

# Risk factors for otitis media in children with special emphasis on the role of colonization with bacterial airway pathogens: the Generation R study

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**Abstract** Acute otitis media is the most frequent diagnosis in children visiting physicians' offices. Risk factors for otitis media have been widely studied. Yet, the correlation between bacterial carriage and the development of otitis media is not entirely clear. Our aim was to study in a population-based prospective cohort the risk factors for otitis media in the second year of life with special emphasis on the role of colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. The study was embedded in the Generation R Study. Data on risk factors and doctor-diagnosed otitis media were obtained by midwives, hospital registries and postal questionnaires in the whole cohort ( $n = 7,295$ ). Nasopharyngeal swabs were obtained at the age of 1.5, 6 and 14 months in the focus cohort ( $n = 1,079$ ). Of these children, 2,515 (47.2%) suffered at least one period of otitis

media in their second year of life. The occurrence of otitis media during the follow-up period in the first 6 months of life and between 6 and 12 months of age was associated with the risk of otitis media in the second year of life (aOR, 1.83 95% CI 1.24–2.71 and aOR 2.72, 95% CI 2.18–3.38, respectively). Having siblings was associated with an increased risk for otitis media in the second year of life (aOR 1.42, 95% CI 1.13–1.79). No associations were found between bacterial carriage in the first year of life and otitis media in the second year of life. In our study, otitis media in the first year of life is an independent risk factor for otitis media in the second year of life. Surprisingly, bacterial carriage in the first year of life did not add to this risk. Moreover, no association was observed between bacterial carriage in the first year of life and otitis in the second year of life.

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## Abbreviations

OR Odds ratio  
CI Confidence interval  
aOR Adjusted odds ratio

## Introduction

Acute otitis media is one of the most common childhood infections and the leading cause for children to visit a doctor [1]. Most children experience at least one episode of otitis media; in 50–85% of the children acute otitis media is diagnosed at least once in the first 3 years of life [2, 3].

Risk factors for otitis media have widely been studied. In addition to host factors like birth weight, gestational age and craniofacial abnormalities, environmental factors like passive smoking, day care attendance, socioeconomic status, pacifier use and breast-feeding have been studied. Frequency of colonization with bacterial airway pathogens was shown to be associated with otitis media in the first years of life [4–8]. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are the most frequently cultured pathogens in acute otitis media. Early age of colonization seems to increase the risk of otitis media [4, 8, 9]. Syrjänen et al. have suggested that carriage of newly acquired bacteria is associated with otitis media [10].

Our aim was to study in a population-based prospective cohort the risk factors for otitis media in children with special emphasis on the role of colonization with *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* in the first year of life.

## Patients and methods

### Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study has been described in detail previously [11, 12]. The cohort includes 9,778 mothers and their children living in Rotterdam, the Netherlands. Detailed assessments of fetal and postnatal growth and development were conducted in 1,232 Dutch pregnant women and their children in the Generation R Focus Study. The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, has approved the study. Written informed consent was obtained from all participants.

### Measurements and outcome

We obtained data on birth weight, gestational age and gender from midwives and hospital registries. Information about maternal smoking, siblings, educational level of the mother, day care attendance, breast-feeding, pacifier use and otitis media in the first year of life was obtained by postal questionnaires at the infants' age of 6, 12 and 24 months. Mothers were asked whether their children suffered from fever in the prior period (no, yes), and subsequently whether this period of fever was accompanied by earache and whether they had visited a doctor. The diagnosis otitis media in the period from 0 to 6 months of age and the period from 6 to 12 months of age was defined as having at least one period of fever accompanied by earache

for which a doctor was visited during any part of the 6 months before reaching the age of respectively 6 and 12 months. Likewise, the diagnosis of otitis media in the second year of life was defined as having at least one period of fever accompanied by earache for which a doctor was visited during any part of the year before reaching the age of 24 months. Furthermore, otitis-proneness was defined as having four or more episodes by 1 year of age, six or more by 2 years of age, or placement of myringotomy tubes, similar to the definition used by Faden et al. [7]. Risk factors for otitis media in the second year of life were studied in the whole cohort.

