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Incidence of acute otitis media in the age of pneumococcal conjugate vaccines: a cohort study

Abstract

Background: AOM is a common bacterial infection. PCV could impact on prevention and reduction of AOM episodes. To estimate the incidence rate (IR) of AOM in newborns from Cartagena-Colombia.

Methods: cohort study from December/2013 to June/2015 on a sample of newborn. Surveys were carried out quarterly telephone/face-to-face follow-up was carried out until 15 months old and assessed by ear-nose-throat specialist (ENT) by otoneumatoscopy to confirm the diagnosis, and took the sample for microbiological study. Positive samples were sent to National Health Institute.

Results: 876 were included. They're followed quarterly for 15 months and the loss in each follow-up was 0%, 23%, 28.6%, 5.5% and 21.5% and 53.1% were male. 23.5% were exposed to cigarette smoking and 44.4% to biomass. 67.9% had siblings younger than ten-years (11.1% had had AOM). Exclusive breastfeeding was 3 months [IQR 2.0; 5.0], onset of ablation 5.0 months [IQR 4.0; 6.0]. Vaccination schedule was optimal in 61.8%, 59.4% and 58.7% of infants-per-doses. The ENT diagnosed 44 cases of AOM. IR was 29.48 episodes-1,000 infants-year. Culture was performed in 44.5% (20/44) of cases, *HiNT* was identified in 20.0% of cases. 15.0% pneumococci, one 6C, and *Streptococcus pyogenes* in 10.0%. Risk factors: use of bottle (OR 4.37 [95%CI 1.83-10.43]), attendance at day care (OR 6.57 [2.33-18.48], low-socioeconomic status (OR 5.94 1.66-21.18]), and protective factors: breastfeeding 3 months (OR 0.27 [95%CI 0.11-0.66]) and not exposure to cigarette smoking (OR 0.03 [0.10- 0.89]).

Conclusion: The IR and risk and protective factors in this study were similar to Latin-American authors.

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Introduction

Acute otitis media (AOM) is the most common bacterial infection in infants and schoolchildren worldwide and is the main cause of medical visits, antibiotic prescription or surgery.[1–3] Generally presents a favorable natural evolution,[4] the treatment with the objective of alleviating symptoms, shortening the time of disease evolution, avoiding secondary hearing loss and preventing complications of the tombs that appear in the evolution of the process, such as mastoiditis and meningitis.[4,5]

AOM is one of the pathologies in childhood with the greatest medical, social and economic effects.[5,6] In 1996, the annual estimated costs in the United States were between $ 3 and $ 5 billion,[6,7] and in Europe the total average cost per episode of AOM can vary between € 28 and € 545,[8] but the true impact is probably underestimated because pocket costs and indirect costs are not usually included in most studies.[8,9]

Between 0.5 and 0.7 episodes per year of AOM are calculated for every child under one year of age and 0.5 to 1.2 episodes in the second year of life.[10–12] In general, most children have at least one episode before school age and one third of them experience two or more episodes or recurrent AOM in the first 3 years of life.[1,9,13–16]

AOM occupies an important place within the burden of pneumococcal disease as children experience the first episode of AOM between 6 and 11 months of age.1 The variability in the incidence rate (IR) ranges from 20952 to 124350 X 100,000 children under 5 years of age with a peak incidence in the first 2 years.[1,17–32] This variability is provided by the differences in the diagnostic criteria, the different expressions of occurrence, the imprecision in the definitions, etc. Therefore, the primary objective of this study was to estimate the incidence rate of AOM and the secondary objective was to determine the cumulative incidence and factors associated with AOM in a cohort of children in the city of Cartagena, Colombia.

Methodology

The present prospective cohort analytical study to estimate the incidence of AOM corresponds to the first phase of a macro-study aimed at estimating the effectiveness and cost-effectiveness of PCV-10 in AOM.

Study population

Between December 10, 2013 and March 31, 2014, children who met the following inclusion criteria were included: live births between gestational weeks 37 to 40 without apparent major congenital malformations (cranio-facial), healthy that did not require entry to the neonatal intensive care unit, weight greater than 1,500 grams at birth. The cohort was selected at the Rafael Calvo Maternity Clinic, because about 60% of the children of the city of Cartagena are born annually born in this location.

Data collection and patient follow-up

Trained researchers were asked to apply a questionnaire at the time of inclusion in the study. Every three months during follow-up, questionnaires were applied and adapted according to the age of the patient. In this study, parents and/or tutors were questioned about socio-economic and socio-demographic factors associated with AOM, such as socio-economic stratum, maternal educational level, exclusive breastfeeding time, ablation, eating habits, bottle feeding, presence of older siblings and siblings with a history of AOM, exposure to tobacco, attendance at day care, number of people with whom they live, as well as the vaccination status.

