








EPIDEMIOLOGICAL AND HEALTH SCIENCES  
ORIGINAL ARTICLE

**Risk factors associated with nasopharyngeal colonization in children vaccinated with pneumococcal vaccines. Cienfuegos, 2015-16**

**Factores de riesgo asociados a colonización nasofaríngea en niños vacunados con vacunas antineumocócicas. Cienfuegos 2015-16**

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**ABSTRACT**

**Introduction:** Nasopharyngeal colonization by pneumococcus is defined as the initial time when

the bacterium lodges in the nasopharynx of the person.



**Objective:** To estimate the proportion of risk factors associated with nasopharyngeal colonization by pneumococcus in children vaccinated with pneumococcal conjugate vaccines (PCV).

**Material and Methods:** One year after pneumococcal vaccination, a follow-up case-case-control study was conducted in children aged 1-5 years by means of a phase II/III controlled, randomized, double-blind clinical trial. The time horizon was from November 2015 to April 2016. The study included 50 % of the total of children vaccinated during the experimental study. The universe consisted of 1,135 children who were vaccinated during the clinical trial. A simple random sampling that included 555 persons was applied. A survey was conducted and nasopharyngeal exudate samples

were taken. Tables of frequencies were presented. Prevalence ratio was used as a measure of association. Also, 95 % confidence intervals were calculated for each proportion.

**Results:** Being between the ages of 2-5 years acts as protective factor against nasopharyngeal colonization with respect to the young child. Living with persons older than 65 years is a risk factor significantly associated with nasopharyngeal colonization.

**Conclusions:** The introduction of pneumococcal vaccines in pre-school children can have a significant impact on colonization burden and the transmission of pneumococcal diseases.

**Keywords:** *Streptococcus pneumoniae*, risk factors, nasopharyngeal colonization, pneumococcal conjugate vaccines.

## RESUMEN

**Introducción:** La colonización nasofaríngea por neumococo se define como el momento inicial en el que la bacteria se aloja en la nasofaringe del individuo.

**Objetivo:** Estimar la proporción de factores de riesgo asociados a la colonización nasofaríngea por neumococo en niños vacunados con vacunas conjugadas antineumocócicas (PCV).

**Material y Métodos:** Un año después de la vacunación antineumocócica mediante un ensayo clínico fase II/III, controlado, aleatorizado y doble ciego en niños de 1 a 5 años, se ejecutó un estudio de seguimiento con un diseño casos y controles, tipo caso-caso. El horizonte temporal fue desde noviembre de 2015 hasta abril de 2016. Se incluyó 50% del total de vacunados en el

estudio experimental. El universo lo constituyó los 1 135 niños vacunados en el ensayo clínico. Se siguió un muestreo aleatorio simple y se incluyeron 555 sujetos. Se realizó una encuesta y una toma de muestra de exudado nasofaríngeo. Se presentaron tablas de frecuencias. Se utilizó la razón de prevalencia como medida de asociación. Se calcularon los intervalos de confianza a 95% para cada proporción.

**Resultados:** Tener entre 2 y 5 años actúa como factor protector para la colonización nasofaríngea con respecto al niño pequeño. Convivir con personas mayores de 65 años constituye un factor de riesgo significativamente relacionado con la colonización nasofaríngea.

**Conclusiones:** La introducción de vacunas



antineumocócicas en niños preescolares puede impactar de manera significativa la carga de colonización y en la transmisión de la enfermedad neumocócica.

## INTRODUCTION

Nasopharyngeal colonization (NPC) by pneumococcus is defined as the initial time when the bacterium lodges in the nasopharynx of the individual. This event can occur early in the first semester of life; however, the subsequent occurrence of pneumococcal disease will be mediate by associated risk factors. Detection and serotyping is performed from nasopharyngeal exudates.<sup>(1)</sup>

It is estimated that between 25% and 60% of children at preschool age, 35% at school age and 29% of young adults suffer from pneumococcal colonization. In turn, in the case of adults, it is related to living with infants and toddlers.<sup>(2)</sup>

A systematic review published in 2014<sup>(3)</sup> reported the indirect effect of pneumococcal vaccination on reducing nasopharyngeal colonization in the partners of vaccinated children as well as the decrease in the prevalence of NPC caused by vaccine serotypes in unvaccinated children under five years of age and adults in the community.

