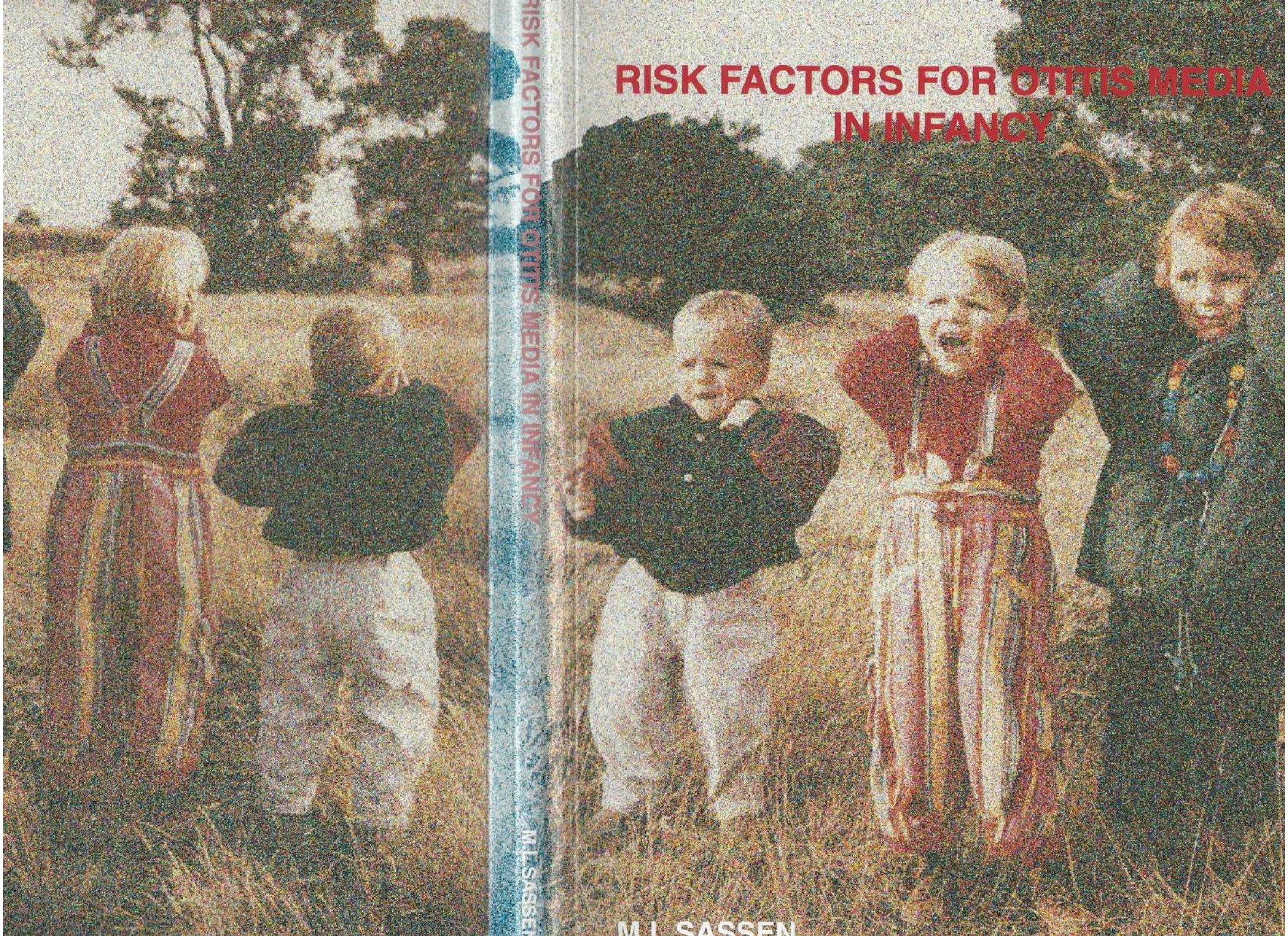
RISK FACTORS FOR OTITIS MEDIA IN INFANCY
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CONTENTS

CHAPTER 1

INTRODUCTION

Otitis media, next to upper respiratory tract infection, is the most common disease in children. Moreover, otitis media has important economic and health care implications for a variety of reasons: it must be considered in the differential diagnosis of obscure fevers in children; it is often the basis for prescribing commonly used agents such as antimicrobials, decongestants and analgesics; and it often constitutes the basis for undertaking one or more of the most frequently performed operations of infancy and childhood, namely, myringotomy with or without tympanostomy tube insertion and adenoidectomy.

Paradise wrote about otitis media in 1980: "its etiology and pathogenesis are imperfectly understood; its natural history is highly variable and, in individual cases, unpredictable; its treatment is controversial and subject to change as new information becomes available both about the disease and about treatment modalities; and finally, its long-term consequences - otologic, audiologic and developmental- are of great importance potentially, but remain to be adequately documented and understood."[1] He could have written exactly the same in 1994.

The disease can be either symptomatic (acute otitis media, AOM) or asymptomatic (otitis media with effusion, OME). Epidemiological studies of both conditions have shown the highest incidence in infants, especially during the first two years of life. Why this should be so is uncertain, but a number of possible factors can be listed:

- The immune defence mechanisms develop early in fetal life, however in the absence of stimulation, specific antibodies are not produced. The newborn child is protected by maternal IgG, transferred across the placenta; the concentration of its own immunoglobulins is still very low, and it takes several years to reach adult levels. The concentration of maternal IgG decreases rapidly, and has practically disappeared after the first year of life.[2]
- Younger subjects have greater susceptibility to infection in general, and respiratory tract infections in particular. A high otitis rate might be a natural by-product of a high rate of upper respiratory tract infection.[1]
- The abundant quantity of nasopharyngeal lymphoid tissue characteristic of infants and children may predispose to recurrent or chronic local infection, with involvement of the Eustachian tube, and consequent middle-ear inflammation.[1]
- Eustachian tube function appears to be less competent in infants than in older children and adults.[1]

Apart from these factors, many other factors which may place children at risk for having otitis media have been described. Recurrent acute otitis media and persistent otitis media with effusion have similar multifactorial causes, including myriad hosts, agents, and environmental factors. Researchers have

identified numerous risk factors for these conditions, using various criteria for recurrent AOM and persistent OME. Some studies have reverted to not attempting diagnostic distinctions among the forms of otitis media. Sometimes incidence and/or prevalence of AOM / OME were used as a criterion for evaluating predisposing factors; sometimes the duration of effusion, or the number of recurrences (OME), or the frequency of attacks (AOM).

The majority of the studies lacks a correction for interdependencies between risk factors.

Many of the studies were population-based, with subjects selected from the community-at-large. Others were clinic-based, reflecting the experience of children being examined and treated for middle ear disease. Still other studies were conducted in the school or day care setting.

The contradictory results of the studies on this topic reflect these differences in criteria, as well as differences in methodology and study populations.

An inventory of risk factors for otitis media , based on recent insights (a modification of an earlier inventory made by Haggard et al.[3]) is shown in table 1.

Most, although not all authors agree on the influence on the occurrence of otitis media of the risk factors, listed in the left side of table 1:

Congenital abnormalities. Children with cleft palate have a high prevalence of recurrent otitis media and chronic OME.[4,5] Possible explanations lie in two areas principally: abnormalities of structure and function of the Eustachian tube; and inadequate velopharyngeal valving, with disturbed aerodynamic and hydrodynamic relationships in the nasopharynx and proximal portions of the Eustachian tubes. Otitis media appears to be highly prevalent also in children with Down's syndrome.[4] It is suggested that the muscular hypotonia characteristic of Down's syndrome might result in Eustachian tube dysfunction.

Race. Studies conducted in biracial populations have reported higher otitis media prevalence in whites than in blacks[6] and a greater prevalence of middle ear disease among Indians and Eskimos than among whites.[7] In two recent European studies, race was not related to OME incidence.[8,9] As Daly[10] mentions, differences in otitis media rates by race may reflect differences in access to medical care, socioeconomic status, and anatomic or biologic susceptibility.

Large adenoids. Three of the most recent studies on the effect of adenoidectomy on otitis media with effusion show a beneficial effect of adenoid removal on the resolution of middle ear fluid[11] and reduced incidence of OME.[12,13] It is conceivable that tubal active ventilatory function is improved by adenoidectomy due to a reduction of inflammation and pollution around the nasopharynx, and that the effect of adenoid mass on the Eustachian tube is minimal.[12]

Table 1. Inventory of risk factors for otitis media (OME and AOM)

ACCEPTED	CONTROVERSIAL
INTRINSIC	INTRINSIC
-Down's syndrome[4,5] -cleft palate[5] -race[6-10] -large adenoids[11-13] -family history of otitis media[8,10,14-16] -early onset of AOM (for AOM)[10,14,16-18] -recurrent AOM (for OME)[11,19] -tympanogram type B (for AOM)[19]	-male gender[8,9,14,16,19,59] -bifid uvula[60] -low birth weight[24,42-52] -family history of allergy[16] -rhinosinusitis proneness[9,61] -immune abnormality[62] -maternal blood group A[63]
EXTRINSIC	EXTRINSIC
-season,[8,15,20-23] -family size[8,24] -bottle feeding[14-17,24-34] -day care[8,15,22-24,30,35-38] -upper respiratory tract infections[8,16,21,37,39] -socio-economic status[9,14,24,30] -passive smoking[8,11,16,17,30,40,41]	-meconium contamination of middle ear[51] -geographical location and climate[8,21] -supine bottle feeding[53-55] -domestic environment[16] -allergy[9,17,30,56,57] -pacifier[56] -late month of birth[14,58] -frequent swimming[8]

Family history of otitis media. Several studies have reported a familial clustering of otitis media. A sibling history of recurrent AOM or OME was significantly related to the incidence of OME[8,14] or AOM;[14,15] family histories of otitis-proneness increased the risk of recurrent acute otitis media in a study of Harsten.[16] A sibling history of otitis media reflects both shared genes and environment; parental history, however, is probably an indicator of shared genes, because parents and their children do not share a common childhood environment.[10]