AOM definition

The clinical diagnosis of AOM required visual alteration of the tympanic membrane (redness, bulging, loss of light cone) or presence of effusion from the middle ear demonstrated by otoneumatoscopy. At least two of the following symptoms: otalgia, ear discharge, hearing loss, lethargy, irritability, anorexia, vomiting or diarrhea,[33] also needed to be present.

Diagnosis of AOM

Patients whose relatives/patients showed signs and symptoms of AOM, and those who were diagnosed with AOM by primary care physicians were assessed by ENT with otoneumatoscopy, which confirmed the diagnosis according to the criteria of the American Academy of Pediatrics,[33] the ENT also decided the sample-taking behavior either by swallowing of secretion auditory canal less than or equal to 72 hours or tympanocentesis for (not clinical improvement despite an adequate intervention and treatment) microbiological study.

Microbiological studies

Samples from the middle ear taken with otoneumatoscope and CDT®Speculum or from the secretion of the external auditory canal taken with calcium alginate swab were transported in medium with Stuart, then inoculated in the different isolation media (sheep blood agar To 5% and chocolate agar (CHA). The samples were distributed on AS and CHA plates, which were incubated at 37°C in a 5% CO_2 atmosphere for 24-48 hours. Phenotypic and microbiological profiles strains identified as pneumococcus and *H. influenzae* were sent to the NHI for serotyping.

In the case of multiple pneumococcal isolates of a patient at the same time or a new admission but less than one month in relation to the previous one, only one isolation per patient was included. In case of having multiple isolates of *S. pneumoniae* but with different serotype or different susceptibility or in a new episode with more than one month in relation to the previous one, they were considered as separate microorganisms.

Sample size

To obtain the sample size of our cohort, the following steps were performed:

1. An RR was calculated based on FINNES-Eskola data,[17] yielding an RR of 0.57 in the group exposed to PCV-7.

2.Taking this RR result, with a confidence level of 95%, an 80% power and a 1: 1 ratio, through the program Epidat®3.1 a total of 361 newborns exposed to the vaccine and 361 not exposed to the vaccine.

However, considering the non-vaccination of infants, due to the demonstrated effectiveness of pneumococcal conjugate vaccines[11,34–36] is not an ethical measure at present, we did not have a group of individuals without vaccine exposure, therefore the entire cohort was followed up, questioning at each visit or review their optimal vaccination status.

In addition, given the cultural characteristics of the population, educational level, difficulties in accessing health services, frequent changes in the use of telephone devices, and considering the limitations presented by David Teele's study[1] as the percentage of loss at the end of the study (53.3%), it was decided that the sample size be increased.

Variable exposure

According to the national guidelines of the Expanded Program of Immunization (EPI), we considered infants with optimal vaccination as those who received:

- 1st dose of pneumococcus: between 2 months and 2 months 29 days, that is between 42 and 89 days of birth.

- 2nd dose of pneumococcus: between 4 months and 4 months 29 days, that is between 84 and 149 days of birth.

- 3rd dose of pneumococcus: between 12 and 15 months 29 days, that is between 360 and 479 days of birth.

This registry was obtained directly from the patient's vaccination card and through PAIWEB (an information medium that allows access to the vaccination coverage records, individual records and guarantees the follow-up of the vaccination history of each person, allowing the information of the EPI to remain up-to-date, timely and reliable www.paiweb.gov.co).

Ethical considerations

The international standards for human research, strictly followed by the Declaration of Helsinki (2000) and Resolution No. 008430 of 1993 of the Ministry of Social Protection, were followed strictly and were approved by the Bioethics Committee of the University of Cartagena.

Medically (antipyretic or antibiotic) management of the AOM episode was handled by the patient's treating physicians and the research group had no influence on it.

Statistical analysis and processing

The database was constructed in the office Excel 2013 program. The database analysis was performed in the IBM SPSS (Statical Package for the Social Service) Statistics version 22 and STATGRAPHICS Centurion XV.

We performed a descriptive analysis of the cohort at their different follow-up periods, for quantitative data (discrete and continuous) we estimated means with their standard deviation (SD), median with interquartile range [IQR], and for qualitative data we calculated Proportions with 95% confidence interval (95% CI).

The incidence of AOM was determined by incidence rate and cumulative incidence. The incidence rate was calculated by considering the number of episodes in the numerator and using as the denominator the person-time that each infant was at risk of acquiring the disease. The following formula (number of episodes/1000 infants-year) was applied

$$Incidence\ episodes\ AOM = \frac{\sum e}{\sum nt} \times 1,000$$

Where $\sum e$ is the number of episodes of AOM per subject, and $\sum nt$ is the number of infants at risk of developing the disease multiplied by the days of each surveillance period. The result was multiplied by 1,000 infants and divided by 12 to spend the unit from day to year.

Cumulative incidence was calculated based on the total number of AOM episodes among subjects in the cohort.