Intrafamily transmission of pneumococcus has not only been found between siblings, but also between children and adults. It is described that the strains that colonize the elderly are similar to those that appear in children living with them. Moreover, it is important to highlight that the risk of nasopharyngeal colonization and consequently of invasive pneumococcal disease is significantly increased in each episode of viral respiratory

**Palabras Claves:** *Streptococcus pneumoniae*, factores de riesgo, colonización nasofaríngea, vacunas conjugadas antineumocócicas.

infection.<sup>(4)</sup>

Reductions in NPC and IPD rates due to vaccine serotypes were found in the review of randomized controlled trials as well as in observational and surveillance studies conducted from 1994 to 2013 in 14 countries.<sup>(5)</sup> It was suggested that the impact of PCVs on the decrease in NPC should be included as a predictor of indirect effect of the licensing process of pneumococcal vaccines.

Despite the Cuban National Health System considers vaccination against infectious diseases as a top priority and has guaranteed high coverage in the child population, it has not had access to the pneumococcal vaccine to guarantee sustainable coverage in the child population due to the high prices on the market.

In Cuba, there are few population studies that give evidence of the risk factors related to nasopharyngeal colonization in children under five years of age vaccinated with pneumococcal conjugate vaccines (PCV).

This research represents the opportunity to show the risk factors that may be associated with nasopharyngeal colonization in vaccinated children, prior to the registration and introduction of pneumococcal conjugate vaccines in the Cuban national vaccination scheme.

Taking into consideration this health problem in



our country, the **objective** of our study was to estimate the prevalence of risk factors associated with nasopharyngeal colonization by

### MATERIAL AND METHODS

One year after conducting the experimental randomized, controlled, double blind phase II / III non-inferiority trial aimed at evaluating the safety and immune response of the Cuban heptavalent conjugate vaccine candidate (PCV7-TT) compared to the commercial vaccine Prevnar13® in children aged 1-5 years, a follow-up study was conducted in Cienfuegos municipality. This study, which was nested within a clinical trial, was carried out using a crossover design where individuals acted as their own controls.

The time horizon of the study was between November 2015 and April 2016 when samples of nasopharyngeal exudates were taken.

The study universe consisted of 1,135 children vaccinated during the phase II / III clinical trial. A simple random sampling was used and a sample that represented the 50 % of the total number of subjects vaccinated was calculated achieving 5 % precision, 95 % significance level, and an estimated loss of around 20 %.

Two randomization lists were developed; one was called selection list and the other replacement list. Both lists were generated using the statistical language S, R implementation, version 3.1.2 or later versions.<sup>(6)</sup>

Moreover, if a child who was randomly selected for vaccination moved or did not meet the requirements for sampling (exited from the study), he/she was replaced following the

pneumococcus in children vaccinated with pneumococcal conjugate vaccines.

criterion of selecting the first child who was not included in random list 1 (selection list) but included in random list 2 (replacement list). Criteria for replacement included: a) vaccinated child that was not present at the time of the visit (e.g. wrong address, moving), b) parents / guardians of vaccinated children with non-feasible options for interview schedule (example: after 5: 00 pm), and c) parent / guardian of vaccinated child who was absent at the time of field visit and after two new unsuccessful visits. A total of 555 subjects were finally included.

Children who received antibiotic treatment during seven days prior to the sampling or those whose parents did not sign the informed consent were excluded from the study. Parents were surveyed to determine sociodemographic characteristics and factors associated with changes in nasopharyngeal colonization in vaccinated children.

A single sample of nasopharyngeal exudate was taken from each subject. The collection of the sample of nasopharyngeal exudate was carried out by previously trained Bachelors of Science in Microbiology. Sterile, flexible flocked nylon swabs (COPAN, Italy) were used. The procedures for conservation, sample transport, isolation, identification and serotyping were conducted by the Immunology Laboratory of the Finlay Institute for Vaccines (IFV), following the recommendations given by the World Health



Organization in 2013.<sup>(7)</sup>

Quality control of the serotyping was carried out in the Reference Laboratory of "Pedro Kourí" Institute of Tropical Medicine, Cuba.