Early onset of AOM. According to Teele, Harsten and Tainio, early occurrence of AOM increases the risk of AOM significantly;[14,16,17] in a study of Alho, early onset of AOM was only a weak predictor of susceptibility for this condition.[18] An early first episode may be the primary event that predisposes a child to recurrent otitis media by setting up an inflammatory process in the middle ear and Eustachian tube. Alternately, an early episode simply may reflect an innate predisposition for otitis media.[10]

(Recurrent) AOM, Tympanogram type B. Maw reports that the duration of effusion in OME is increased if there was a history of earache;[11] bilateral AOM and tympanogram type B or C2 on an AOM ear were significant risk factors for the duration of effusion in a study of Iino; the most significant prognostic factor was a tympanogram type B or C2 on an opposite ear at the acute onset of otitis media.[19]

Season. Higher incidences in cold weather seasons as compared to the summer months have been widely described.[8,15,20] One study investigated the distribution of otitis media by mean temperature, humidity and rainfall and found no relation.[21]

It is not certain whether seasonal effects on otitis media follow merely from the known seasonal variation in incidence of upper respiratory tract infection. A likely confounding factor lies in the seasonal pattern of attendance at day care and school. Children under two years of age do not attend school; the majority of these children are cared for at home. According to Fiellau-Nikolajsen,[22] the occurrence of otitis media is to a remarkable extent independent of season in home cared children. The summer decrease in school children may be due to the fact that many children revert to home rather than school or other care, and leave the towns and cities for the summer. Williamson also reported a lack of seasonal variability for recurrent otitis media in very young children.[23]

Family size. Considering the fact that the occurrence of otitis media is more or less independent of season in home cared children, it is very likely that the presence of older siblings already attending school enhances the risk of otitis media in preschool children. Zielhuis found a significant influence of family size on OME in children of 2-4 years of age;[8] Kero on AOM in children of 0-12 months of age.[24]

Bottle feeding. It has been hypothesized that breast-feeding offers protection against otitis media. This effect may be attributed to characteristics of the breast milk itself, to the harmful effects of bottle-feeding, or to the formula of cow's milk.[25,26] In clinical studies that consider a possibly protective effect of breast-feeding on the risk of otitis media, the results are controversial.[14-17,24,25,27-34]

Day care. The majority of researchers report that OME and AOM are significantly more common in day care attendees;[8,15,17,2224,30,35-38] the majority of children attending day-care centers belong to the pre-school age-group. Harsten,[16] studying the occurrence of recurrent AOM in children of 0-3 years of age found no relation with the attendance at day care centers.

Upper respiratory tract infections. It is generally accepted that upper respiratory tract infections play an important role in the pathogenesis of otitis

media. Children with pathology of the upper respiratory tract, such as simple rhinitis, run an increased risk of developing AOM and/or OME. [8,16,21,37,39]

Socioeconomic status. The data have not been consistent. Stahlberg and Kero both found that the infants of mothers belonging to a lower socioeconomic class run a higher risk of AOM than infants of the highest classes.[24,30] Other studies have reported no relation between socioeconomic status and OME.[9,14] It seems that low socio-economic status is associated with augmented prevalence of purulent, but not of secretory otitis media.

Passive smoking. Most of the more recent studies examining the effect of parental smoking report that exposure of the child to parental smoking increases the risk of OME and AOM;[11,17,30,40] Others however found no relation between the occurrence of OME/AOM and smoking by household members.[8,16] Hinton suggests that both irritation by smoke of the middle ear mucosa, and increased frequency of infection are less likely explanations than an indirect route via an inflammatory immune reaction in the adenoids.[40] Passive smoking probably functions as a risk factor by increasing the frequency of non-allergic respiratory infections and by aggravating mucosal inflammation and respiratory allergies. The best evidence that passive smoking is indeed causal in families where the parents smoke was provided by Strachan et al, by measuring salivary concentrations of cotinine in 7-year old children, and relating this to the probability of a type B tympanogram.[41]

On the right side of table 1, risk factors are listed who are considered controversial or need further research to confirm their influence on the occurrence of OME and/or AOM.
Only the risk factors which are especially applicable to very young children will be discussed; literature references of the other factors can be seen in table 1.

Low birth weight, meconium contamination of the middle ear. Several studies have reported that otitis media is common in children admitted to neonatal intensive care units[24,42-50] and suggest that there is a higher incidence of middle ear disorders in children with low birthweight. [45,46,48-50] Several factors have been suggested as being responsible for this higher incidence: infection,[44,47] nasotracheal[42,47] or nasogastric tubes,[43] meconium contamination of the middle ear,[51] and supine position for extended periods.[43] Early episodes of otitis media experienced in the neonatal intensive care unit might predispose some infants to recurrent middle ear disease, with persistent or frequently recurring conductive hearing losses during childhood.[46,49,50] Gravel et al. found no difference in incidence and age at onset of otitis media between full-term and very low birthweight children;[52] Zielhuis and Souchal-Delacour found no relation between birthweight and risk of OME in children of 2-4 years of age.[8,9]

Supine bottle feeding. Some authors[53,54] have implicated postural factors in the feeding method; they suggested that when infants are fed in the supine position, either milk or nasopharyngeal secretions may gravitate to the area adjoining the nasopharyngeal orifices of the Eustachian tube, thus setting the stage for obstruction and inflammation. In a study of special feeding bottles for infants with cleft palate, infants who were fed with a bottle containing breast milk had fewer days of middle ear effusion than did infants fed with the device containing formula, suggesting that protection was more likely because of a constituent in breast milk rather than the mode of feeding.[55]

Allergy. Allergy is difficult to diagnose in infants and small children, who are at highest risk of otitis media. Cow's milk protein intolerance occurring in early infancy is often accompanied by recurrent respiratory tract infections. This in turn can lead to an increased incidence of otitis media. Tainio found a positive relation between otitis media and a high plasma concentration of IgM antibodies to cow's milk.[17] In a study of Niemela, the risk of AOM was not increased in children with atopic eczema.[56]

Pacifier. In a recent study in 5-year-old children, the children who had used a pacifier had a greater risk of having recurrent attacks of acute otitis media in their history than those who had not used a pacifier.[56]

Late month of birth. Biles et al.[58] reported that recurrent otitis media was more common among children born in June to December, whereas a prospective study in Boston found no relation between season of birth, recurrent otitis media, and duration of otitis media with effusion.[14]

DESIGN OF THE STUDY

The present thesis was designed to study the occurrence and risk factors of otitis media, especially in young children.
This was done with a series of three study populations.

As we decided to use tympanometry to diagnose otitis media with effusion, we started with a validity study in different age groups. **Chapter 2** describes this study in a group of 266 children, ranging in age from 5 months to 11 years. These children were candidates for insertion of middle ear ventilation tubes, or adenoidectomy and/or tonsillectomy with myringotomy. We also verified the validity of the tympanometer we wanted to use and compared this with a second tympanometer, used in another Dutch cohort study.[64]

The second study population consisted of 289 children, visiting three health care centers. In the Netherlands, Youth Health Care (JGZ) provides preventive care for 0-19 years-olds. For infants, the care is given in child health care centers; for school children, School Health Care is provided. The

health care centers are in the children's direct neighbourhood and have a free admission. In 1987, 95% of all children aged between 0 - 1 year in our country visited a health care center, and more than 80% of all children aged between 1-4 years.[65]

In co-operation with Youth Health Care, we started a project in 1987 to investigate the occurrence and risk factors of otitis media in a healthy population of children of 0 - 2 years of age.

Three health care centers were selected: one was situated in Leiden, a city of approximately 120.000 inhabitants, one in Voorhout, a small coastal village and one in Nieuwkoop, a small village in the country. All children making their first visit to one of the three health care centers after 1 August 1987 were invited to participate in the study. Usually, in the first year of life about 6-10 visits are made (every 1-2 months), and in the second year about 3 visits (every 3-6 months). In our country every new born child is visited at home, approximately 4 weeks after birth by a district nurse from the health care center, who makes an appointment for the first visit at the center. The district nurse informed the parents about our project, and if they agreed to participate with their child, they completed a consent form and received a first questionnaire. At the first visit they handed in the completed questionnaire, and received a new one. This was repeated at each subsequent visit. In the first questionnaire some general information was asked about child and family, in succeeding questionnaires parents were asked about relevant events in the child's medical history regarding the preceding period. At each visit, a tympanogram of each ear was made by the medical staff or by the district nurse, this depended on the local organisation. Relevant data from the medical records at the child health care centers, including a hearing test at approximately 9 months of age were also evaluated.

Chapter 3a describes risk factors associated with the occurrence of otitis media with effusion, especially in the age-group of 0-2-years. A supplementary analysis was made of the relation between the type of tympanogram (A, C1, C2 and B) and the occurrence of both acute otitis media and upper respiratory tract infections. **Chapter 3b** describes risk factors associated with the occurrence of acute otitis media, with special attention to the association with breast-feeding. In **Chapter 3c** an inventory was made of medical consumption related to otitis media and upper respiratory tract infections in this age group, and of differences in medical treatment in the three areas investigated. The impact of hearing screening on medical consumption was observed.

In the third study, the effect of prematurity and low birthweight on otitis media and hearing was studied. In the Netherlands a nation-wide cohort study was started in 1983 involving nearly all paediatric and neonatal departments in the country. 1338 infants, liveborn before 32 completed weeks of gestation and/or with a birthweight of less than 1500 g, were enrolled in this collaborative "Project On Preterm and Small for gestational age infants" (POPS). Between birth and 5 years of age, 966 children were alive; 927 (96%) having been examined. All 927 children were assessed at home by three paediatricians, with special emphasis upon the following 10 features: congenital malformation, neuro-motor function, mental development, hearing, visual function, language and speech development, musculo-skeletal system, respiratory tract and ear nose throat disorders, behaviour and growth. Otitis media, respiratory tract infections and hearing loss were evaluated by means of history and audiometry. Audiometric examination was performed by one of the three paediatricians, trained at our department, with a hand-held pure-tone audiometer. In **Chapter 4a** an assessment of ENT morbidity in this population of pre-term and low birthweight infants is made and compared with ENT morbidity in full-term children of the same age group. **Chapter 4b** presents the prevalence of conductive and sensorineural hearing loss in two ways: as any hearing loss in dB categories with respect to the worst ear, and as impairment, disability and handicap due to hearing loss in the better ear. Comparisons between extremely low birthweight and very low birthweight infants within the study population, and with former studies, as well as with children from the general population are made. Attention is paid to the age of detection of sensorineural hearing loss.