To determine the factors associated with the first AOM episode, a univariate analysis was performed first comparing the variables of the cases of AOM and infants of the initial cohort to determine their relationship with the presence of AOM, and calculating the value of *p* by chi square, U by Man witney or Anova according to the homogeneity of variance. Subsequently, the variables with p value <0.2 were selected to be included in a bivariate logistic regression model, for which the quantitative ratio variables and ordinal qualitative variables were categorized into nominal variables Yes= 1 No = 0 in the IBM SPSS 22 program.

Results

From December 10, 2013 to March 31, 2014, 1536 newborns were captured at the Maternidad Rafael Calvo Maternity Clinic, of which 660 (57%) were excluded, who did not meet inclusion criteria or those whose relatives/relatives didn't wish to participate and refused to sign informed consent. A total sample of 876 were followed quarterly until the last participants included were 15 months of age.

At the time of the first follow-up (3 months), 100% of participants were contacted in the second follow-up (6 months) 678/876 (77.3%), the third follow-up (9 months of age) 427/876 (49%), the fourth follow-up (12 months) 378/876 (43%) and in the fifth follow-up (15 months) 189/876 that mean 21.5% of the cohort of children started (Table 1). The reasons for not being able to contact the individuals in the study were as follows: wrong telephone numbers, telephone line change, other contact number, change of address, and so on. Despite the loss of patients in each of the follow-ups performed, the proportions of the socio-demographic characteristics of the initial cohort remained the same.

Table 1 Sociodemographic data of cohort follow-up

Variables		1st follow up	2nd follow up	3rd follow up	4th follow up	5th follow up
		876 (%) [CI95%]	678 (%) [CI95%]	427 (%) [CI95%]	378 (%) [CI95%]	189 (%) [CI95%]
Sex	Female	411(46.9) [43.6-50.3]	318(46.9) [43.1-50.7]	207 (48.5) [43.7-53.3]	189(50.0) [44.9-55.1]	97(51.3) [44.0-58.6]
	Male	465(53.1) [49.7-56.4]	360(53.1) [49.3-56.9]	220(51.5) [46.7-56.3]	189(50.0) [44.9-55.1]	92(48.7) [41.4-56.0]
Health affiliation	Subsidized	851(97.1) [95.8-98.1]	657(96.9) [95.2-98.0]	413(96.7) [94.4-98.1]	367(97.1) [94.7-98.5]	184(97.4) [93.9-99.1]
	Contributive	13 (1.5) [0.8-2.6]	12(1.8) [1.0-3.2]	9(2.1) [1.0-4.1]	6(1.6) [0.6-2.6]	2(1.1) [0.1-3.8]
	Without affiliation	9 (1.0) [0.0-0.9]	6(0.9) [0.4-2.0]	4(0.9) [0.3-2.5]	4(1.1) [0.3-2.9]	2(1.1) [0.1-3.8]
Economic level	1	756(86.3) [83.8-88.5]	582(85.8) [82.9-88.3]	360(84.3) [80.4-87.6]	318(84.1) [80.0-87.7]	165(87.3) [81.7-91.7]
	2	95(10.8) [8.9-13.1]	75(11.1) [8.9-13.7]	52(12.2) [9.3-15.8]	46(12.2) [9.1-16.0]	19(10.1) [6.2-15.3]
	3	24(2.7) [1.8-4.1]	20(2.9) [1.9-4.6]	14(3.3) [1.9-5.6]	13(3.4) [1.9-6.0]	4(2.1) [0.6-5.3]
	4	0	0	0	0	0
	5	1 (0.1) [0.0-0.7]	1(0.1) [0.0-1.0]	1(0.2) [0.0-1.5]	1(0.3) [0.0-1.7]	1(0.5) [0.0-2.9]
Origin	Urban	644(73.5) [70.4-36.4]	495(73.0) [69.5-76.3]	310(72.6) [68.1-76.7]	272(72.0) [67.1-76.4]	140(74.1) [67.2-80.2]
	Rural	232(26.4) [23.3-29.2]	183(27.0) [23.7-30.5]	117(27.4) [23.3-41.9]	106(28.0) [23.6-32.9]	49(25.9) [67.2-80.2]

Citation: Coronell-Rodríguez W, Arteta-Acosta C, Mejia-Bermudes S, et al. Incidence of acute otitis media in the age of pneumococcal conjugate vaccines: a cohort study. *J Cardiol Curr Res.* 2018;11(2):106–115. DOI: 10.15406/jccr.2018.11.00381

