11	44
<b>Total</b>	<b>127</b>	<b>24.6</b>	<b>1.30</b>	<b>192</b>	<b>37.2</b>	<b>1.12</b>	<b>98</b>	<b>19.0</b>	<b>1.06</b>	<b>66</b>	<b>12.8</b>	<b>0.80</b>	<b>33</b>	<b>6.4</b>	<b>0.40</b>	<b>516</b>

\* Cases/100,000 inhabitants;

\*\* Deaths/100,000 inhabitants.

compared to PCV7<sup>27</sup>. Importantly, the surveillance data used in the current study did not identify the pneumococcal serotypes, which would have allowed assessing the vaccine's specific impact on the vaccine serotypes, thus representing a limitation to the study. The vaccine's impact on the incidence of pneumococcal meningitis depends on the prevalence of circulating serotypes in the population, vaccine coverage, and time since the vaccine's introduction. Although this study did not aim to discuss State-by-State differences in incidence and mortality rates for pneumococcal meningitis, it is important to mention that four States of Brazil (Distrito Federal, Ceará, Rio de Janeiro, and São Paulo) implemented vaccination schemes that differed from the guidelines of the PNI in terms of age at application of the doses.

A study in Salvador, Brazil, estimated 77% coverage for PCV10 in children younger than 2 years<sup>28</sup>. In Goiânia, another study suggested 80% coverage in children 28 days to 36 months of age<sup>29</sup>. The reductions in the rates identified in this study two years after the introduction of PCV10 can be attributed to introduction of the vaccine, corroborating a study in the United

States that reported a 64% decline in the incidence of pneumococcal meningitis in children younger than 2 years, five years after the introduction of PCV7<sup>23</sup>.

According to studies in France, England, and Wales, two years after the introduction of PCV7 and with vaccine coverage of 75% or higher, there was a 30%-65% reduction in the incidence of invasive pneumococcal disease from all serotypes. Just one year after vaccination, Germany, Norway, and Denmark reported a 45-57% decline in invasive pneumococcal disease. Thus, the reduction in Europe was systematically lower than in the United States, where the incidence of invasive pneumococcal disease in children younger than 2 years decreased 69% only one year after introduction of the vaccine<sup>16</sup> and 76% in children younger than 5 years, seven years after introduction of PCV7<sup>12</sup>. In Calgary, Canada, the results in children younger than 2 years were similar: overall incidence of invasive pneumococcal disease decreased by 69.9%, and the reduction for the PCV7 serotypes was 88.7%<sup>17</sup>.

As for mortality, the current study's results show a consistent drop in the number of deaths when comparing pre- and post-introduction of

PCV10, with a reduction in both the absolute number and mortality rate, especially in the 6-11 month age group, and in the second year post-vaccination in children younger than six months, representing a herd effect, as described in previous studies<sup>21</sup>.

The reduction in the number of deaths and in the mortality rate corroborate the findings by Hicks et al.<sup>30</sup> in the United States, reporting a decline in mortality from invasive pneumococcal disease due to vaccine serotypes in children younger than 2 years, and other studies reporting reductions of 62.5% and 57.1% in overall mortality from invasive pneumococcal disease in children eligible for vaccination<sup>12,31</sup>. A study in Gambia using a 9-valent pneumococcal vaccine (PCV9) showed a 16% reduction in infant mortality, with similar reductions in disease shown in South Africa<sup>32</sup>.

In terms of case-fatality, the current study's findings corroborate those of Berezin et al.<sup>33</sup>, with 20% case-fatality from pneumococcal meningitis, and the results published by Menezes et al.<sup>28</sup>, with a 28.6% drop in children younger than 15 years and 41.9% in those younger than 5 years. Despite the observed impact on pneumococcal disease and even with advances in patient care, the case-fatality rates vary between adults<sup>34</sup> and children<sup>35,36</sup>. For meningitis, the observed decrease is 16% to 37% in children and 1% to 3% in adults<sup>37</sup>, consistent with the estimates of 8% and 12% that have not changed in 20 years, despite progress in diagnosis and treatment<sup>38,39</sup>.

Concerning gender, a study in the United States found that the proportion of cases of pneumococcal meningitis was higher in males than in females<sup>40</sup>. In Brazil, results of different studies are similar<sup>15,28,41</sup> and consistent with the current study's findings.

The use of secondary data in epidemiological studies can pose limitations, prone to biases, ranging from case capture to data entry. In addition, ecological analyses are not indicated for determining causality, since other changes that occur simultaneously with introduction of the vaccine are not controlled and demonstrated in the study, thus suggesting the need for future work to consolidate the findings. Still, this study's results provide important evidence on the impact of the 10-valent pneumococcal conjugate vaccine in reducing pneumococcal meningitis in Brazil.

Finally, the current study's results demonstrate that two years after introduction of PCV10 in Brazil there were important decreases in incidence and mortality rates, highlighting the importance of prevention. Active surveillance of pneumococcal disease is necessary, with continuing evaluation of the epidemiological profile and pattern of circulating serotypes.

## Resumen

*El objetivo de este estudio fue analizar el impacto de la vacunación contra el Streptococcus pneumoniae en la morbilidad y mortalidad de la meningitis neumocócica en niños ≤ 2 años en Brasil, 2007-2012. Se trata de un estudio descriptivo ecológico que analiza los datos del Sistema de Información Enfermedades de Notificación Obligatoria en Brasil. El período previo (2007-2009) y posterior a la vacunación (2011-2012) fueron examinados para comparar las tasas de incidencia y mortalidad. 1.311 casos de meningitis neumocócica con 430 muertes se registraron durante el período de estudio. Hubo una disminución de la incidencia de 3,70 ca-*

*sos por 100.000 habitantes en 2007, a 1,84/100.000 en 2012, mientras que la tasa de mortalidad cayó 1,30 a 0,40 óbitos/100.000, se produjeron reducciones del 50% y 69%, respectivamente, con mayores impactos identificados entre los niños de 6-11 meses de edad. Los resultados indican una reducción en la morbilidad y mortalidad por meningitis neumocócica dos años después de la introducción de la vacuna conjugada antineumocócica 10-valente, lo que sugiere su eficacia.*

*Streptococcus pneumoniae; Meningitis; Vacunas*



### Contributors

I. M. Grando, C. Moraes, B. Flannery, W. M. Ramalho, M. A. P. Horta, D. L. M. Pinho, and G. L. Nascimento contributed to the project conceptualization and design, data analysis and interpretation, writing of the article, relevant critical revision of the intellectual content, and approval of the final version for publication. They were responsible for all aspects involved in guaranteeing the accuracy and integrity of all parts of the work.

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