The interviewers were trained by the author of the research and, at the end of each day, all questionnaires and records were reviewed in detail in order to ensure the quality of the information and to identify errors in the information record.

The main study variables were: age; sex; place of origin; nasopharyngeal colonization by vaccine serotypes (1, 5, 6B, 14, 18C, 19F, 23F) and related serotypes (6A and 19A); individual risk factors (breastfeeding, respiratory diseases associated with pneumococcal infection, previous hospitalization in the last year, use of antibiotics, attendance to nursery schools); and household risk factors (exposure to cigarettes, number of people living in the house).

The prevalence ratio was used as an association measure, with 95 % confidence intervals for each ratio and significance level for a  $p \leq 0.05$ .

In the bivariate analysis, the selected risk factors were described in those children who eliminated the post-vaccination carrier status (change from NPC + to NPC-). Similarly, it was carried out with those who did not develop NPC (change from NPC - to NPC -). At this same analytical level, the association between risk factors for the elimination and non-acquisition of NPC by vaccine serotypes (VT) as well as by more related vaccine serotypes (VT + RS) was estimated in vaccinated individuals.

Estimates of the strength of the association between PCV vaccination and nasopharyngeal

colonization were made in two subgroups: when NPC was due to vaccine serotypes (VT) and when it was due to vaccine serotypes plus related serotypes (VT + RS). In all cases, the OR-P was obtained with its 95 % confidence intervals and the age-adjusted rates considered in the study.

The research met the ethical principles for medical research involving humans, adopted by the Declaration of Helsinki and amended by the 64th General Assembly, Fortaleza, Brazil, October 2013.<sup>(8)</sup> The medical duty of ensuring the wellbeing of each subject and respecting the rights of the children included in the research was fulfilled and the ethical principles of autonomy, beneficence, non-maleficence and justice were achieved.

The Research Ethics Committee (REC) of the "Pedro Kourí" Institute of Tropical Medicine (IPK) and the "Dr. Raúl Dorticós Torrado" Medical School of Cienfuegos approved the study protocol.

In all cases, the parents or guardians of the children included in the study were requested to sign the informed consent to carry out the surveys and the medical procedure.

The study is in agreement with the international standards (STROBE) on how to report observational studies.<sup>(9)</sup>

The main *limitation* of the analytical design chosen for the follow-up study is the absence of a concurrent comparison group since the subject of study acts as its own control in two independent cross-sections. The evaluation of the risk factors associated with changes in NPC, which was carried out one year after vaccination, limits the knowledge of the dynamics of exposure