Table Continued

Variables		1st follow up	2nd follow up	3rd follow up	4th follow up	5th follow up
		876 (%) [CI95%]	**678 (%) [CI95%]**	**427 (%) [CI95%]**	**378 (%) [CI95%]**	**189 (%) [CI95%]**
Education level	Never	36(4.1) [2.9-5.7]	25(3.7) [2.4-5.5]	14(3.3) [1.9-5.6]	13(3.4) [1.9-6.0]	5(2.6) [0.9-6.1]
	Primary	228(26.0) [23.2-29.1]	187(27.6) [24.3-31.1]	124(29.0) [24.8-33.6]	114(30.2) [25.6-35.1]	66(34.9) [28.1-42.2]
	Secondary	444(50.7) [47.3-54.0]	336(49.6) [45.7-53.4]	213(49.9) [45.0-54.2	183(48.4) [43.3-53.6]	91(48.1) [40.8-55.5]
	Technical	139(15.9) [13.5-18.5]	106(15.6) [13.0-18.6]	60(14.1) [11.0-17.8]	53(14.0) [10.8-18.0]	20(10.6) [6.6-15.9]
	University	29(3.3) [2.3-4.8]	24(3.5) [2.3-5.3]	16(3.7) [2.2-6.1]	15(4.0) [2.3-6.6]	7(3.7) [1.5-7.5]
Civil status	Married	72(8.2) [6.5-10.3]	54(8.0) [6.1-10.3]	35(8.2) [5.9-11.3]	29(7.7) [5.3-11.0]	14(7.4) [4.1-12.1]
	Free union	703(80.3) [77.4-82.8]	545(80.4) [77.1-83.3]	343(80.3) [76.2-83.9]	304(80.4) [76.1-84.1]	160(84.7) [78.7-89.5]
	Separated	12(1.4) [0.7-2.5]	11(1.6) [0.9-3.0]	8(1.9) [0.9-3.8]	7(1.9) [0.8-3.9]	2(1.1) [0.1-3.8]
	Single	88(10.0) [8.2-12.3]	67(9.9) [7.8-12.4]	41(9.6) [7.1-12.9]	38(10.1) [7.3-13.6]	13(6.9) [3.7-11.5]
	widow	1(0.1) [0.0-0.7]	1(0.1) [0.0-1.0]	0	0	0
Exposure to cigarette smoking		206(23.5) [20.8-26.5]	157(23.2) [20.1-26.6]	125(29.3) [25.0-33.9]	107(28.3) [23.9-33.9]	45(23.8) [17.9-30.5]
Exposure to biomass		389(44.4) [41.1-47.8]	320(47.2) [43.4-51.0]	180(42.2) [37.4-47.0]	166(43.9) [38.9-49.1]	72(38.1) [31.1-45.4]
Average of smokers	Mean±SD	1.2±0.5	1.3±0.6	1.3±0.6	1.3±0.6	1.3±0.6
Children younger 10 years old	1	279 (31.8) [28.8-35.1]	219(32.3) [28.8-36.0]	145(34.0) [29.5-38.7]	131(34.7) [29.9-39.7]	71(37.6) [30.6-44.9]
	2	304(34.7) [31.6-38.0]	231(34.1) [30.5-37.8]	133(31.1) [18.5-26.6]	115(30.4) [25.9-35.4]	55(29.1) [22.7-36.1]
	3	189 (21.6) [18.9-24.5]	148(21.8) [18.8-25.2]	95(22.2) [18.5-26.6]	88(23.3) [19.2-27.9]	37(19.6) [14.2-26.0]
	4	60(6.8) [5.3-8.8]	45(6.6) [4.9-8.8]	32(7.5) [5.3-10.5]	28(7.4) [5.1-10.6]	19(10.1) [6.2-15.3]
	≥ 5	42(4.8) [3.5-6.5]	34(5.0) [3.5-7.0]	22 (5.4) [3.5-8.1]	16(4.2)	7(3.7) [1.5-7.5]
N° of people living in the same house	Mean±SD	5.4±2.5	5.4±2.3	5.4±2.3	5.4±2.3	5.4±2.3
N° rooms	Mean±SD	2.4±1.0	2.4±1.0	2.4±1.0	2.4±1.0	2.4±1.0
Sibling with AOM		97(11.1) [9.1-13.4]	71(10.5) [8.3-13.1]	44(10.3) [7.7-13.7]	38(10.1) [7.3-13.6]	18(9.5) [5.7-14.6]