Chapter 5 contains a summary, conclusions and recommendations, based on the preceding chapters.

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CHAPTER 2

VALIDITY OF TYMPANOMETRY IN THE DIAGNOSIS OF MIDDLE EAR EFFUSION

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ABSTRACT

A group of 266 children (515 ears), ranging in age from 5 months to 11 years, was studied. These children were candidates for the insertion of ventilation tubes, or adenoidectomy and/or tonsillectomy with myringotomy. Before surgery, tympanometry was performed. The surgical and tympanometric findings were compared afterwards.
Two different tympanometers were used (GSI-27A and TYMP-85TT). This study showed a comparable validity of these two tympanometers. The sensitivity and specificity of tympanometry in the age group of 5 months to 2 years did not show a significant difference from that in the age group of 2 - 12 years.
Otoscopy has limited value for the diagnosis of middle ear effusion in this age group.

INTRODUCTION

The aim of this study was to test the validity of tympanometry, when used in a population of children up to two years of age. This investigation was planned within the framework of an observational cohort study on the occurrence of middle ear effusion amongst children from a few months old to 2 years old and was launched in our department in 1987. Several authors[1-4] report that tympanometry, performed in the first 6 months of life, is not reliable. From 7 months of age, tympanometry seems to be a valuable method of investigation,[2, 3, 5-14] but there has been no comparison between validity in infants and older children. Most of the validity studies have been performed in older children, from 3 to 4 years of age. In our study, we compared two age groups: children of 6 months - 2 years of age and children from 2 - 11 1/2 years of age. Two tympanometers were used: type TYMP-85TT, (used in our epidemiological research) and type GSI-27A (used in a cohort study on the occurrence of otitis media with effusion in preschool children of 2 - 4 years of age);[15] the validity of this tympanometer was studied by Dirix and Doveren.[7] We verified and compared the validity of these tympanometer types. We also studied the appearance of the tympanic membrane and the viscosity of the fluid in the middle ear in relation to the tympanometric findings.

PATIENTS AND METHODS

A total of 266 children was entered into the study yielding 515 ears suitable for analysis. The children ranged in age from 5 months to 11 years and 5 months (table 1).

Table 1. Population: age and sex

Age	Boys	Girls	Total
0-6 months		1	1
6-12 months	1	4	5
1 year	20	15	35
2 years	17	9	26
3 years	19	25	44
4 years	21	22	43
5 years	31	21	52
6 years	17	9	26
7 years	7	6	13
8 years	9	5	14
9 years	1	2	3
10 years		1	1
11 years		3	3
Total	143	123	226

These children were candidates for the insertion of ventilation tubes (indication: chronic otitis media with effusion [3 months or longer] or recurrent otitis media), or adenoidectomy and/or tonsillectomy with myringotomy (indication: recurrent upper respiratory tract infections and otitis media with effusion). Children with a perforation of the tympanic membrane, a history of more than six myringotomies and/or more than three insertions of middle ear ventilation tubes were excluded from the study. This study was performed in two hospitals: the Gemini-Hospital in Den Helder (hospital A) and the St. Elisabeth-Hospital in Leiderdorp (hospital B). In hospital B, children undergoing (adeno-)tonsillectomy with myringotomy, i.e. selected because of upper respiratory tract infections, were included in the study. In hospital A, these children were excluded: only children undergoing insertion of tympanostomy tubes, i.e. selected because of middle ear problems, were included. Two different tympanometers were used: type GSI-27A and type Tymp-85TT. Both meters have a stimulus frequency of 226 Hz and a pressure-variation from + 200 daPa to - 200 daPa (1 daPa = 1.02 mm H20). In the first 6 weeks, the Tymp-85TT was used in hospital A and the GSI-27A in hospital

B. After 6 weeks, the tympanometers were interchanged. One hour before surgical intervention, tympanometry was performed with the informed consent of the parents. If possible a tympanogram of each ear was taken in all children. If only one tympanogram could be obtained, this one was included in the study. The classification of the tympanograms (Figure 1) was a modification of the classification of Jerger[15,16] with compliance and middle ear pressure as parameters.

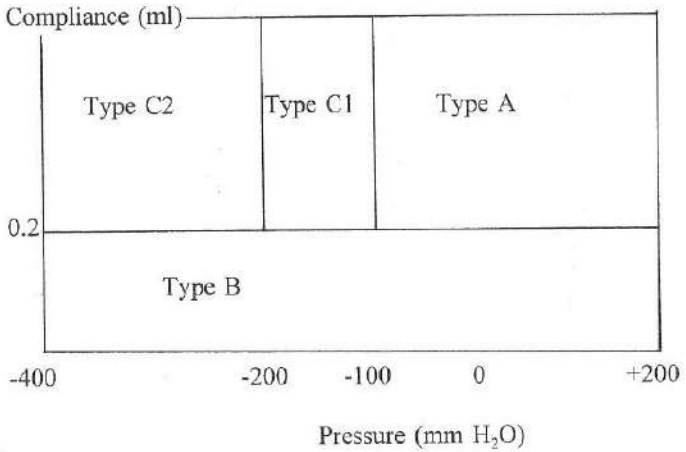

Figure 1. Classification of tympanogram types according to Jerger (modification)

We considered a type B tympanogram as indicating otitis media with effusion, i.e. fluid in the middle ear. Myringotomy and/or insertion of middle ear ventilation tubes (and, if indicated adenoidectomy/tonsillectomy) took place under general anaesthesia, with the use of nitrous oxide. The ENT surgeons described the appearance of the tympanic membrane and the content of the middle ear, after myringotomy. They were not informed about the tympanometric findings. In both hospitals, three ENT surgeons were participating. The findings at surgery were only used if the surgeon used an operating microscope. In hospital A, the operating microscope was not used when an adenoidectomy and/or tonsillectomy with myringotomy was performed, therefore those cases were not included in the study on the appearance of the tympanic membrane.

Data were processed with the "SPSS-X"(SPSS Inc, Chicago, Illinois, USA) and "SAS" (SAS Institute, Cary North Carolina, USA) programs.

RESULTS

A total of 515 ears (266 children) were examined; 273 ears in hospital A and 242 ears in hospital B. With the GSI-27A, 278 tympanograms were obtained and 210 tympanograms with the TYMP-85TT. Tables 2 and 3 show the sensitivity and specificity, with predictive values, for the two tympanometers in both hospital A and B.

Table 2. Validity of Tymp-85TT and GSI-27A in hospital A

GSI-27A

Tympanogram	No fluid	Fluid	Total
A	13	3	16
C1	7	4	11
C2	14	17	31
B	8	71	79
Total	42	95	137 (n)

sensitivity 75%
specificity 81%

(n = no. of tympanograms)

positive predictive value 90%
negative predictive value 59%

TYMP-85TT

Tympanogram	No fluid	Fluid	Total
A	9	5	14
C1	2	3	5
C2	8	12	20
B	10	64	74
Total	29	84	113 (n)

sensitivity 76%
specificity 66%

(n = no. of tympanograms)

positive predictive value 86%
negative predictive value 49%

Table 3. Validity of Tymp-85TT and GSI-27A in hospital B

GSI-27A

Tympanogram	No fluid	Fluid	Total
A	6		16
C1	4	1	5
C2	9	9	18
B	19	93	112
Total	38	103	141 (n)

sensitivity 90%
specificity 50%

(n = no. of tympanograms)

positive predictive value 83%
negative predictive value 66%

TYMP-85TT

Tympanogram	No fluid	Fluid	Total
A	6		6
C1	7	3	10
C2	7	2	9
B	17	55	72
Total	37	60	97 (n)

sensitivity 92%
specificity 54%

(n = no. of tympanograms)

positive predictive value 76%
negative predictive value 80%

These results demonstrate that there is no statistically significant difference in the validity of the two tympanometers. However, there is a difference between the two hospitals. Because the validity of the two tympanometers is comparable, we combined the tympanometric findings of the two in further analysis.
When a type C2-tympanogram was also considered to indicate otitis media with effusion, higher sensitivity was found (92% and 98% in hospitals A and B respectively) but lower specificity (44% and 31%).

The results for the different age-groups are shown in table 4. There is no statistically significant difference in sensitivity and specificity for the two age-groups.

Table 4. Tympanometric findings in different age groups

5 months-2 years of age

Tympanogram	No fluid	Fluid	Total
A	4	2	6
C1	4	2	6
C2	2	1	3
B	5	47	52
Total	15	52	67 (n)

sensitivity 90%
specificity 67%

positive predictive value 90%
negative predictive value 67%

2-12 years of age

Tympanogram	No fluid	Fluid	Total
A	30	6	36
C1	16	9	25
C2	36	39	75
B	49	236	285
Total	131	290	421 (n)

sensitivity 81%
specificity 63%

(n = no. of tympanograms)

positive predictive value 83%
negative predictive value 60%

The age-group of 5 months - 2 years old (41 children) consisted of only 15% of the whole group of children. In this age-group, tympanometric examination was more frequently unsuccessful because of a lack of co-operation of the children. Table 5 shows a sub-division of this group in 5 months to 1 year, 1 to 1.5 years, and 1.5 to 2 years of age.

Table 5. Tympanometric findings in three age groups of 0-2 yrs

Validity in age group 5 months-1 year

Tympanogram	No fluid	Fluid	Total
A		1	1
C1			
C2	2		2
B	1	4	5
Total	3	5	8 (n)

sensitivity 80%
specificity 67%

Validity in age group 1-1.5 years

Tympanogram	No fluid	Fluid	Total
A	4		4
C1	2	1	3
C2		1	1
B	3	18	21
Total	9	20	29 (n)

sensitivity 90%
specificity 67%

Validity in age group 1.5-2 years

Tympanogram	No fluid	Fluid	Total
A		1	1
C1	2	1	3
C2			
B	1	25	26
Total	3	27	30 (n)

sensitivity 93%
specificity 67%

(n = no. of tympanograms)

This demonstrates that there is almost no difference in the tympanometric findings in these sub-groups. The number of children in these groups is very small, therefore a formal statistical comparison could not be made.