In the Focus cohort, samples were taken at the infants' age of 1.5, 6, and 14 months to detect nasopharyngeal bacterial carriage. Nasopharyngeal samples were taken with rayon tipped dacron pernasal swabs (Copan Italia, Brescia, Italy) and transported in Amies transport medium and plated within 6 h of sampling on a blood agar plate with 5% sheep blood, a chocolate agar plate and a *Haemophilus* selective agarplate. The plates are kept at 35°C in a CO<sub>2</sub> rich environment for 2 days. Bacterial growth was determined daily. All bacteria were determined by use of standard methods.

### Analyses

In the whole cohort associations of birth weight, gestational age, gender, maternal smoking, siblings, educational level of mother, day care attendance, duration of breast-feeding, pacifier use and otitis media in the first year of life with otitis media in the second year of life were assessed by logistic regression models resulting in odds ratios (OR) with their 95% confidence interval (CI). Additionally, a multivariate logistic regression model was performed to assess the association of each risk factor separately with otitis media in the second year of life was adjusted for all the other risk factors resulting in adjusted odds ratios (aOR). In the focus cohort association of bacterial carriage in the first year of life with otitis media in the second year of life was assessed for the airway pathogens *S. pneumoniae*, *M. catarrhalis* and *H. influenzae*. The analyses were performed using frequency of specific bacterial carriage in the first year of life, and at ages of first bacterial carriage. Furthermore, we did the same analysis with the three bacteria grouped as any airway pathogen. Additionally, regression models were adjusted including all determinants presented in Table 1. Furthermore, possible interaction between otitis media in the first year of life and bacterial carriage and the risk of otitis media in the second year of life was tested. According to the national Dutch vaccination policy all children were vaccinated against *H. influenzae B*, but non of the children were vaccinated against pneumococci.

**Table 1** Population descriptive

	Otitis media 12–24 months of age			OR	aOR
	<i>n</i> = 5,323	No <i>n</i> = 2,808 (52.8%)	Yes <i>n</i> = 2,515 (47.2%)		
Birthweight	3,438 (574)	3,422 (577)	3,456 (570)	<b>1.11* (1.01–1.22)</b>	1.07 (0.84–1.37)
Gestational age	40.0 (25.3–43.4)	40.0 (25.3–43.3)	40.1 (27.1–43.4)	1.02 (0.99–1.05)	1.04 (0.97–1.12)
Gender					
Male (ref)	2,643 (49.7)	48.4%	51.0%		
Female	2,680 (50.3)	51.6%	49.0%	0.90 (0.81–1.00)	0.89 (0.72–1.11)
Smoking					
No (ref)	3,110 (84.9)	85.1%	84.6%		
Yes	554 (1.15)	14.9%	15.4%	1.04 (0.87–1.25)	1.16 (0.86–1.55)
Siblings					
No (ref)	2,159 (58.9)	62.9%	54.1%		
Yes	1,508 (41.1)	37.1%	45.9%	<b>1.44*** (1.26–1.65)</b>	<b>1.42* (1.13–1.79)</b>
Educational level mother					
Low	292 (5.8)	4.7%	7.0%		
Middle	1,911 (37.8)	37.3%	38.4%	<b>0.69** (0.54–0.88)</b>	0.84 (0.36–1.95)
High	2,851 (56.4)	58.1%	54.5%	<b>0.62*** (0.49–0.80)</b>	1.03 (0.44–2.40)
Day care					
No (ref)	730 (22.3)	21.3%	23.5%		
Yes	2,543 (77.7)	78.7%	76.5%	0.88 (0.75–1.04)	0.86 (0.66–1.13)
Breastfeeding					
Never (ref)	450 (19.0)	17.7%	20.4%		
Less than 3 months	1,031 (43.5)	46.3%	40.3%	<b>0.76* (0.61–0.95)</b>	0.86 (0.63–1.16)
More than 3 months	890 (37.5)	36.0%	39.3%	0.95 (0.76–1.19)	1.14 (0.83–1.55)
Pacifier use					
No (ref)	1,242 (34.4)	34.5%	34.4%		
Yes	2,364 (65.6)	65.5%	65.6%	1.01 (0.88–1.16)	0.95 (0.75–1.20)
Otitis from 0 to 6 months					
No (ref)	3,309 (91.9)	94.7%	88.5%		
Yes	292 (8.1)	5.3%	11.5%	<b>2.34*** (1.82–3.00)</b>	<b>1.83** (1.24–2.71)</b>
Otitis from 6 to 12 months					
No (ref)	2,808 (52.8)	67.4%	45.8%		
Yes	2,515 (47.2)	32.6%	54.2%	<b>2.44*** (2.16–2.76)</b>	<b>2.72*** (2.18–3.38)</b>