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Table Continued

Variables		1st follow up	2nd follow up	3rd follow up	4th follow up	5th follow up
		876 (%) [CI95%]	**678 (%) [CI95%]**	**427 (%) [CI95%]**	**378 (%) [CI95%]**	**189 (%) [CI95%]**
Earned salary	< 1 MLW	448 (51.1) [47.8-54.5]	335(49.4) [45.6-53.2]	195(5.7) [40.9-50.5]	168(44.4) [39.4-49.6]	83(43.9) [36.7-51.3]
	1-2 MLW	341(38.9) [35.7-42.3]	274(40.4) [36.7-44.2]	192(45.0) 40.2-49.8]	171(45.2) [40.2-50.4]	93(49.2) [41.9-56.6]
	2-4 SMLV	36(4.1) [2.9-5.7]	27(4.0) [2.7-5.8]	21(4.9) [3.1-7.5]	21(5.6) [3.6-8.5]	6(3.2) [1.2-6.8]
	> 4 SMLV	9(1.0) [0.5-2.0]	8(1.2) [0.5-2.4]	6(1.4) [0.6-3.2]	6(1.6) [0.6-3.6]	2(1.1) 0.1-3.8]
	Unknown	42(4.8) [3.5-6.5]	34(5.0) [3.5-7.0]	13(3.0) [1.7-5.3]	12(3.2) [1.7-5.6]	5(2.6) [0.9-6.1]
Electricity		858(97.9) [96.7-98.7]	665(98.1) [96.7-98.9]	420(98.4) [96.5-99.3	372(98.4) [96.4-99.4]	184(97.4) [93.9-99.1]
Radio		581(66.3) [63.1-69.4]	449(66.2) [62.5-69.8]	282(66.0) [61.3-70.5]	248(65.6) [60.5-70.3]	125(66.1) [58.9-72.8]
Television		837(95.5) [93.9-96.8]	653(96.3) [94.5-97.6]	412(96.5) [94.1-97.9]	363(96.0) [93.4-97.7]	184(97.4) [93.9-99.1]
Refrigerator		667(76.1) [73.1-78.9]	525(77.4) [74.1-80.5]	327(76.6) [72.2-80.5]	293(77.5) [73.0-81.6]	147(77.8) [71.2-83.5]
Bike cycle		349 (39.8) [36.6-43.2]	275(40.6) [36.9-44.4]	180(42.2) [37.4-47.0]	158(41.8) [36.8-47.0]	74(39.2) [32.2-46.5]
Motorcycle		248(28.3) [25.4-31.4]	187(27.6) [24.3-31.1]	117(27.4) [23.3-31.9]	101(26.7) [22.4-31.5]	43(22.8) [17.0-29.4]
Car		45(5.1) [3.8-6.9]	37(5.5) [3.9-7.5]	23(5.4) [3.5-8.1]	20 (5.3) [3.3-8.2]	8(4.2) [1.8-8.2]
Telephone		588 (67.1) [63.9-70.2]	405(59.7) [55.9-63.4]	218 (51.1) [46.2-55.9]	198(52.4) [47.2-57.5]	142(75.1) [68.3-81.1]
Computer		235(26.8) [23.9-29.9]	181(26.7) [23.4-30.2]	112(26.2) [22.2-30.7]	101(26.7) [22.4-31.5]	53(28.0) [21.8-35.0]
water		735(83.9) [81.3-86.2]	572(84.4) [81.4-87.0]	359(84.1) [80.2-87.3]	320(84.7) [80.6-88.1]	158(83.6) [77.5-88.6]
Sewerage		507(57.9) [54.5-61.2]	401(59.1) [55.3-62.9]	248(58.1) [53.2-62.8]	220(58.2) [53.0-63.2]	109(57.7) [50.3-64.8]
Natural gas		649(74.1) [71.0-76.9]	507(74.8) [71.3-78.0]	314 (73.5) [69.0-77.6]	282(74.6) [69.9-78.9]	142(75.1) [68.3-81.1]
Propane gas		178(20.3) [17.7-23.2]	131(19.3) [16.5-22.5]	90(21.1) [17.4-25.3]	76(20.1) [16.3-24.6]	37(19.6) [14.2-26.0]

MLW, Minimum legal wage; N° number

Considering the cohort of 876 newborns selected at the start of the study: 53.1% were male, 97.0% had subsidized health affiliation, and approximately 9 out of 10 households were of very low socioeconomic strata (stratum 1), 26.4% of the mothers came from rural areas. 50.7% of them reached secondary or partial education at the time of the interview and 15.9% higher studies (technical/university). 80.3% of them lived with their partner in a free union.

23.5% of infants were exposed to cigarette smoking from birth because at least one person smoked at home and 44.4% were exposed to biomass. 67.9% of the infants lived with at least one child younger than 10 years, 11.1% of these had a sibling with a history of AOM.

An average 5 people lived at the home with 2 rooms per household. Half of people earned less than a legal minimum wage (effective monthly in 2014), and 38.9% of households had monthly income

between 1 and 2 legal minimum wages. 97.9% of the mothers reported having electrician permanently in their home, however 17.3% lacked water, 43.1% sewerage and 26.9% natural gas (Table 1). The median with IQR of the anthropometric measurements obtained from the newborns of the cohort were 3200 grams [2945; 4650], size 50.6 centimeters [49; 52], gestational age 39 weeks [38; 39.5] (Table 2).