Table 6 and 7 show the appearance of the tympanic membrane and the presence or absence of fluid in the middle ear, as described by the ENT surgeon. To assess the simultaneous overall predictive value of all these factors together, multivariate discriminant analysis was performed.

Table 6. Tympanometry and appearance of tympanic membrane

Tympanic membrane	No fluid (n = 101)	Fluid (n = 279)	P
Normal	14 (14%)	9 (3%)	< 0.01
Opaque	45 (45%)	127 (46%)	0.96
Retracted	35 (35%)	146 (52%)	< 0.01
Bulging	6 (6%)	54 (19%)	< 0.01
Desquamation		3 (1%)	0.70
Bubbles/fluid level	1 (1%)	23 (8%)	0.02
Atrophy	11 (11%)	12 (4%)	0.03
Tympanic sclerosis	9 (9%)	13 (5%)	0.19
Retraction pocket/ atelectasis	3 (3%)	8 (3%)	1.00

Table 7. Discriminant analysis on classification results of Table 6

Actual group	Predicted no fluid	Predicted fluid	Total
No fluid	61	40	101
Fluid	72	207	279

Sensitivity 74.2% ; Specificity 60.4% (equal priors assumed);
Percent of "grouped" cases correctly classified: 70.5%.

Table 8 shows the tympanometric findings in relation to the viscosity of fluid in the middle ear. The majority of the fluid containing middle ear cavities consisted of mucoid fluid.

Table 8. Tympanometry and viscosity of middle ear fluid

Tympa-nogram	No fluid	Fluid				Total
		Purulent	Serous	Mucous	?	
A	16	1	2	1		20
C1	15	3	5			23
C2	26		10	18		54
B	42	19	40	164	2	267
O	2		3	11		16
Total	101	20	58	199	2	380

DISCUSSION

In our study, the sensitivity (83%) to detect middle ear effusion by means of tympanometry is similar to that of earlier reports,[2,3,5-14] the specificity (63%) is rather low. This could be an effect of anaesthesia, with the use of nitrous oxide. Several studies show some variability in the effects of anaesthesia on the condition of the middle ear.[17-19] Therefore, comparison of our results with other studies is unreliable, the fact that different classifications of tympanogram-types have been used in these studies makes comparison even more difficult. However, a comparison of different groups in the same study, as we have done, is still possible.

The tympanogram classification we used is a modification of the classification of Jerger with compliance and middle ear pressure as parameters.[15,16] Other parameters, such as the relative gradient and the stapedial reflex do not lead to a higher validity.[1-3,7,8]

Otoscopy has limited value for the diagnosis of middle ear effusion, a fact other authors have also experienced.[2,3,6,10] Pneumatic otoscopy seems to be more reliable, as is reported by Toner[13] and Vaughan-Jones.[14]

The children participating in this project were selected from two different hospitals. The selection criteria in those two hospitals appeared to have been slightly different. This could explain the difference in validity we found in these two populations. In hospital A, 39% of the tympanograms were of type A, C1 or C2, whereas in hospital B they amounted to 23%. In hospital A, tympanogram-types A, C1 and C2 showed a higher percentage of "dry" middle ears (21%), compared with tympanogram-types A, C1 and C2 in hospital B (16%). The total percentage of "dry" middle ears in both hospitals (28% and 31% respectively) was comparable. This results in a higher specificity, but a lower sensitivity in hospital A, compared with hospital B.

We found a comparable validity of the two tympanometers used, and also the validity in the age group of 5 months - 2 years did not show a significant difference from that in the age group of 2 - 12 years. Yong Park[20] found no different validity of tympanometry in the two age groups, divided into two groups of less than 6 years and 7 - 15 years of age. As far as we know, comparison of the validity of tympanometry in younger age groups has not been done before. In a study of Combs[21] there appeared to be a progressive increase in mean acoustic reflectivity with age.

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CHAPTER 3

COHORT STUDY ON THE OCCURRENCE AND RISK FACTORS OF OTITIS MEDIA IN A HEALTHY POPULATION OF CHILDREN OF 0-2 YEARS IN THE NETHERLANDS

OORONTSTEKING NUL-TOT-TWEE-JAAR

een onderzoek op het consultatie-bureau
naar het voorkomen van oorontstekingen
bij kinderen van nul tot twee jaar

*Academisch Ziekenhuis Leiden
afdeling keel-neus-oorheelkunde
*Provinciale Kruisvereniging Zuid-Holland

CHAPTER 3a

RISK FACTORS FOR OTITIS MEDIA WITH EFFUSION IN CHILDREN OF 0-2 YEARS OF AGE

M.L. Sassen, R. Brand and J.J. Grote

submitted for publication

ABSTRACT

Introduction: Possible risk factors associated with the occurrence of otitis media with effusion were determined.
Materials and Methods: Two hundred eighty-nine children born between July 1987, and October 1988, were studied up to the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different health care centers.
Results: Having older siblings was the most important risk factor, for both the time elapsed until the first occurrence and for the probability of otitis media with effusion at each visit. Other significant risk factors for the probability at each visit were: having had acute otitis media prior to the visit or prior to the previous visit, age, a positive family history of otitis media, and upper respiratory tract infections.
The probability of acute otitis media increased with deterioration of the tympanogram.
Conclusion: having older siblings is the most important risk factor for otitis media with effusion in this age group.

INTRODUCTION

Otitis media in its various forms is a common childhood disease; it is especially prevalent in children under 2 years of age. A large number of epidemiological studies on this subject has been published, especially from Scandinavian countries. In the Netherlands, a longitudinal study started in 1984 in Nijmegen, in which children were screened for OME from 2 to 4 years of age[1].
The fluctuating nature of otitis media makes the definition of incidence and prevalence more complicated than in the case of permanent conditions such as sensorineural hearing impairment. In prospective studies providing estimates of incidence, prevalence and descriptions of the natural history of otitis media, the annual incidence estimates range between 14% and 62%, whereas prevalence estimates are between 2% and 52%. In all studies, otitis media incidence and prevalence peak in the preschool years and decrease as age increases[2].
In a review of 23 studies, Zielhuis[3] found a typical age-prevalence curve: a bimodal curve with the largest peak at around 2 years of age and a second peak some years later.
Summarizing the gross prevalence data of the epidemiological investigations, it can be said that there is a subsidiary prevalence peak for the years 4 and 5, but this is variable in relation to timing of day-care, nursery schooling, and school entry.
In our country, 95% of all newborn children visit a child health-care center in their neighbourhood. In 1987, we started a cohort study of children from birth till the age of two in three health-care centers, two in a rural, and one in an urban area. We investigated the occurrence and risk factors of otitis media in this age group, the relationship with upper respiratory tract infections and medical consumption directly related to this disease.
In this study, tympanometry was performed during the visits of the children at the child health-care center. The intervals between the visits were sometimes irregular and the total number of visits was not the same for every child. As tympanometry in this age group is more difficult to perform than in older children, quite a number of tympanograms were "missing" or not interpretable. To describe the natural history of OME all ears with missing values should be excluded or be replaced by some well chosen values, which is not a very sophisticated approach[4]. For these reasons we decided not to interpret our data as absolute incidence and prevalence numbers in our population.
In this study we focused our attention to possible risk factors associated with the occurrence of otitis media, especially in this age-group of 0-2-year-olds.
As a supplementary analysis, we investigated the relation between the type of tympanogram (A,C1,C2 and B) and the occurrence of both acute otitis media and upper respiratory tract infections.

PATIENTS AND METHODS

Our study population consisted of 289 children born between July 1987 and October 1988, followed up to the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different child health-care centers, one of them in an urban, and two in a rural area. In the first year of life mostly 2-monthly visits were made, in the second year the majority consisted of 3-6-monthly visits. In total 3021 visits were made (mean 10.5 visits/child). 232 children (80%) completed a follow-up of 24 months or more (range 2-37 months; mean f.u. 23.6 months). Non-completion was almost always due to families moving away from the area. Of the total population of 289 children, 53% were boys and 47% girls. Most of the children (96.6%) were of Dutch origin, because many of the allochtone parents were incapable of answering the questionnaires, due to language problems. Relevant epidemiological data (table 1) were collected by questionnaires, answered by the parents at the beginning of the follow-up (most children being then 2 months old), and at every following visit at the child health-care center.

Table 1. Relevant epidemiological data on questionnaires

CHILD	MOTHER
place of residence date of birth age race sex congenital malformations special diet type and duration of day care date of visit (seasonal influence) upper respiratory tract infections (URTI) treatment of URTI snoring mouth-breathing AOM treatment of AOM consultations with primary physician adenoidectomy tonsillectomy placement of middle ear ventilation tubes hearing test (Ewing) at child health care center	gestation (weeks) delivery (normal/disturbed) smoking during pregnancy duration of breastfeeding (months)
	HOUSEHOLD
	socioeconomic status (mother and father) number of siblings family history smoking habits

Relevant data from the medical records at the child health-care centers, including a hearing distraction test at approximately 9 months of age were also evaluated.

Otitis media with effusion (OME) was defined as an inflammation of the middle ear accompanied by accumulation of liquid in the middle ear cleft without the signs and symptoms of acute infection[5]. To detect the presence of OME, at each visit a tympanogram of each ear was made (tympanometer type Tymp-85TT, with a stimulus frequency of 226 Hz and a pressure-variation from +200 daPa to -200 daPa). The tympanograms were classified according to a modified classification of Jerger[1,6], with compliance and middle-ear-pressure as parameters; a type B-tympanogram was considered as OME. Several authors[7-10] report that tympanometry, performed in the first half year of life, is not reliable. This was also our experience; moreover, tympanometry was difficult to perform, and the children were less cooperative in this age group. Consequently, we did not include the results of tympanometry during the first 6 months of life in our analysis.

In a previous study we tested the validity of the tympanometer we used in different age groups[11]: the sensitivity and specificity of tympanometry in the age group of five months to two years did not show a significant difference from that in the age group of two to twelve years. Otoscopy had limited value for the diagnosis of middle ear effusion in this age group.