Values of birth weight is mean (standard deviation), gestational age is median (range). Other values are absolute numbers (percentages). Data were missing on birth weight ( $n = 8$ ), gestational age ( $n = 1$ ), maternal smoking ( $n = 1,659$ ), siblings ( $n = 1,656$ ), educational level of mother ( $n = 269$ ), day care attendance ( $n = 2,050$ ), breast feeding ( $n = 2,952$ ), pacifier use ( $n = 1,717$ ), otitis from 0 to 6 months ( $n = 1,722$ ) and otitis from 6 to 12 months ( $n = 815$ ). No data was missing on gender. OR univariate model, aOR full model. Birthweight entered in analyses in Kg. \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$

Differences of infant characteristics between infants with and without data on otitis media in the second year of life were assessed by the independent sample  $t$ -test for continuous normal distributed variables, non-parametric Mann–Whitney test for continuous non-normal distributed variables and the chi-square test for categorical variables. Differences of frequency of otitis media in the second year of life between groups with missing risk factors and complete data were assessed in the same way. All tests were carried out using a two-sided alpha level of 5%. The

statistical analyses were performed using the Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

## Results

In the Generation R Cohort, 7,295 children, with a delivery date from April 2002 until January 2006, participated in the postnatal phase of the study. Data on otitis media in the

second year of life was available in 5,323 (response rate 73%) children. Characteristics of the children of the whole cohort and their association with otitis media in the second year of life are presented in Table 1. Having siblings is associated with an increased risk of otitis media in the second year of life (aOR 1.42, CI 1.13–1.79). Furthermore, the occurrence of otitis media during the follow-up period between 0 and 6 months and the occurrence of otitis media during the follow-up period between 6 and 12 months of age was associated with the occurrence of otitis media in the second year of life (respectively, aOR 1.83, CI 1.24–2.71 and aOR 2.72, CI 2.18–3.38).

Bacterial carriage was studied in the focus cohort, in which 1,079 children, with a delivery date from February 2003 until August 2005, participated. The children were planned to visit the Generation R Focus Study research centre at the age of 1.5 month (response rate 81.8%), 6 months (response rate 81.6%) and 14 months (response rate 80.0%). Of the infants 379 (43.3%) had at least one episode of otitis media in the second year of life.

In Table 2 the associations between the frequency of bacterial carriage in the first year of life and otitis media in the second year of life are presented. We analysed the association between bacterial carriage in the first year of life and otitis media in the second year of life in two different ways. First, we defined carriage by adding the three sampling time points and assessed whether the frequency of bacterial carriage was associated with otitis media. Second, we assessed whether early age of bacterial carriage was associated with otitis media (data not shown). Both

analyses were done for the bacteria separately and for any airway pathogen. No associations were observed. In addition to this, we assessed whether bacterial carriage in the first year of life was associated with otitis-proneness. Again, no associations were observed (data not shown).

Possible interaction between otitis media in the first year of life and bacterial carriage was tested. The interaction term was not significant. In Table 3 we present the associations between otitis media in the first year of life (6–12 months) and otitis media in the second year of life stratified for different bacterial carriage states in the first year of life. Bacterial carriage did not significantly change the increased risk for otitis media in the second year of life in case previous otitis media (6–12 months) was registered.