Of 876 infants who were followed up, exclusive breastfeeding had a median duration of 3 months, where 60% of the women breastfed sitting and sometimes lying down. The median age of ablation was 5.0 months [4.0; 6.0]. Half of the infants were fed formula milk through a bottle (Table 2). The optimal vaccination schedule for pneumococcus was 61.8% (541/876) at 3 months, 59.4% (403/678) at 6 months and 58.7% (222/378) at one year of age (Table 2).

Table 2 General cohort follow-up data

Variables	Unit of measurement	Data	
Weight	Median [IQR]	3200 [2945;4650]	
Size	Median [IQR]	50.6 [49;52]	
Gestational age	Median [IQR]	39 [38;39.5]	
Breastfeeding (months)	Median [IQR]	3.0 [2.0;4.0]	
Breastfeeding form	Sit n (%)[CI95%]	312 (35.6)	[32.5-38.9]
	lying n (%)[CI95%]	14(1.6)	[0.9-2.7]
	Mix n (%) [CI95%]	525(59.9)	[56.6-63.2]
	Does not apply	25(2.7)	[1.8-4.1]
Ablactating age (months)	Median [IQR]	5.0 [4.0;6.0]	
Pacifier	Yes n (%)[CI95%]	20(2.3)	[1.4-3.6]
Feeding bottle	Yes n (%)[CI95%]	453(51.7)	[48.3-55.1]
Optimal vaccination at two months	Yes n (%)[CI95%]	541 (61.8)	[57.9-64.5]
	No n (%)[CI95%]	335(38.7)	[35.5-42.1]
Optimal vaccination at 4-12 months	Yes n (%)[CI95%]	403(59.4)	[56.3-63.0]
	No n (%)[CI95%]	275(40.5)	[37.3.5-45.1]
	ND (%)[CI95%]	239(27.3)	[24.4-30.4]
Child care	Yes n (%)[CI95%]	43(4.9)	[3.6-6.6]
	No n (%)[CI95%]	336 (38.4)	[35.1-41.7]
	ND n (%)[CI95%]	497 (56.7)	[53.4-60.0]

ND, No data

During the follow-up, a total of 55 cases were reported by primary care attendants/physicians as compatible with AOM, however the ENT confirmed 44 cases of AOM by otoneumatoscopy, 8 cases with otitis externa and 3 cases with chronic otitis media. Three patients from the 44 cases had a second episode of AOM with an interval greater than 30 days (Table 3).

The number of episodes diagnosed with AOM during each follow-up (3, 6, 9, 12, 15 months) were: 7, 8, 11, 6 and 12, and the optimal vaccination schedule against pneumococcus for this patients were 100% , 73%, 0% and 50%, respectively (Table 3).

The IR AOM of the cohort was 29.48 [21.69 - 39.23] episodes per 1,000 infants-year. The relative risk (RR) calculated in cases with first episode (41 cases) of AOM was 1.01 [95% CI 1.00-1.03], when all 44 cases were included, RR remained at 1.01 [95% CI 0.99-1.03].

However, taking into account the follow-up performed in the cohort (3, 6, 9, 12, 15 months), the IR AOM was 32.0, 23.6, 34.3, 15.9 and 50.8 episodes per 1,000 infants-year respectively (Table 3). IR with and without optimal vaccination was 29.9 and 28.8 episodes per 1,000 infant-years, respectively. For a calculated RR of 1.04 [95% CI 0.56-1.90] (Table 3), the cumulative incidence of AOM was 5.0%.

41 of 44 patients had a single episode of AOM until the end of the follow-up period and three of them had a second episode with 30 days difference.

The univariate analysis compared the characteristics of the cases of AOM and the infants of the follow-up cohort, the socioeconomic stratum, bottle use, ablation, exposure to passive cigarette smoking, history of sibling with AOM and the attendance to the nursery were statistically significant ($p < 0.05$) (Table 4). To determine the factors associated with the first AOM episode, a logistic regression model

was made, finding risk factors: daycare assistance (OR 6.57 [95% CI 2.33-18.48]), medium-low socioeconomic stratum (OR 5.94 [95% CI 1.66 - 21.18]) and use of bottles (OR 4.37 [95% CI 1.83 - 10.43]); as a protective factors: No early exposure to passive cigarette smoking (OR 0.03 [95% CI 0.10 – 0.89]) and exclusive breastfeeding for at least 3 months (OR 0.27 [95% CI 0.11-0.66]). There was no statistically significant difference in the optimal vaccination status, sibling with history of AOM, ablation and living in the urban/rural area (Table 5).