A disease was regarded as acute otitis media (AOM) if it had been diagnosed as such by their physician (primary physician or physician at the child health-care center), if there had been purulent otorrhea, or if treatment for otitis media had been given. The criteria for AOM consist of both acute symptoms (ear-ache, fever, irritability, restless sleep, etc.) and otoscopic signs (distinct redness and/or outward bulging of the tympanic membrane).

Statistical analysis.

To study the occurrence of OME and possibly related risk factors, two - clinically different - approaches can be used. One approach would concentrate on the "period of time until first occurence of OME", the other on the "risk of OME" at any arbitrary moment during follow-up.

The "time-related" approach can be made through a survival analysis (which will model the "disease-free" period until the first occurrence of OME); even though the "endpoint" OME can (and will) occur more than once during the observation period, analysing only the first occurrence will provide a measure that is clinically readily interpretable and useful.

The second approach does not a priori incorporate a time-effect, but estimates the probability of OME at any moment during follow-up (which requires a rather advanced statistical methodology because of the repeated measurements on each infant: logistic regression with random effects[12]); age at visit will be included as a (time depending) covariate.

Both approaches allow for investigation of possible risk factors (predictors) for OME (see table 2).

Finally we investigated the relationship between tympanogram type and the occurrence of AOM and URTI to see whether the specific definition of OME as a B-type tympanogram (as opposed to e.g. B+C2 type) is reflected in the associations with AOM and URTI.

To describe the results of the modelling process the odds ratio's and their associated 95% confidence intervals are reported.

P values below 5% are considered statistically significant: all tests are two-sided. The modelling was performed with the EGRET-package (logistic binomial for distinguishable data)[13].

Table 2. Statistical approaches.

"survival" analysis	
outcome	**time elapsed until the first occurrence of OME in left and/or right ear**
unit of analysis	child
univariate model	Kaplan-Meier estimation; log rank test (each risk factor considered separately)
multivariate model	a proportional hazards model (Cox regression) is used to quantify the effect of several possible risk factors simultaneously.
"logistic regression"	
outcome:	**(the probability of) occurrence of OME in any ear, at any visit**
unit of analysis:	ear
model:	random effects model: as the children were repeatedly seen and two ears were measured, the model has to incorporate the "within-patient-correlation"; this is achieved by extending it with a random effects term to account for these correlations.
multivariate model	The confounding effects on the OME-probability of AOM, upper respiratory tract infections (URTI), daycare, season of the year, place of birth, sex, number of siblings, socio-economic status, passive smoking and otitis in the family are incorporated into the model in the usual way.
outcome:	**(the probability of) occurrence of AOM and URTI**
unit of analysis	ear
model	random effects model to describe the relation between each tympanogram type (A,C1,C2,B) and the occurrence of AOM as well as URTI

RESULTS

Time from age 6 months until first occurrence of OME ("survival" analysis)

Fig. 1 shows that at approximately 9 months of age, 50% of the children have already had OME; the curve approaches the baseline, because during the observation period, OME is diagnosed at least once in nearly all (91.8%) children (in 21 children, 8.2%, OME was never diagnosed).

To detect possible risk factors, we computed both Kaplan-Meier estimates of the survival curves according to the subgroups defined by the predictors rural versus urban, gender, breast- feeding and number of siblings respectively (Logrank test) as well as a Cox (proportional hazard) model in a stepwise fashion. Because of the time depending structure of AOM and URTI, we used those extensively in the logistic regression analysis described below but not in the survival context. The models were examined both for the left and right ear separately as well as for "time to first occurrence in any ear".

Fig. 2 shows the (separate) Kaplan-Meier estimates by "number of older siblings". Although the log-rank test for the "number of siblings" effect is highly significant both as a test on 4 categories (0,1,2 and ≥3 siblings) and as a linear trend test, the fact that the curves do not show a systematic decrease in survival with increasing number of siblings (the order is 0 > 2 > 1 > 3; both in a proportional hazards model and in the Kaplan Meier estimates) leads to the conclusion that the major part of the effect is due to the difference between the "single child situation" and "having at least one brother or sister", without any clear trend among the actual number of siblings.

Results are displayed in table 3; the number of infants available for this analysis was 275 out of 289.

The other predictors were not significantly related to the otitis-free period (all p-values >0.25).

In the subgroup reaching the "endpoint" (OME), consisting of 91.8% of the children, we looked in detail for differences between the right and the left ear (using a repeated measurements analysis of variance). The "left versus right ear" within-patient effect was negligeable and insignificant: the length of the "OME-free" period can be assumed to be the same when analysing separately for left and right ear.

Table 3. Relation between number of older siblings and OME-free period.

	Survival (=probability of being free of OME)				
# of siblings	median (months)	mean (months)	n (% censored)	12 months (% OME-free)	Log Rank
0	8	13	137 (18%)	28%	p=0.002
1	7	9	92 (03%)	13%	
2	8	11	37 (11%)	16%	
3 or more	9	9	9 (00%)	11%	

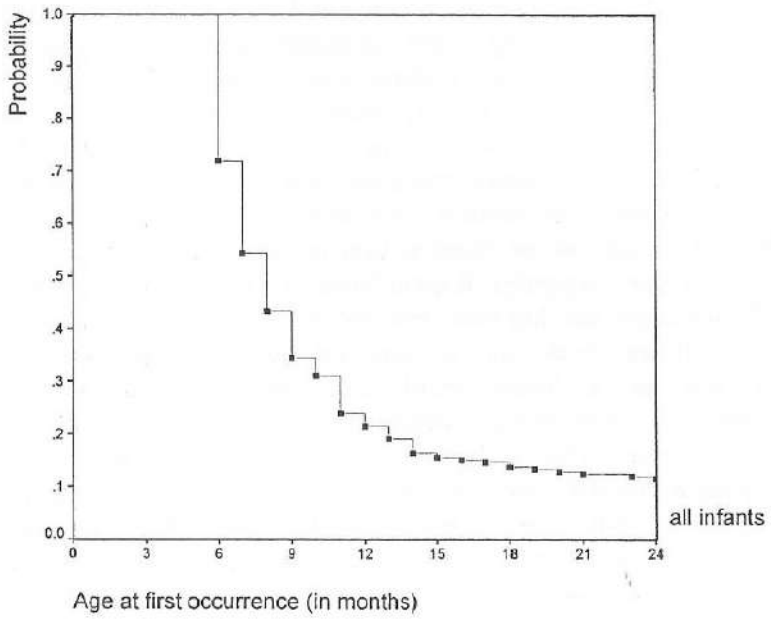

Figure 1. OME - free period (from 6 months onwards)

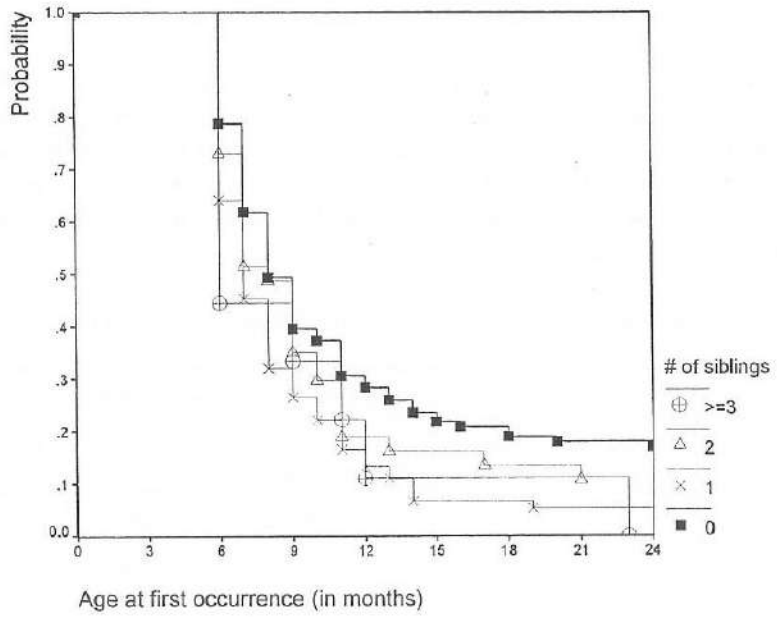

Figure 2. OME-free period (from 6 months onwards) in relation to number of older siblings

The probability of occurrence of OME and its associated risk factors; logistic regression.

The analyses to be presented here were designed to cover two different questions:

[1] How is the probability of the occurrence of OME related to other risk factors, both univariately and multivariately, when OME is defined as a dichotomous variable (tympanogram type B versus types A, C1 and C2).

[2] How is the probability of the occurrence of AOM and URTI related to the tympanogram type (comparing types A, B and C1+C2), both univariately and multivariately and is a distinction B versus A+C a reasonable one compared to B versus C versus A.

As stated in the "methods" section, all analyses have the "ear" as unit of analysis and all analyses (through the application of the random effects logistic model) take explicitly into account the fact that repeated measurements are observed for each patient (both through time and because two ears are observed). All p-values are based on likelihood ratio test statistics (comparing models with and without a specific variable) between random effects models.

Table 4 describes the univariate relationships between all risk factors under study and OME. Although - as stated earlier - we accounted for the correlation between visits and ears respectively within each infant, for descriptive purposes we simply consider each ear and each visit as separate observations to avoid unnecessary complexity in table 4 which merely serves to provide some order of magnitude. The OR is calculated as a Mantel_Haenszel stratified OR where the right and left ear as well as the age (in months) at visit make up the strata.

In a multivariate analysis relating the above mentioned risk factors to OME, the probability of occurrence of OME at any visit was significantly influenced by AOM; AOM_PREV (multivariately, so even after correction was applied for the confounding effect of the AOM-status at the current visit); age (exhibiting no evidence of a decrease or stabilisation in the second year of life as we found for the occurrence of AOM[14], the effect can be approximated adequately by a linear trend); number of siblings; a positive family history of otitis media; and upper respiratory tract infections (borderline significant, but the occurrence of URTI itself is strongly related with the number of siblings, so after adjustment the effect disappears).

Table 4. Univariate relations between OME and risk factors stratified by ear (left vs right) and age.