## Discussion

We observed a positive association between having siblings and otitis media. Also, we observed a tendency that low education of the mother might attribute to the risk for otitis media, while breast-feeding might be a protective factor. No associations were observed between birth weight, gestational age, gender, maternal smoking, day care attendance or pacifier use and otitis media in the second year of life. In a meta-analysis of risk factors for acute otitis media by Uhari et al. [13] day care attendance was shown to be the most significant risk factor. Furthermore, similar to the trend we observed, Uhari et al. showed a positive association between siblings and otitis media and a

**Table 2** Association between bacterial carriage in the first year of life and otitis media in the second year of life

	Otitis media 12–24 months of age			OR	aOR
	n (%)	No (n = 384) (%)	Yes (n = 287) (%)		
<i>Streptococcus pneumoniae</i>					
Never (reference)	316 (47.1)	47.1	47.0	Reference	Reference
Once	241 (35.9)	35.4	36.6	1.04 (0.74–1.45)	0.64 (0.35–1.17)
2 or more	114 (17.0)	17.4	16.4	0.94 (0.61–1.45)	0.72 (0.33–1.57)
<i>Moraxella catarrhalis</i>					
Never (reference)	354 (52.8)	54.7	50.2	Reference	Reference
Once	240 (35.8)	33.1	39.4	1.30 (0.93–1.81)	1.57 (0.88–2.80)
2 or more	77 (11.5)	12.2	10.5	0.93 (0.56–1.54)	0.91 (0.38–2.15)
<i>Haemophilus influenzae</i>					
Never (reference)	381 (56.8)	58.3	54.7	Reference	Reference
1 ×	224 (33.4)	31.5	35.9	1.22 (0.87–1.69)	1.08 (0.60–1.96)
Once	66 (9.8)	10.2	9.4	0.99 (0.58–1.68)	1.16 (0.44–3.08)
Airway pathogen					
Never (reference)	136 (20.3)	20.6	19.9	Reference	Reference
Once	163 (24.3)	25.3	23.0	0.94 (0.59–1.50)	0.58 (0.25–1.35)
2 or more	372 (55.4)	54.2	57.1	1.09 (0.73–1.63)	0.86 (0.40–1.84)

OR univariate model, aOR full model including all risk factors as shown in Table 1

**Table 3** Association between otitis media in the first year of life (6–12 months) and otitis media in the second year of life stratified by carriage state of different bacteria

		Otitis media (12–24 months of age)			OR	aOR
		n (%)	No (n = 308) (%)	Yes (n = 217) (%)		
Never <i>S. pneumoniae</i>	Otitis media 6–12 months of age					
	No	176 (71.5)	81.9	56.9	Reference	Reference
	Yes	70 (28.5)	18.1	43.1	3.44 (1.93–6.14)	2.81 (1.14–6.92)
Once or more <i>S. pneumoniae</i>	Otitis media 6–12 months of age					
	No	192 (68.8)	78.0	55.7	Reference	Reference
	Yes	82 (31.2)	22.0	44.3	2.83 (1.68–4.77)	2.81 (1.27–6.24)
Never <i>M. catarrhalis</i>	Otitis media 6–12 months of age					
	No	194 (70.3)	79.5	56.4	Reference	Reference
	Yes	82 (29.7)	20.5	43.6	3.01 (1.76–5.12)	2.26 (1.00–5.12)
Once or more <i>M. catarrhalis</i>	Otitis media 6–12 months of age					
	No	174 (69.9)	80.3	56.1	Reference	Reference
	Yes	75 (30.1)	19.7	43.9	3.19 (1.82–5.60)	3.19 (1.31–7.74)
Never <i>H. influenzae</i>	Otitis media 6–12 months of age					
	No	197 (68.2)	77.3	54.7	Reference	Reference
	Yes	92 (31.8)	22.7	45.3	2.82 (1.70–4.70)	2.90 (1.34–6.28)
Once or more <i>H. influenzae</i>	Otitis media 6–12 months of age					
	No	171 (72.5)	83.1	58.0	Reference	Reference
	Yes	65 (27.5)	16.9	42.0	3.56 (1.96–6.48)	3.25 (1.30–8.12)
Never airway pathogen	Otitis media 6–12 months of age					
	No	77 (72.6)	84.1	55.8	Reference	Reference
	Yes	29 (27.4)	15.9	44.2	4.20 (1.70–10.37)	4.20 (1.70–10.37)
Once or more airway pathogen	Otitis media 6–12 months of age					
	No	291 (69.5)	78.8	56.3	Reference	Reference
	Yes	128 (30.5)	78.8	43.7	2.88 (1.88–4.42)	2.76 (1.50–5.09)

