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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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► To cite this version:

Joost A. M. Labout, Liesbeth Duijts, Ankie Lebon, Ronald Groot, Albert Hofman, et al.. Risk factors for otitis media in children with special emphasis on the role of colonization with bacterial airway pathogens: the Generation R study. *European Journal of Epidemiology*, 2010, 26 (1), pp.61-66. 10.1007/s10654-010-9500-2 . hal-00619928

HAL Id: hal-00619928

<https://hal.science/hal-00619928v1>

Submitted on 7 Sep 2011

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1 **RISK FACTORS FOR OTITIS MEDIA IN CHILDREN WITH SPECIAL**
2 **EMPHASIS ON THE ROLE OF COLONIZATION WITH BACTERIAL AIRWAY**
3 **PATHOGENS.**

4 **THE GENERATION R STUDY.**

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17
18 Abbreviations: odds ratio (OR), confidence interval (CI), adjusted odds ratio
19 (aOR)

20
21 Key words: otitis media, risk factors, *Streptococcus pneumoniae*, *Haemophilus*
22 *influenzae* and *Moraxella catarrhalis*

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32 Sources of support: Erasmus Medical Center, Rotterdam, the Erasmus University

33 Rotterdam, the Netherlands Organization for Health Research and Development

34 (Zon Mw), Stichting W.H. Kröger, Rotterdam (Grant No. 00-048), and AGS

35 Kinderstichting.

36

37 **Abstract**

38 Objective

39 Acute otitis media is the most frequent diagnosis in children visiting physicians'
40 offices. Risk factors for otitis media have been widely studied. Yet, the correlation
41 between bacterial carriage and the development of otitis media is not entirely
42 clear. Our aim was to study in a population-based prospective cohort the risk
43 factors for otitis media in the second year of life with special emphasis on the role
44 of colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae* and
45 *Moraxella catarrhalis*.

46 Patients and methods

47 The study was embedded in the Generation R Study. Data on risk factors and
48 doctor-diagnosed otitis media were obtained by midwives, hospital registries and
49 postal questionnaires in the whole cohort (n=7295). Nasopharyngeal swabs were
50 obtained at the age of 1.5, 6 and 14 months in the focus cohort (n=1079).

51 Results

52 Of these children, 2515 (47.2%) suffered at least one period of otitis media in
53 their second year of life. The occurrence of otitis media during the follow-up
54 period in the first 6 months of life and between 6 and 12 months of age was
55 associated with the risk of otitis media in the second year of life (aOR, 1.83 95%
56 CI 1.24-2.71 and aOR 2.72, 95% CI 2.18-3.38, respectively). Having siblings was
57 associated with an increased risk for otitis media in the second year of life (aOR
58 1.42, 95% CI 1.13-1.79). No associations were found between bacterial carriage
59 in the first year of life and otitis media in the second year of life.

60 Conclusions

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

66

67 **Introduction**

68 Acute otitis media is one of the most common childhood infections and the
69 leading cause for children to visit a doctor. (1) Most children experience at least
70 one episode of otitis media; in 50-85% of the children acute otitis media is
71 diagnosed at least once in the first 3 years of life. (2, 3) Risk factors for otitis
72 media have widely been studied. In addition to host factors like birth weight,
73 gestational age and craniofacial abnormalities, environmental factors like passive
74 smoking, day care attendance, socioeconomic status, pacifier use and breast-
75 feeding have been studied. Frequency of colonization with bacterial airway
76 pathogens was shown to be associated with otitis media in the first years of life.
77 (4-8) *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella*
78 *catarrhalis* are the most frequently cultured pathogens in acute otitis media. Early
79 age of colonization seems to increase the risk of otitis media. (4, 8, 9) Syrjänen
80 et al. have suggested that carriage of newly acquired bacteria is associated with
81 otitis media. (10)

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

85

86 **Patients and methods**

87 Design

88 This study was embedded in the Generation R Study, a population-based
89 prospective cohort study from fetal life until young adulthood. The Generation R
90 Study has been described in detail previously. (11, 12) The cohort includes 9778
91 mothers and their children living in Rotterdam, the Netherlands. Detailed
92 assessments of fetal and postnatal growth and development were conducted in
93 1,232 Dutch pregnant women and their children in the Generation R Focus
94 Study. The Medical Ethics Committee of the Erasmus Medical Centre,
95 Rotterdam, has approved the study. Written informed consent was obtained from
96 all participants.