Risk factor		OME absent	OME present	% OME	stratified crude OR
Time-dependent					
AOM *)	absent present	1346 137	1120 227	45% 62%	 2.06
AOM-PREV **)	absent present	1393 96	1185 166	46% 63%	 2.12
URTI ***)	absent present	1101 388	896 455	45% 54%	 1.46
Breast-feeding	no yes	536 953	489 862	48% 47%	 .98
Day care	no yes	1355 134	1175 176	46% 57%	 1.67
Time-independent					
Number of Siblings	0 1 2 ≥3	882 417 175 15	556 518 224 53	39% 55% 56% 78%	 1.97 2.15 5.60
Otitis in family	never sometimes often	916 423 34	681 540 67	43% 56% 66%	 1.73 2.68
Place of birth	rural 1 rural 2 urban	603 434 452	499 479 373	45% 53% 45%	 1.36 .97
Socio-economic status	low middle high	313 511 665	320 423 606	51% 45% 48%	 .81 .90
Smoking in household	no yes	1077 412	991 360	48% 47%	 0.95
Sex	male female	835 654	685 666	45% 50%	 1.24

*) acute otitis media in period prior to visit
**) acute otitis media in period prior to previous visit
***) upper respiratory tract infection in period prior to visit

The other items (daycare, place of birth, breast-feeding, sex, socio-economic status, passive smoking) did not have a significant association with OME after adjustment for the above mentioned significant predictors. Table 5 describes the (multivariate) model and the calculated odds ratio's, adjusted for each other.

Table 5. Relation between OME and risk factors significantly associated in a multivariate logistic regression model (each odds ratio is adjusted for the effect of all other factors in the table)

Outcome: OME	Random effects logistic regression			
Risk factor	categories/ units	OR (adjusted)	95% conf.interval	p-value (L.R. test)
No of siblings	per sibling increase	1.56	[1.29,1.89]	<0.001
AOM	yes <=> no	1.56	[1.18,2.06]	0.002
AOM-PREV	yes <=>. no	1.69	[1.22,2.35]	0.002
age	per months increase	0.98	[0.97,0.99]	0.007
Otitis in family	yes <=> no	1.37	[1.09,1.73]	0.008
(random effect)				<0.001

We also investigated a possible relationship between the actual month of the year the visit took place and the risk of OME, adjusted for the risk factors determined to be significant in the above analysis (table 5). The adjusted odds ratios and log(odds) from the random effects model are presented in table 6.

Until now, the OME-status was considered a dichotomous variable: tympanogram type B = OME; type A, C1 and C2 = no OME. In the following analysis, the tympanogram types were divided into 4 categories, from score 0 (normal, A) to score 3 (OME, B).
As can be seen in table 7 the probability of AOM increases significantly with "deterioration" of the tympanogram-type. There is also a correlation (though less pronounced and systematic) with the probability of URTI.

Table 6. Odds ratios and Log(Odds) comparing the probability of OME relative to 'january', adjusted for 'No of siblings', 'age', 'AOM', 'AOM_PREV' and 'Otitis in family'.

Month of visit	Adjusted OR	Log(Odds)
january	(1)	
february	.80	
march	1.05	
april	1.27	
may	.78	
june	1.26	
july	.71	
august	.63	
september	.45	
october	.77	
november	.71	
december	1.07	

Table 7. "sensitivity" of the tympanogram type in terms of AOM and URTI

Odds ratio's adjusted for N-SIB and AGE	outcome			
Tympanogram type	AOM	p-value	URTI	p-value
A	(1.0)		(1.0)	
C1	1.05	0.02	1.4	0.04
C2	1.24		1.0	
B	1.70		1.4	

Table 8 shows the results of a random-effects analysis with a classification of 3 tympanogram types: A, C1+C2 and B.

Table 8. "adequacy" of a dichotomy in tympanogram types (B vs A, C1+C2 vs A) in terms of AOM and URTI

	"Crude" odds ratio's in random effects model					
Outcome =>	AOM			URTI		
Tympanogram	+ vs. -	OR	p-value	+ vs -	OR	p-value
A	72:825	(1.0)		214:683	(1.0)	
C1+C2	65:513	1.2	0.43	170:410	1.45	0.025
B	227:1120	1.7	0.003	455:896	1.55	0.002

DISCUSSION

Are risk factors for the occurrence of OME in children of 0- 2 years of age different from risk factors for this disease in older children? Several authors describe age-related differences in the risk of OME: Hurwitz[15] reported an increased risk of respiratory illness associated with attending day care especially for children in the age group of 6 weeks trough 17 months of age and children 18 through 35 months of age who had no older siblings; day-care attendance was not associated with an increased risk of respiratory illness in children 18 through 35 months of age with older siblings. For children aged 6 weeks through 17 months, the exposure to older siblings was associated with an increased risk of respiratory illness; however, for children aged 36 through 59 months, older siblings were protective against respiratory illness. Birch and Elbrond[16] note that the excess of otitis media after colds in the day-care child is greater at 1 year (83% as compared to 56% in home care) than at 5 years, congruent with an explanation for the excess in terms of low resistance to infection. Likewise, Fiellau-Nikolajsen[17] notes that the risk factors of day care, gender and setting that apply at 3 years do not apply at 6 years.

Our results indicate that, as in all other studies, URTI, AOM and OME are very much correlated. The fact that the AOM-status at a previous visit had an important influence on the occurrence of OME suggests a longlasting effect of AOM. However, it is not possible to distinguish what is the primary causal factor, AOM or OME, with a statistical analysis; this can only be postulated on clinical grounds.

In our study, having older siblings was the most important risk factor, for both the time elapsed until the first occurrence and for the probability of occurrence of OME at each visit. Birch et al[18] mentioned that there appears to occur a type of "threshold" for an increased prevalence and incidence of acute

otitis media when about 3 or 4 children are in one place, with no significant difference in rates across day-care centres catering for 19 to 72 children. In our population we did not find such a threshold for the occurrence of OME: having one older sibling was already a significant risk factor for the 'time elapsed until first occurrence' and for the probability of OME at each visit which increased with each additional brother or sister.

Being breast-fed did not have the same protective effect for the risk of occurrence of OME as it had for AOM in our population[14]. We had no very preterm or very low birthweight infants in our study population; in a previous study[19] it appeared that very preterm and very low birthweight children did not have an increased frequency of middle ear disorders during childhood compared to children in the general population.

The risk of occurrence of OME was significantly influenced by the month of the year the visit took place, but we did not find a clear summer-winter pattern. There is a general agreement in the literature on seasonal effects for the temperate zones in older children, with the lowest incidence and prevalence rates occurring in the summer and the highest in winter[20-22]. In our study the risk was relatively decreased from july to november (table 6). A possibly confounding factor lies in the seasonal pattern of attendance at day care and school (by older siblings). The summer decrease, Ingvarsson et al[21] suggest, may be due to the fact that many children revert to home rather than school or other care, and leave the towns and cities for the summer. According to Fiellau-Nikolajsen[23], the occurrence of otitis media is to a remarkable extent independent of season in home cared children. This suggests that cross-infection may be a more important factor than weather as such, and explains that in our study group of children, not yet attending school and for the majority home cared, seasonal influence was not very obvious.

Since the rationale behind the division into tympanogram-types A, C1, C2 and B is a systematic increase from a normal state towards an affected state, inferences concerning the relation between OME and for example AOM can be strengthened if one is able to show a kind of "dose response" relationship; moreover, the choice of only classifying "B" as truly OME might be substantiated by showing that A and C1/C2 are more or less "alike" and different from B. The results described in table 7 make these hypotheses very probable.

A random-effects analysis with a classification of 3 tympanogram types (table 8) demonstrates, that the definition of OME (type B = OME; A, C1 and C2 = no OME) is quite adequate with respect to AOM since the odds ratio comparing A with C1/C2 is nearly 1 and the odds ratio comparing B to A is significantly above 1. With respect to URTI, however, C1/C2 has approximately the same increased risk compared to A as the B-type has.

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CHAPTER 3b

BREAST FEEDING AND ACUTE OTITIS MEDIA

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ABSTRACT

Introduction: The risk of acute otitis media (AOM) is estimated as a function of a number of covariates, with special emphasis on changes to this risk after breast-feeding is discontinued.
Materials **and Methods:** Two hundred eighty-nine children born between July 1987, and October 1988, were studied up to the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different child health care centers.
Results: The risk of AOM was significantly decreased until 4 months after breast-feeding was discontinued; then, without the protective effect of breast-feeding, and with increasing months, the children approached the risk level estimated in the group of children who were never breast-fed. Approximately 12 months after breast-feeding was discontinued, the risk was virtually the same as if the child had never been breast-fed. The risk of AOM was also significantly dependent on the infant's number of siblings and socioeconomic status.
Conclusion: The risk of AOM depends on the number of months an infant is breast-fed and the number of months that pass after breast-feeding is discontinued.

INTRODUCTION

It has been hypothesized that breast-feeding offers protection against acute otitis media (AOM). This effect may be attributed to characteristics of the breast milk itself, to the harmful effects of bottle-feeding, or to the formula of cow's milk.[1,2]
In clinical studies that consider a possibly protective effect of breast-feeding on the risk of the occurrence of AOM, the results are controversial.[1,3-18]
In the Netherlands, 95% of all newborn infants visit a child health care center in their neighbourhood, which has a free admission. In 1987, we began a cohort study in three health care centers (two in a rural area, and one in an urban area) to investigate the occurrence and risk factors of otitis media (OM) and medical consumption directly related to this disease. We also studied the relationship of OM with upper respiratory tract infections. In this article, we focus on the association between breast-feeding and the occurrence of AOM, with special emphasis on changes to the risk of AOM after breast-feeding is discontinued.