Table 4 Factors associated with first episode of AOM. Univariate analysis

VARIABLES		Cohort N 835 (%) [CI95%]	Cases N 41 (%) [CI95%]	p
Sex	Female	392(46.9)[43.5-50.4]	19(46.3)[30.7-62.6]	1.0*
	Male	443(53.1)[49.6-56.5]	22(53.7)[37.4-69.3]	
Economic level	1	730(87.4)[84.9-89.6]	26(63.4) [46.9-77.9]	**0.00**
	2	85(10.2)[8.3-12.5]	10(24.4)[12.4-40.3]	
	3	19(2.3)[1.4-3.6]	5(12.2)[4.1-26.2]	**0.00**
	4	0	0	0.81
	5	1(0.2)[0.0-0.8]	0	
Origen	Urban	609(72.9)[69.8-75.9]	35(85.4)[70.8-94.4]	0.54*
Breastfeeding (months)	Time Median [IQR]	3.0 [2.0-4.0]	3.0 [1.0-5.0]	0.69^
	0-3	577 (69.1) [68.0-73.7]	23(56.0)[39.2-71.4]	0.08
	3-6	243(29.1) [26.4-32.6]	17(41.4)[23.6-54.4]	0.09
	>6	14(1.67) [1.0-2.8]	1(2.4) [0.1-12.9]	0.71
Breastfeeding form	Sit	303(36.3)[33.0-39.7]	9(22.0)[10.6-37.6]	0.06
	Lying	13(1.6)[0.9-2.7]	1(2.4)[0.1-12.9]	0.69
	Both	499(59.8)[56.3-63.1]	26(63.4)[46.9-77.9]	0.61
	NA	20 (2.4)[1.5-3.7]	5(12.1) [4.1-26.2]	**0.00**
Feeding bottle	Yes	423(50.7)[47.2-54.1]	31(75.6)[57.1-85.8]	**0.001**
	No	411(49.2)[45.8-52.7]	8(19.5) [8.8-34.9]	
	NA	1(0.1)[0.0-0.8]	2(4.8) [0.8-22.8]	
Ablactating age (months) N (%)[CI95%]	Median [IQR]	5.0 [4.0-6.0]	4.0 [3.0-6.0]	0.05
	0-3	105(12.5)[9.2-15.3]	9(22.0)[10.6-37.6]	0.08
	3-6	496(59.4)[53.2-62.5]	21(51.2)[35.1-67.1]	0.29
	>6	43(5.1)[2.3-8.5]	3(7.3)[1.4-23.0]	0.54
Pacifier	Yes	19(2.3) [1.4-3.6]	1(2.4) [0.1-12.9]	0.945*
	No	816(97.7)[95.0-97.6]	37(90.2) [76.9-97.3]	
Exposure to cigarette smoking	Yes	200(24.0)[21.1-27.0]	6(14.6)[5.6-29.2]	**0.005***
	No	635(76.0)[72.0-78.0]	34(82.9) [60.2-88.4]	
Sleep along	N° people Mean±SD	5.0 [4.0-7.0]	5.0 [4.0-7.0]	1.0
Optimal vaccination against pneumococcal	Yes	521(62.4)[59.0-65.7]	20(51.2)[32.9-64.9]	0.080
	No	314(37.6)[34.3-41.0]	21(51.2)[35.1-67.1]	
Sibling with history AOM	Yes	89(10.7)[8.7-13.0]	8(19.5)[8.8-34.9]	**0.032**
	No	691(82.8)[80.0-85.2]	29(70.7)[54.5-83.9]	
	Unknown/NA	55(6.5)[4.2-8.7]	4(9.8)[2.7-23.1]	
Child care	Yes	27(3.2) [2.2-4.7]	10(24.4) [12.4-40.3]	**0.000**
	No	149(17.8) [15.3-20.6]	7(17.1)[7.2-31.1]	
	NA	659(78.9) [76.0-81.6]	24(58.5) [42.1-73.7]	

NA, not apply

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Table 5 Factors associated with first episode of AOM. Multivariate analysis

Variables	Regression coefficient	Standard error	p valor	OR	CI 95%
Pacifier	**1,476**	**0,443**	**0.001**	**4.37**	**1.83 - 10.43**
Not Exposure to tobacco	**-1,188**	**0,550**	**0.031**	**0.03**	**0.10 – 0.89**
Child care	**1,883**	**0,528**	**<0.001**	**6.57**	**2.33 – 18.48**
Optimal vaccination	-0,655	0,357	0.066	0.52	0.25 – 1.04
Sibling with history AOM	0,218	0,774	0.778	0.80	0.17 – 3.66
Ablactating before 3 months	0,502	0,564	0.374	1.65	0.54 – 4.98
Ablactating 3-6 months	-0,612	0,523	0,242	0,54	0,19- 1.51
Ablactating after 6 months	-0,050	0,842	0,952	1,05	0,202 – 5.48
Urban	0,722	0,476	0,130	2,05	0,80- 5.23
Low socioeconomic	**1,782**	**0,649**	**0,006**	**5,94**	**1,66 – 21,18**
Breastfeeding 3 months	**-1,295**	**0,454**	**0,004**	**0,27**	**0,11 – 0.66**