97 Measurements and outcome

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

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

116 In the Focus cohort, samples were taken at the infants' age of 1.5, 6, and 14
117 months to detect nasopharyngeal bacterial carriage. Nasopharyngeal samples
118 were taken with rayon tipped dacron pernasal swabs (Copan Italia, Brescia, Italy)
119 and transported in Amies transport medium and plated within 6 hours of sampling
120 on a blood agar plate with 5% sheep blood, a chocolate agar plate and a
121 Hemophilus selective agarplate. The plates are kept at 35°C in a CO₂ rich
122 environment for two days. Bacterial growth was determined daily. All bacteria
123 were determined by use of standard methods.

124 Analyses

125 In the whole cohort associations of birth weight, gestational age, gender,
126 maternal smoking, siblings, educational level of mother, day care attendance,
127 duration of breast-feeding, pacifier use and otitis media in the first year of life with
128 otitis media in the second year of life were assessed by logistic regression
129 models resulting in odds ratios (OR) with their 95% confidence interval (CI).
130 Additionally, a multivariate logistic regression model was performed to assess the
131 association of each risk factor separately with otitis media in the second year of

132 life was adjusted for all the other risk factors resulting in adjusted odds ratios
133 (aOR). In the focus cohort association of bacterial carriage in the first year of life
134 with otitis media in the second year of life was assessed for the airway pathogens
135 *S. pneumoniae*, *M. catarrhalis* and *H. influenzae*. The analyses were performed
136 using frequency of specific bacterial carriage in the first year of life, and at ages
137 of first bacterial carriage. Furthermore, we did the same analysis with the three
138 bacteria grouped as any airway pathogen. Additionally, regression models were
139 adjusted including all determinants presented in Table 1. Furthermore, possible
140 interaction between otitis media in the first year of life and bacterial carriage and
141 the risk of otitis media in the second year of life was tested. According to the
142 national Dutch vaccination policy all children were vaccinated against *H.*
143 *influenzae B*, but non of the children were vaccinated against pneumocci

144 Differences of infant characteristics between infants with and without data on
145 otitis media in the second year of life were assessed by the independent sample
146 t-test for continuous normal distributed variables, non-parametric Mann-Whitney
147 test for continuous non-normal distributed variables and the chi-square test for
148 categorical variables. Differences of frequency of otitis media in the second year
149 of life between groups with missing risk factors and complete data were
150 assessed in the same way. All tests were carried out using a two-sided alpha
151 level of 5%. The statistical analyses were performed using the Statistical
152 Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL,
153 USA).

154

155 **Results**

156 In the Generation R Cohort, 7295 children, with a delivery date from April 2002
157 until January 2006, participated in the postnatal phase of the study. Data on otitis
158 media in the second year of life was available in 5323 (response rate 73%)
159 children. Characteristics of the children of the whole cohort and their association
160 with otitis media in the second year of life are presented in Table 1. Having
161 siblings is associated with an increased risk of otitis media in the second year of
162 life (aOR 1.42, CI 1.13-1.79). Furthermore, the occurrence of otitis media during
163 the follow-up period between 0 to 6 months and the occurrence of otitis media
164 during the follow-up period between 6 to 12 months of age was associated with
165 the occurrence of otitis media in the second year of life (respectively, aOR 1.83,
166 CI 1.24-2.71 and aOR 2.72, CI 2.18-3.38).

167 Bacterial carriage was studied in the focus cohort, in which 1079 children,
168 with a delivery date from February 2003 until August 2005, participated. The
169 children were planned to visit the Generation R Focus Study research centre at
170 the age of 1.5 month (response rate 81.8%), 6 months (response rate 81.6%)
171 and 14 months (response rate 80.0%). Of the infants 379 (43.3%) had at least
172 one episode of otitis media in the second year of life.

173 In Table 2 the associations between the frequency of bacterial carriage in
174 the first year of life and otitis media in the second year of life are presented. We
175 analysed the association between bacterial carriage in the first year of life and
176 otitis media in the second year of life in two different ways. First, we defined
177 carriage by adding the three sampling time points and assessed whether the

178 frequency of bacterial carriage was associated with otitis media. Second, we
179 assessed whether early age of bacterial carriage was associated with otitis media
180 (data not shown). Both analyses were done for the bacteria separately and for
181 any airway pathogen. No associations were observed. In addition to this, we
182 assessed whether bacterial carriage in the first year of life was associated with
183 otitis-proneness. Again, no associations were observed (data not shown).