PATIENTS AND METHODS

Patients

Our study consisted of 289 children born between July 1987, and October 1988, who were followed-up until the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different child health care centers, one of which was in an urban area, and two in a rural area. In the first year, mostly +/- 6 visits were made, and in the second year, mostly 3 to 4 visits. A total of 3021 visits were made (mean 10.5 visits/child). Two hundred thirty-two children (80%) completed a follow-up of 24 months or more (range 2 to 37 months; mean follow-up 23.6 months). Noncompletion was mostly because of families moving away from the area.
Relevant epidemiological data (Table 1) were collected by questionnaires that were answered by the parents at the beginning of the follow-up (most children being then 2 months old) and at every following visit at the child health care center.
At each visit, a tympanogram of each ear was made. The tympanograms were classified according to a modified system of Jerger.[19,20]
Relevant data from the medical records at the child health care centers, including a hearing distraction test (first described by Ewing) at approximately 9 months of age, were also evaluated.
A disease was classified as AOM if it had been diagnosed as such by their physician (primary physician or physician at the child health care center); if there had been purulent otorrhea; or if treatment for AOM had been given. The criteria for AOM consist of both acute symptoms (ear ache, fever, irritability, restless sleep, etc.) and otoscopic signs (distinct redness and/or outward bulging of the tympanic membrane). The results of tympanometry were not used as a criterion for AOM because the tympanograms were made at each regular visit at the child health care center, not when the child actually suffered from AOM. We also agree with Zielhuis et al, that type B tympanograms indicate otitis media with effusion (OME). AOM can appear in various other ways: overpressure (type A), uninterpretable tympanogram, or refusal of the child.[21]
The total number of available observations in the subgroup of children who were never breast-fed was 1354 in 130 infants. All other measurements are from 141 infants who at least once received breast milk, for a total of 1547 observations. For 18 infants, we had no information about the type of feeding they received.

Table 1. Relevant epidemiological data on questionnaires

CHILD	MOTHER
place of residence date of birth age race sex congenital malformations special diet type and duration of day care date of visit (seasonal influence) upper respiratory tract infections (URTI) treatment of URTI snoring mouth-breathing AOM treatment of AOM consultations with primary physician adenoidectomy tonsillectomy placement of middle ear ventilation tubes hearing test (Ewing) at child health care center	gestation (weeks) delivery (normal/disturbed) smoking during pregnancy duration of breastfeeding (months)
	HOUSEHOLD
	socioeconomic status (mother and father) number of siblings family history smoking habits

Statistical analysis

The ultimate goal of the present investigation was to estimate the possible protective effect of breast-feeding on the probability of the occurrence of AOM and, more specifically, how long such an effect remains after breast-feeding is discontinued. However, the elapsed time from the last occurrence of breast-feeding is highly correlated with age itself, which in turn is known to be related to the probability of AOM. To separate both effects, the effect of age on the occurrence of AOM was first estimated in the sample of children who were never breast-fed. To that end, we used the logistic regression model; as the children were repeatedly observed, the model was extended with a random effect to account for the correlations between the repetitions (ie, the repeated measurements on the same infant).[22]

We assume that the effect of age itself (as estimated in children who were never breast-fed) on the occurrence of AOM is the same in the sample of children who were breast-fed. In the latter sample, we further estimate the effect of the time elapsed since breast-feeding was stopped. The time after breast-feeding was discontinued was categorized into eight classes: up to 2 months before; 2 to 0 months before; 0 to 2 months after; 2 to 4 months after; 4 to 6 months after; 8 to 12 months after; and more than 12 months after breast-feeding was stopped. Also, the confounding effects of gestational age and sex of the child on the probability of AOM are investigated, as are the effects of season of the year, place of birth, socioeconomic status, passive smoking by the mother or father, number of siblings, and family diseases.

To describe the data, simple cross-tabulations are presented; to describe the results of the modelling, the odds ratios and their associated 95% confidence intervals are reported.

P-values less than 5% are interpreted as statistically significant; all tests are two-sided. The modelling was performed with the Epidemiological Graphics Estimation and Testing (EGRET, Seattle, WA) package (Analysis Module [Pecan], version 0.26.6;Epixact [R], version 0.03) (logistic binomial for distinguishable data).[23]

RESULTS

Of the 289 children, 53% were boys and 47% were girls. Most of the children (96.6%) were Dutch; many of the parents from foreign countries were incapable of answering the questionnaires because of language problems.

One hundred sixty-three children (56.4%) never had AOM; 32 children (11.0%) had recurrent AOM (3 times or more). Fourteen children (4.9%) had their first episode of AOM in their first half year of life (early onset AOM); 7 of these children developed recurrent otitis media (3 times or more) during the remainder of their follow-up period. Until the age of 3 months, 52.5% of the children were breast-fed, in the next 3 months, this decreased to 34.5%, and 3 months later to 21.6%; 2.5% of the children were breast-fed for more than 12 months.

Simple cross-tabulations of the risk of AOM within age and other risk factors are given in Table 2 for both the sample of children who were never breast-fed and those who were.

Table 2. univariate relations between occurrence of AOM and several risk factors

		never breastfed infants visits with AOM / total nr. visits	breastfed infants visits with AOM / total nr. visits
Age (months)	1,2,3	4/328 1%	
	4,5,6	29/224 13%	
	7,8,9	27/182 15%	
	10,11,12	17/131 13%	
	13-18	12/ 56 21%	
	19-	29/190 15%	
SES	high	17/208 8%	26/456 6%
	middle	47/461 10%	33/539 6%
	low	57/685 8%	57/552 10%
Nr. of siblings	0	30/639 5%	45/821 5%
	1	63/460 14%	39/515 8%
	2	23/222 10%	19/170 11%
	3	3/ 27 11%	4/ 22 18%
	4	2/ 6 33%	9/ 19 47%
Nr. of months before/after quitting breastfeeding			
	up to 2 before		10/351 3%
	2 - 0 before		6/233 3%
	0 - 2 after		3/181 2%
	2 - 4 after		4/161 2%
	4 - 6 after		17/138 12%
	6 - 8 after		14/104 13%
	8 -12 after		22/155 14%
	over 12 after		40/224 18%

In the sample of children who were never breast-fed, the relation between age (in months) and the risk of AOM seemed to be quadratic (Average [log(odds(AOM))] = -4.6 + 0.32Age - 0.00676Age^2), which is in accordance with the known pattern for the risk of AOM (starting very low, increasing with age for a while, and then decreasing afterwards).

This pure age effect is shown in Figure 1 as a solid curve. Assuming the above estimated age effect to be the same in the sample of children who were breast-fed, breast-feeding seemed to significantly decrease the risk of AOM ($P < .001$). The odds ratios for AOM (the first month is used as a base line) were relatively constant below 1 up to 4 months after breast-feeding was discontinued, but rapidly increased afterwards (Table 3) to a level virtually identical to that of children of the same age who were never breast-fed.

Table 3. relative risks of AOM adjusted for independently assessed age-risk score

No of months	Odds Ratio AOM adjusted for age only	Odds Ratio AOM adjusted for age, no of siblings, SES and allergy in family
No of months before/after breastfeeding is stopped		
up to 2 before	(1)	(1)
2 - 0 before	0.8	0.8
0 - 2 after	0.5	0.4
2 - 4 after	0.6	0.6
4 - 6 after	2.8	2.8
6 - 8 after	2.8	2.7
8 -12 after	2.7	2.3
over 12 after	3.3	3.1

Abbreviation: SES, socioeconomic status

This effect is shown in Figure 1 for a hypothetical child breast-fed up to the age of 9 months (dotted curve).

In the time period before breast-feeding was stopped, the following was observed: the age of the infant increases (and hence the risk of AOM) and the number of months that the infant is being breast-fed also increases; the latter results in the overall risk of AOM decreasing, even until about 4 months after breast-feeding is stopped.

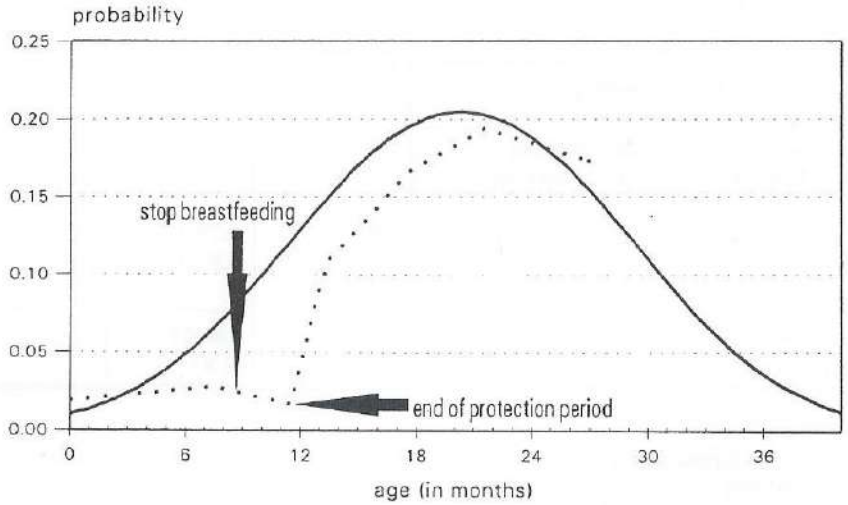

Fig. 1. Estimated probability of AOM in an infant who is breast-fed up to 9 months of age. (__ , never breast-fed; ..... , breast-fed until age 9 months)

Then the protective effect of breast-feeding suddenly wears out, and with increasing months, the child approaches the risk level estimated in the subgroup of children who were never breast-fed (Fig.1, Table 3). Approximately 12 months after breast-feeding is stopped, the risk of AOM is virtually the same as if the child had never been breast-fed at all.

Of the other risk factors analyzed, only the socioeconomic status and the number of siblings seemed to be significantly related (Table 4); family allergy also showed some relation with the risk of AOM. When correcting for these confounders, the effect of breast-feeding remained highly significant ($P < .001$; Table 3).