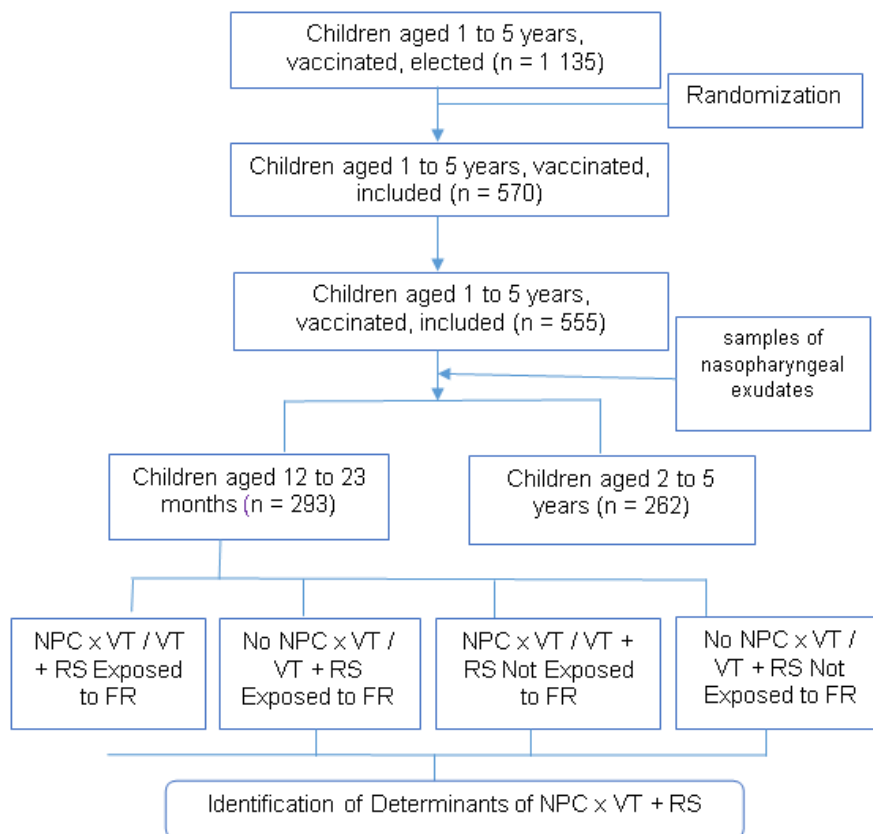
/ elimination / acquisition of nasopharyngeal colonization. However, the random selection of the subsample and the rigorous measurement of the exposure status as well as the implementation of vaccination through the

controlled clinical trial suggest that there is no underestimation of the efficacy of the intervention among those individuals exposed to the vaccine.

**RESULTS**

Of the total eligible children (1 135 vaccinated with pneumococcal conjugate vaccines in the clinical trial), 555 were included and distributed by age groups; 293 (52,8 %) were between 12-23

months of age, and 262 (47, 2 %) belonged to the age group of 2-5 years, as it is observed in the Figure.



**Fig. -** Flow chart of study of the risk factors associated with nasopharyngeal colonization one year after PCV administration.

The demographic characteristics of those vaccinated subjects included in the study are presented in Table 1. There was a predominance

of the male sex (53,5 %). Health areas identified as I and III contributed to the 55,4 % of the children studied



**Table 1** - Distribution of children by age groups and demographic characteristics

Demographic Characteristics		1-5 years N=555		12-23 months N=293		2-5 years N=262	
		No.	%	No.	%	No.	%
Sex	Female	258	46,5	129	44	129	49,2
	Male	297	53,5	164	56	133	50,8
Health areas	I	164	29,5	58	19,8	106	40,5
	III	144	25,9	45	15,4	99	37,8
	V	130	23,4	73	24,9	57	21,8
	VI	37	6,7	37	12,6	0	0
	Others	80	14,4	80	27,3	0	0

In the analysis of the changes in the NPC in the 555 children studied (Table 2), it was confirmed that, in the group aged 12 to 23 months, the NPC was eliminated by more than 70 % one year after being vaccinated with PCV. Similarly, in the 2-to 5-year-old group, the elimination of vaccine and

related serotypes was greater than 80 % for both the individuals vaccinated with PCV7-TT and those vaccinated with Pevnar 13®. On the other hand, it is important to highlight that for both vaccines and ages, more than 97 % of children did not acquire pneumococcal colonization.

**Table 2** - Changes in nasopharyngeal colonization according to vaccines, vaccine serotypes and related serotypes

Age / VT- RS	Elimination of the NPC (+ a -)						Does not acquire NPC (- a -)					
	PCV7-TT			Pevnar13®			PCV7-TT			Pevnar13®		
	N1	n1	%	N1	n1	%	N2	n2	%	N2	n2	%
<b>12-23 months (N: 293)</b>												
6B	4	4	100	7	7	100	142	138	97,0	140	137	97,9
14	0	0	0	3	3	100	146	143	98,0	144	143	99,3
18C	0	0	0	0	0	0	146	146	100	147	147	100
19F	8	8	100	10	7	70,0	138	135	98,0	137	131	95,6
23F	5	4	80,0	2	2	100	141	138	98,0	145	144	99,3
6A	2	2	100	7	6	85,7	144	132	92,0	140	133	95,0
19A	3	3	100	2	2	100	143	139	97,0	145	143	98,6
<b>2-5 years (N: 262)</b>												
6B	7	7	100	11	11	100	120	118	98,0	124	123	99,2
14	4	4	100	6	6	100	123	123	100	129	129	100
18C	1	1	100	0	0	0	126	126	100	135	135	100