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

191

192 **Discussion**

193 We observed a positive association between having siblings and otitis
194 media. Also, we observed a tendency that low education of the mother might
195 attribute to the risk for otitis media, while breast-feeding might be a protective
196 factor. No associations were observed between birth weight, gestational age,
197 gender, maternal smoking, day care attendance or pacifier use and otitis media
198 in the second year of life. In a meta-analysis of risk factors for acute otitis media
199 by Uhari et al., day care attendance was shown to be the most significant risk
200 factor. (13) Furthermore, similar to the trend we observed, Uhari et al. showed a
201 positive association between siblings and otitis media and a negative association
202 between breast feeding and otitis media. This study, in contrast to our results,
203 also showed that parental smoking and pacifier use was associated with otitis
204 media.

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

211 Next, we analyzed in the focus cohort the association between bacterial
212 carriage and otitis media in the second year of life, and otitis-proneness. No
213 associations were observed between frequency of bacterial carriage, age of first
214 bacterial carriage or the different species of bacterial carriage and otitis media or

215 otitis-proneness. In addition, we observed no role for bacterial carriage in
216 recurrent otitis media. Bacterial carriage in the first year of life is not associated
217 with otitis media later on. In other studies the frequency of carriage with different
218 bacteria was shown to be associated with otitis media. (4, 5, 7, 8) Faden et al.
219 have shown that carriage of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* was
220 associated with otitis-proneness in 17 otitis prone children vs 17 non-otitis prone
221 children, during healthy periods and during periods of otitis media, in children
222 aged 0-36 months in. The association in healthy periods was only significant for
223 *H. influenzae* carriage but not for the other two bacteria studied. (7) In another
224 study in 157 infants, an association between carriage of *H. influenzae*, measured
225 at 13 routine visits in the first year of life, and otitis-proneness was shown. (8) In
226 another study in 306 children aged 0 to 24 months, an association between *M.*
227 *catarrhalis* and otitis-proneness was observed. (5) In this population they also
228 showed an association between the frequency of carriage of the three airway
229 pathogens and the frequency of otitis media episodes. (4) Prellner et al. did not
230 show an increased risk for otitis media when *S. pneumoniae*, *H. influenzae* or *M.*
231 *catarrhalis* were present. (15) Early age of first colonization was also shown to be
232 associated with the risk for otitis media. (4, 8, 9) But, Syrjänen et al. have shown
233 in their study on the temporal association between pneumococcal carriage and
234 otitis media that not preceding pneumococcal carriage state, but newly acquired
235 carriage is associated with otitis media. (10) Their data support the hypothesis
236 that viral respiratory infection might enhance the acquisition of pneumococci.
237 Recently, Revai et al. have shown an association between presence of

238 pathogenic bacteria in the nasopharynx during upper respiratory tract infections
239 and the risk for otitis media following the upper respiratory tract infection. (16)
240 Taken together, it appears that the presence of newly acquired pathogenic
241 bacteria in combination with (viral) upper respiratory tract infections increases the
242 risk for otitis media, rather than the presence of pathogenic bacteria itself
243 increases the risk for otitis media.

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

258 Conclusion: In our study, otitis media in the first year of life is an
259 independent risk factor for otitis media in the second year of life. Surprisingly,
260 bacterial carriage in the first year of life did not add to this risk. Moreover, no

261 association was observed between bacterial carriage in the first year of life and
262 otitis in the second year of life.

263

264

265 **Acknowledgements**

266 The Generation R Study is conducted by the Erasmus Medical Center,
267 Rotterdam in close collaboration with the School of Law and Faculty of Social
268 Sciences of the Erasmus University Rotterdam, the Municipal Health Service
269 Rotterdam area, the Rotterdam Homecare Foundation and the Stichting
270 Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. We
271 gratefully acknowledge the contribution of general practitioners, hospitals,
272 midwives and pharmacies in Rotterdam. The first phase of the Generation R
273 Study was made possible by financial support from the Erasmus Medical Center,
274 Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization
275 for Health Research and Development (Zon Mw). The present study was
276 supported by an additional grant from Stichting W.H. Kröger, Rotterdam (Grant
277 No. 00-048), and AGS Kinderstichting.

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 326 development of acute otitis media. Clin Infect Dis 2008;46(4):e34-7.