OR univariate model, aOR full model including all risk factors as shown in Table 1

negative association between breast feeding and otitis media. This study, in contrast to our results, also showed that parental smoking and pacifier use was associated with otitis media.

We observed that otitis media in the first year of life is a risk factor for otitis media in the second year of life. Corbeel has stated that the first period of otitis media determines the risk for recurrence because inflammation causes dysfunction of the Eustachian tube in young children due to the small caliber and the horizontal direction and is, therefore, predisposing for a high risk for recurrent of otitis media [14].

Next, we analyzed in the focus cohort the association between bacterial carriage and otitis media in the second year of life, and otitis-proneness. No associations were observed between frequency of bacterial carriage, age of first bacterial carriage or the different species of bacterial carriage and otitis media or otitis-proneness. In addition, we observed no role for bacterial carriage in recurrent otitis media. Bacterial carriage in the first year of life is not associated with otitis media later on. In other studies the frequency of carriage with different bacteria was shown to

be associated with otitis media [4, 5, 7, 8]. Faden et al. have shown that carriage of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* was associated with otitis-proneness in 17 otitis prone children versus 17 non-otitis prone children, during healthy periods and during periods of otitis media, in children aged 0–36 months in. The association in healthy periods was only significant for *H. influenzae* carriage but not for the other two bacteria studied [7]. In another study in 157 infants, an association between carriage of *H. influenzae*, measured at 13 routine visits in the first year of life, and otitis-proneness was shown [8]. In another study in 306 children aged 0–24 months, an association between *M. catarrhalis* and otitis-proneness was observed [5]. In this population they also showed an association between the frequency of carriage of the three airway pathogens and the frequency of otitis media episodes [4]. Prellner et al. did not show an increased risk for otitis media when *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* were present [15]. Early age of first colonization was also shown to be associated with the risk for otitis media [4, 8, 9]. But, Syrjänen et al. have shown in their study on the

temporal association between pneumococcal carriage and otitis media that not preceding pneumococcal carriage state, but newly acquired carriage is associated with otitis media [10]. Their data support the hypothesis that viral respiratory infection might enhance the acquisition of pneumococci. Recently, Revai et al. have shown an association between presence of pathogenic bacteria in the nasopharynx during upper respiratory tract infections and the risk for otitis media following the upper respiratory tract infection [16]. Taken together, it appears that the presence of newly acquired pathogenic bacteria in combination with (viral) upper respiratory tract infections increases the risk for otitis media, rather than the presence of pathogenic bacteria itself increases the risk for otitis media.

To appreciate the results some limitations of our study had to be considered. In contrast to other studies, our definition of otitis media was based on parental reported questionnaire data, we do not have a doctor verified diagnosis of otitis media. We observed that 49 (7.2%) of the children had at least one period of otitis media in their first 6 months of life, 247 (31.3%) had otitis media in their second 6 months of life and 379 (43.3%) of the children had at least one period of otitis media in their second year of life. 511 (71.8%) of the children had at least one period of otitis media by the age of 24 months. This might be an overestimation of the number of children experiencing otitis media, resulting in less contrast between children with and without otitis media. This might explain that we did not find significant risk factors for otitis media. On the other hand, children with fever and earache were only classified as otitis “yes” if they visited a doctor. To our opinion this makes our definition of otitis media reliable.

## Conclusion

In our study, otitis media in the first year of life is an independent risk factor for otitis media in the second year of life. Surprisingly, bacterial carriage in the first year of life did not add to this risk. Moreover, no association was observed between bacterial carriage in the first year of life and otitis in the second year of life.

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