19F	10	10	100	8	7	87,5	117	115	98,0	127	124	97,6
23F	2	2	100	9	8	88,9	125	123	98,0	126	125	99,2
6A	11	9	81,8	6	5	83,3	116	115	99,0	129	126	97,7
19A	6	6	100	7	6	85,7	121	119	98,0	128	128	100

**Legend:** NPC: nasopharyngeal colonization; VT: vaccine serotypes; RS: Related serotypes. N1: colonized pre-vaccination; n1: eliminate colonization post-vaccination; N2: non-colonized pre-vaccination; n2: non-colonized post-vaccination.

After evaluating the risk factors associated with the elimination and non-acquisition of vaccine and related serotypes in children vaccinated with PCV s (Table 3), it was observed that the age

group of 2-5 years was significantly related to the elimination ( $p = 0,0383$ ) and non-acquisition ( $p = 0,0069$ ) of these serotypes.

**Tabl3 3** - Risk factors associated with the elimination and non-acquisition of nasopharyngeal colonization by vaccine and related serotypes in children vaccinated with PCVs

Vaccine serotypes and related serotypes				
Risk factors	Elimination		Non-acquisition	
	<i>p</i>	OR 95% CI	<i>p</i>	OR 95% CI
<b>Individual factors</b>				
Age (2-5 years old)	0,0383	0,36 (0,13-0,96)	0,0069	0,40 (0,19-0,80)
Exclusive breastfeeding until six months	0,634	0,73 (0,26-1,94)	0,8816	0,91 (0,48-1,17)
Previous hospitalization in the last year	1	0,97 (0,02-9,3)	0,197	1,97 (0,55-5,86)
Antibiotic use in the last 2 months	0,3911	0,53 (0,12-1,74)	1	1 (0,48-1,98)
Respiratory infection in the last 30 days	0,5692	0,62 (0,11-2,36)	0,3595	1,46 (0,68-3)
More than five episodes of respiratory infections in the last year	0,463	1,55 (0,56-4,22)	0,9453	1,07 (0,56-2,02)
<b>Household factors</b>				
Sharing the room with more than two people	0,3202	0,49 (0,11-1,62)	0,6243	0,79 (0,35-1,64)
Exposure to cigarettes	0,8121	1,24 (0,44-3,37)	0,6673	0,83 (0,41-1,60)
Cohabiting with children under 5 years of age	0,9773	1,16 (0,34-3,48)	0,2882	1,5 (0,73-2,98)
Cohabiting with people over 65 years of age	0,2281	1,95 (0,55-6,13)	0,1088	1,83 (0,86-3,72)

SV: vaccine serotypes; RS: Related serotypes

In general, it is important to highlight that age between 2 and 5 acts as a protective factor for nasopharyngeal colonization with regard to

young children; in turn, living with people over 65 years of age is a risk factor related to nasopharyngeal colonization.





## DISCUSSION

It is important to highlight that despite the prevalence of invasive pneumococcal disease, nasopharyngeal colonization by pneumococcus is much more important for the environment than for the colonized individual due to the potential contagiousness.<sup>(10)</sup>

Numerous investigations have demonstrated a decrease in the prevalence of invasive pneumococcal disease and in NPC caused by vaccine serotypes associated with the routine use of pneumococcal conjugate vaccines,<sup>(11,12,13)</sup> but to date, there is no clear evidence of the time it takes to develop a new episode of colonization, especially by emerging serotypes.<sup>(14,15)</sup>