327

328 **Table 1.** Population descriptive.

	n=5323	Otitis media 12-24 months of age		OR	aOR
		no n=2808 (52,8%)	yes n=2515 (47,2%)		
Birthweight	3438 (574)	3422 (577)	3456 (570)	1,11* (1,01-1,22)	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)	2643 (49,7)	48,4%	51,0%		
Female	2680 (50,3)	51,6%	49,0%	0,90 (0,81-1,00)	0,89 (0,72-1,11)
smoking					
No (ref)	3110 (84,9)	85,1%	84,6%		
Yes	554 (15,1)	14,9%	15,4%	1,04 (0,87-1,25)	1,16 (0,86-1,55)
siblings					
No (ref)	2159 (58,9)	62,9%	54,1%		
Yes	1508 (41,1)	37,1%	45,9%	1,44*** (1,26-1,65)	1,42* (1,13-1,79)
educational level mother					
low	292 (5,8)	4,7%	7,0%		
middle	1911 (37,8)	37,3%	38,4%	0,69** (0,54-0,88)	0,84 (0,36-1,95)
high	2851 (56,4)	58,1%	54,5%	0,62*** (0,49-0,80)	1,03 (0,44-2,40)
day care					
No (ref)	730 (22,3)	21,3%	23,5%		
Yes	2543 (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	1031 (43,5)	46,3%	40,3%	0,76* (0,61-0,95)	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)	1242 (34,4)	34,5%	34,4%		
Yes	2364 (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)	3309 (91,9)	94,7%	88,5%		
Yes	292 (8,1)	5,3%	11,5%	2,34*** (1,82-3,00)	1,83** (1,24-2,71)
Otitis from 6 to 12 months					
No (ref)	2808 (52,8)	67,4%	45,8%		
Yes	2515 (47,2)	32,6%	54,2%	2,44*** (2,16-2,76)	2,72*** (2,18-3,38)

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=1659), siblings (n=1656), educational level of mother (n=269), day care attendance (n=2050), breast feeding (n=2952), pacifier use (n=1717), otitis from 0 to 6 months (n=1722) 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

329

330

331 **Table 2.** Association between bacterial carriage in the first year of life and otitis
 332 media in the second year of life.
 333

	n (%)	Otitis media 12-24 months of age			
		no (n=384)	yes (n=287)	OR	aOR
<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
1X	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)

334 Or univariate model, aOR full model including all risk factors as shown in table 1.
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 337 **Table 3.** Association between otitis media in the first year of life (6-12 months)
 338 and otitis media in the second year of life stratified by carriage state of different
 339 bacteria.

		n (%)	Otitis media (12-24 months of age)			
			no (n=308)	yes (n=217)	OR	aOR
Never <i>S. pneumoniae</i>	otitis media 6-12 months of age					
	no	176 (71,5)	81,9%	56,9%	refrence	refrence
Once or more <i>S. pneumoniae</i>	otitis media 6-12 months of age					
	yes	70 (28,5)	18,1%	43,1%	3,44 (1,93-6,14)	2,81 (1,14-6,92)
Never <i>M. catarrhalis</i>	otitis media 6-12 months of age					
	no	192 (68,8)	78,0%	55,7%	refrence	refrence
Once or more <i>M. catarrhalis</i>	otitis media 6-12 months of age					
	yes	87 (31,2)	22,0%	44,3%	2,83 (1,68-4,77)	2,81 (1,27-6,24)
Never <i>H. influenzae</i>	otitis media 6-12 months of age					
	no	194 (70,3)	79,5%	56,4%	refrence	refrence
Once or more <i>M. catarrhalis</i>	otitis media 6-12 months of age					
	yes	82 (29,7)	20,5%	43,6%	3,01 (1,76-5,12)	2,26 (1,00-5,12)
Never <i>H. influenzae</i>	otitis media 6-12 months of age					
	no	174 (69,9)	80,3%	56,1%	refrence	refrence
Once or more <i>H. influenzae</i>	otitis media 6-12 months of age					
	yes	75 (30,1)	19,7%	43,9%	3,19 (1,82-5,60)	3,19 (1,31-7,74)
Never airway pathogen	otitis media 6-12 months of age					
	no	197 (68,2)	77,3%	54,7%	refrence	refrence
Once or more airway pathogen	otitis media 6-12 months of age					
	yes	92 (31,8)	22,7%	45,3%	2,82 (1,70-4,70)	2,90 (1,34-6,28)
Never airway pathogen	otitis media 6-12 months of age					
	no	77 (72,6)	84,1%	55,8%	refrence	refrence
Once or more airway pathogen	otitis media 6-12 months of age					
	yes	29 (27,4)	15,9%	44,2%	4,20 (1,70-10,37)	4,20 (0,43-41,32)
Never airway pathogen	otitis media 6-12 months of age					
	no	291 (69,5)	78,8%	56,3%	refrence	refrence
Once or more airway pathogen	otitis media 6-12 months of age					
	yes	128 (30,5)	21,2%	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.

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