Discussion

AOM is the most common multifactorial, middle ear polymicrobial disease occurring in infants and schoolchildren worldwide.[37] It is one of the pathology of childhood with greatest medical, social and economic effects.[1,3] The incidence of AOM is one of the key assumptions in the cost-effectiveness studies of the new pneumococcal conjugate vaccines.[8] Different studies of cost-effectiveness in Latin America[34,35,38] have been based on the incidence of AOM reported by the studies of D. Teele,[1] Fireman,[39] Eskola[17] and Prymula.[2]

However, estimating the incidence of AOM is controversial even today. The three main reasons why it is difficult to homogenize the results found in the different studies are: 1) differences in the definition of cases of AOM, 2) how to make the diagnosis, either by differences in the evaluator (general practitioner, (Otoscope, otoneumatoscope, signs and symptoms referenced by patients, use of scales such as ¨otoscopic severity OS-8), and 3) the unit of measurement used to calculate incidence rate, which varies from: number of episodes per (100, 1,000 or 100,000) person-years, number of ears, number of visits per year. All above complicate the interpretation and adequate use of results for making decisions regarding on the true burden of disease by AOM in different countries.

In this study we found an AOM incidence rate of 29,5 per 1,000 infants-year, similar to other Latin American countries,[38,40,41] for example, Mexico and Chile have reported lower incidence rates of pre-pneumococcal conjugate vaccine,[42–44] while in developed countries higher incidence rates have been reported,[10] which may be influenced by different ways of diagnosing AOM. It is important to emphasize, that in Israel in pre-vaccination period (from 2004 to 2010) AOM incidence rate changed from 30.0 per 1,000 episodes in children under 2 years of age, to 19.9 per 1,000 infant-year episodes[45] and post-introduction of pneumococcal conjugate vaccines (PCV-13 2010-2013) decreased from 21.5 to 10.1 x 1,000 infant-year episodes.[45]

We found a cumulative incidence of AOM of 5%, similar to the COMPAS study[40] carried out in Latin American countries (Panama, Argentina and Colombia), where the cumulative incidence was 7.1% of AOM to the group with the PCV and 8.5% to the control group. In both studies the diagnosis of AOM was first made by the symptoms reported to the parents and then confirmed or discarded by the ENT specialist.

Regarding to the factors associated with AOM, the literature reports since D. Teele studies,[1] that males (OR 1.70 CI95% 1.21-2.38), siblings with AOM history (OR 2.23 95% CI 1.49-3.32) were risks factors, in our study we did not find that association, as reported by other authors.[46,47] In subsequent studies, different researchers have found particular risk factors such as child care,[46–50] bottle feeding[48] and low socioeconomic status,[51] which have been consistent with our findings. Likewise, breasthfeeding (1,46,48,51) (OR entre 0.19 y 0.64) has been determined as a protective factor, as it was in our study (OR 0.27) [95% CI 0.11-0.66].

Non-exposure to cigarette smoke was a protective factor in the logistic regression of our study (OR 0.03 95% CI 0.10-0.89), so its presence can be interpreted as a risk factor for the development of AOM. While this has been found in different studies[51] (OR 2.38 IC95% 1.51-3.75), other authors have not found this association.[46,47,49]

Limitations

Within the limitations of this study is the loss of patients during follow-up, which was taken into account at the time of the initial capture that increased by 20% of the calculated data. The loss of patients in the present study were significant and even compare with the losses of D. Teele Study,[1] so new studies with a larger sample size are required. However, in the present study, spite of these losses, the general characteristics were maintained between the different groups of follow-up cohorts, in addition to the remaining n of the cohort allowed us to perform a respective analysis.

In the present study, the final diagnosis of AOM was performed by the ENT specialist using pneumatoscopy, when the family members/caregivers reported signs and symptoms related to AOM or patients whose diagnosis was made by primary care physicians, similar to the Prymula's study[2] and Tregnaghi,[40] these studies makes the diagnosis more strict when compared with other author, so that the number of cases of otitis may be lower.

Likewise, certain actions were taken to reduce selection and information bias. The participants were newborns at term, healthy, and

had no exposure to the study event and the quarterly questionnaires allowed us to analyze and compare information about the same variable.

Conclusion

This is the first study about incidence of AOM in the post-PCV10 era in Colombia. The incidence rate found was lower than others studies, but in similar with Latin American studies,[40,41] where like the present study the diagnosis made ENT specialist.[40] Day care, bottle use and low socioeconomic status were risk factors, while breastfeeding for at least 3 months and non-exposure to cigarette smoke were identified as protective factors against AOM. We suggest further analytical studies in developing countries, to have a statistical data reflecting the true burden of the disease.

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