Classically, several predisposing factors for pneumococcal disease have been associated. Among them we can mention: extreme ages, geographical areas, poor socioeconomic conditions, overcrowding, attendance to day-care centers or nursery schools, congenital or acquired immunodeficiencies, previous or concomitant respiratory infections (mainly those of viral origin), living with people aged 65 years or older as well as with children under five years old, to be infected with the human immunodeficiency virus, and having leukosis or lymphomas. Chronic respiratory diseases, heart and kidney disorders, alcoholism, and smoking, especially in adults are also described.<sup>(16)</sup>

Nasopharyngeal colonization frequently occurs at ages ranging from one month to five years of life, which are associated with the highest incidence of pneumococcal disease. It is estimated that almost all children have been colonized by pneumococci at some point in their preschool

stage.<sup>(2)</sup>

The presence of factors that limit the elimination of pneumococci from the nasopharynx is known. These factors include overcrowding, attendance at day-care centers, exposure to cigarette smoke, and the routine use of antibiotics among others.<sup>(17)</sup>

Living with people over 65 years of age was found to be a risk factor associated with nasopharyngeal colonization by pneumococcus. We would like to highlight that several authors agree that sex, overcrowding, household products for cooking, and living with children under five years of age are also considered as factors associated with NPC due to pneumococcus.<sup>(14,18)</sup>

In a study conducted in children, Abdullahi et al.<sup>(19)</sup> observed that of 2 840 children aged 3 - 59 months, 1 868 were colonized by pneumococcus (65,77 %) during a two-year period. They also described the transmission and prevalence of the 28 most frequent serotypes found. It was also demonstrated that the acquisition was strongly related to the prevalence of pneumococcus in the population as well as to the elimination mechanisms dependent on the degree of immunological maturity.

Intrafamily transmission of pneumococcus has not only been identified between siblings, but also between children and adults. It is described that the strains that colonize the elderly are similar to those of the children who live with them. Moreover, it is important to note that the risk of nasopharyngeal colonization and that of invasive pneumococcal disease is significantly



increased in each episode of viral respiratory infection.<sup>(20)</sup>

The results of the Cuban context are not significantly different from those presented in other reports on this matter in other regions of the world where it has been demonstrated that nasopharyngeal colonization is associated with several risk factors such as age, geographic area,

overcrowding, use of antibiotics, and coexistence with the elderly among others.<sup>(21,22,23)</sup>

The authors consider that the conduction of the study, which is based on good clinical practices and the respect for the principles and ethical concerns, adds reliability and robustness to the results presented.

### CONCLUSIONS

Nasopharyngeal colonization by pneumococcus is mediated by risk factors that may favor the elimination and non-acquisition of vaccine-related pneumococcal serotypes. NPC is a

dynamic, changing, preventable process that can be modified with the introduction of pneumococcal vaccines.

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### Conflict of interests

The authors of this work declare that there are no conflicts of interest taking into account the non-participation of basic and preclinical research and pharmaceutical development of the product in the processes. PhD. Dunia M Chávez Amaro works at the University of Medical Sciences of Cienfuegos; PhD. María F Casanova González and MSc. Dr. Jorge L Capote Padrón work at the «Paquito Gonzalez Cueto» University Pediatric Hospital in Cienfuegos; PhD. María E. Toledo-Romaní works at the “Pedro Kouri” Institute of Tropical Medicine (IPK) in Havana, all of them belonging to the National Health System. None of them has a contractual relationship nor do they receive financing from the center that produces the vaccine. PhD. Nivaldo Linares-Pérez is an employee of the IFV, which is the Cuban center for the production of vaccines; he is the coordinator of the strategies related to the design and implementation of clinical research, surveillance studies, and evaluation of the impact of the «Pneumococcal Project».

### Authorship contribution

DMCA: Conceptualization and methodology of the study, data curation, formal analysis and writing of the original manuscript, research coordinators.



MFCG: Conceptualization and methodology of the study, data curation, formal analysis and writing of the original manuscript, research coordinators.

NLP: Conceptualization and methodology of the study, data curation, formal analysis and writing of the original manuscript.

METR: Conceptualization and methodology of the study, data curation, formal analysis and writing of the original manuscript.

JLCP: Review and editing of the manuscript.

All the authors participated in the discussion of the results and have read, reviewed, and approved the final text of the article.



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