Table 4. risk of AOM adjusted for independently assessed age-risk-score and estimated as separate effects up to and from 4 months after breast-feeding is stopped (multivariate analysis)

Covariate		Odds Ratio AOM (adjusted for all other risk factors)	95% confidence interval	P value
age		NA		
number of siblings (OR per additional child)		1.89	1.33-2.68	<0.001 (LR)
SES	high	(1)		0.02 (LR)
	medium	1.25	0.56-2.8	
	low	1.99	0.92-4.28	
overall effect of breast-feeding				0.007 (LR)
	up to 4 months after stopping	(1)		0.023 (LR)
	beyond 4 months after stopping	2.77	1.14-6.73	
	before stopping (OR per month)	0.92	0.79-1.07	0.27 (Wald)
	after stopping (OR per months)	1.13	0.97-1.32	0.11 (Wald)
random effects term (correlation between visits within children)		NA	<0.001 (LR)	

NA = not applicable
LR = Likelihood ratio test
Wald = Wald test
SES = socioeconomic status

DISCUSSION

As previously stated, it has been hypothesized that breast-feeding protects against otitis media, and that this effect may be attributed to characteristics of the breast milk itself, to the harmful effects of bottle-feeding, or to the formula of cow's milk. Breast-feeding also seems to have a protective effect on the occurrence of other illnesses, such as gastrointestinal disease and lower respiratory tract infections.[1,2,12,23] The direct protective effect of breast-feeding may be explained by different mechanisms: reduction of exposure to pathogenic microorganisms, improved nutrition, and antibacterial effect of the milk. Human milk contains immunoglobulin with antibody activity against common bacteria such as Haemophilus influenzae and Streptococcus pneumoniae. Furthermore, it contains components that interfere with the attachment of H influenzae and S pneumoniae to nasopharyngeal epithelial cells. The intermittent administration of milk with antiadhesive substances into the nasopharynx of the nursing child may, therefore, reduce the extent of colonization and protect against infection.[24] Because infants are usually held upright while breast-feeding, milk may be less likely to enter the middle ear through the eustachian tube during feeding. In contrast, bottle-fed infants who are fed in the supine position may be at increased risk for drainage of milk into the middle ear, thus setting the stage for obstruction and inflammation. In a study of special feeding bottles for infants with cleft palate, infants who were fed with a bottle containing breast milk had fewer days of middle ear effusion than did infants fed with the device containing formula, suggesting that protection was more likely because of a constituent in breast milk rather than the mode of feeding.[25]

In clinical studies on the protective effect of breast-feeding on the risk of the occurrence of AOM, the results are controversial. These results are shown in Table 5. In the more recent studies, still different results are obtained. This cannot be explained by differences in study design (whether it is a cohort study) or by statistical analysis (whether the influence of other risk factors, such as day care and number of siblings, was controlled by using multivariate analysis). In nearly all studies, if a protective effect was shown, it was dependent on the duration of breast-feeding.

Only Teele[10] found that even a few months of breast-feeding was associated with decreased risk for AOM during the first year of life, and this decreased risk was independent of the duration of breast-feeding. In the study by Pukander,[13] this effect was only observed during the first 12 months of life, especially among those who had been breast-fed longer than 6 months; Saarinen[3] mentions that protection from recurrent AOM by prolonged breast-feeding was found not only during the breast-feeding period, but also as a long-term effect up to 3 years of age.

Table 5. Studies on the protective effect of breast-feeding for recurrent AOM

Author	protective effect *	duration dependent	multivariate analysis	follow-up
Cunningham[1],1977	-	-	-	0-12 mnths
Saarinen[3],1982	+	+	-	0-3 yrs
Persico[4],1983	+	+	-	NCS
Visscher[5],1984	-	-	+	NCS.
Stahlberg[6],1986	-	-	-	NCS
Kero[7],1987	+	+	+	0-12 mnths
Sipila[8],1988	-	-	+	7-32 mnths
Tainio[9],1988	-	-	+	0-2.3 yrs
Teele[10],1989	+	-	+	0-7 yrs
Harsten[11],1989	-	-	-	0-3 yrs
Howie[12],1990	-	-	+	0-2 yrs
Pukander[13],1990	+	+	-	NCS
Alho[14],1990	+	+	+	0-2 yrs

* : statistically significant
NCS : no cohort study

If the effect of age is not explicitly accounted for, the results may very well be biased because of the marked dependence of the risk of AOM on the actual age of the child.
The methodology applied in this paper does not only work well in the current situation; it is nearly impossible to avoid a rather advanced statistical model in dealing with data like the repeated observation of AOM in children during follow-up. On statistical grounds, the repeating structure requires taking into account the interdependence of different observations made on the same infant. Because the outcome is a binary variable (yes/no), the use of logistic models or discriminant analysis is suggested. Because the outcome can be repeatedly present or absent (contrary to an outcome like death), survival analysis (unless applied to something like "first occurrence of AOM") is not called for. Within the logistical framework, the random-effects model is appropriate to account for the within-patient correlation of measurements.
In our experience, the age effect cannot reliably be assessed within the subgroup of breast-fed infants because of a high correlation with the exposure of interest: the duration of breast-feeding itself. Simply computing (adjusted) percentages of AOM at any moment (either relatively to the birth of the child or relatively to the moment of breast-feeding) will yield highly biased and uninterpretable results. By estimating the age effect in an independent non-breast-fed sample, the effect of age can be incorporated in the logistic model just as any other "risk-score" (see reference 26). The advantage of this approach is that other factors could also be included in such a score if necessary.
The only way to make a possible causal effect of breast-feeding on AOM plausible in the framework of an observational prospective study (which is nonrandomized and can therefore never prove causality as such) is to show that the risk of AOM does indeed depend not only on the breast-feeding status (ie, never, currently, or stopped), but also on the actual number of months a child receives breast milk and the number of months that pass after breast-feeding is stopped.

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CHAPTER 3c

MEDICAL CONSUMPTION RELATED TO OTITIS MEDIA AND HEARING SCREENING IN THE FIRST TWO YEARS OF LIFE

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ABSTRACT

Two hundred eighty-nine children born between July 1987, and October 1988, were studied up to the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different health care centers. An inventory was made of medical consumption related to otitis media and upper respiratory tract infections, and of differences in medical treatment in the three areas investigated. The impact of hearing screening on medical consumption was observed. Nearly half of all visits to the general practitioners were made because of middle ear problems and/or upper respiratory tract infections. A considerable variety in treatment was found, despite the existence of uniform treatment policies. A hearing distraction test was failed by 8% of the children investigated; in this group medical consumption was increased.

INTRODUCTION

Otitis media (otitis media with effusion, OME and acute otitis media, AOM) is a very common disease, especially prevalent in children. According to Zielhuis[1] otitis media with effusion is nearly a "physiological" event from which virtually every child will suffer at some time in early life. He reviewed 23 population based impedance studies of OME[2]; according to these data, the prevalence rises from birth onwards and reaches its maximum at about two years of age. After the age of two there is a steady decrease in OME prevalence with a second peak at around 5 years of age, smaller than the peak at the age of two.

In a recent cohort study of 2512 children Alho[3] found a cumulative incidence of the first episode of AOM of 42% up to 12 month of age, and of 71% up to 24 months of age.

Several studies[1, 4-7] have suggested that incidence and prevalence of OME is increasing, while the suppurative complications of AOM have decreased. Black[8] mentioned that the presence of effusion in the middle ear has been recognized as a commonly occurring problem from at least the early 19th century, and suggested that changes in the surgical rate are more likely to reflect an "apparent" rather than a "real" increase in the underlying morbidity rate. On the other hand, Croteau et al.[9] compared the trends in the rates of surgical intervention and the rates of medical consultations for otitis media among children in Canada from 1981-1983, and concluded that most of the so-called surgical epidemic for middle ear effusion is related to a higher frequency of the underlying condition and not to more aggressive patterns of therapy during the years studied.

In the Netherlands screening for hearing impairment is performed at the age of 9 months with a hearing distraction test (Ewing test). Between 1976 and 1983, the failure rate on all 3 tests of the 9-month hearing screen using this test increased substantially. After 1983 it remained stable, around 6-7%.[10] Baart de la Faille[11] found a strong correlation between the result of the Ewing test and tympanometry, indicating that the 3 tests over a period of approximately 3 months select children with longstanding conductive hearing loss. In a report for the Dutch "Gezondheidsraad"[12] in 1986, further research was recommended to find out which children should be treated, and in what way, so as to avoid both overtreatment and undertreatment. A rough calculation at the time showed that the annual amount spent on the direct treatment of this disease was 112 million guilders. In 1986 30.000 ventilation tubes a year were inserted in the Netherlands; in 1991 this number had increased up to 43.000.[13]

In our country, 95% of all newborn children visit a child health-care center in their direct neighbourhood. In 1987, we started a cohort study of children from birth till the age of two in three health-care centers, to investigate the occurrence and risk factors of otitis media. In this article, we make an inventory of medical consumption related to otitis media and upper respiratory tract infections in this age group, and of differences in medical treatment in the three areas investigated. We also observe the impact of hearing screening on medical consumption.

PATIENTS AND METHODS

Our study population consisted of 289 children born between July 1987 and October 1988, followed up to the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different child health-care centers, one of them in an urban, and two in a rural area. In the first year of life mostly 2-monthly visits were made, in the second year mostly 3-6-monthly visits. In total 3021 visits were made (mean 10.5 visits/-child). 232 children (80%) completed a follow-up of 24 months or more (range 2-37 months; mean f.u. 23.6 months). Non-completion was mostly due to families moving away from the area. Of the total population of 289 children, 53% were boys and 47% girls. Most of the children (96.6%) were of Dutch origin, because many of the parents from foreign countries were incapable of answering the questionnaires, due to language problems.

Relevant epidemiological data (table 1) were collected by questionnaires, answered by the parents at the beginning of the follow-up (most children being then 2 months old), and at every following visit at the child health-care center.

At each visit the parents were asked to report treatment for upper respiratory tract infections (salt water or decongestant nose drops, antibiotics, homeopathics) and for otitis media (nose drops, ear drops, antibiotics, homeopathics, myringotomy). Any consultation of the general practitioner (GP) was mentioned, and also the reason for consultation. An inventory of surgical ENT-treatment was made.

Table 1. Relevant epidemiological data on questionnaires

CHILD	MOTHER
place of residence date of birth age race sex congenital malformations special diet type and duration of day care date of visit (seasonal influence) upper respiratory tract infections (URTI) treatment URTI snoring mouth-breathing otitis media treatment otitis media consultations primary physician adenoidectomy tonsillectomy placement of middle ear ventilation tubes hearing test (Ewing) at child health-care center	gestation (weeks) delivery (normal/disturbed) smoking during pregnancy duration of breastfeeding (months)
	HOUSEHOLD
	socioeconomic status (mother and father) number of siblings family history smoking habits

Relevant data from the medical records at the child health-care centers were evaluated, including the results of a hearing distraction test which is usually carried out for the first time at approximately 9 months of age (Ewing test). This test, first described in 1944[14] takes about 5 minutes, and is performed by two people, one of them observing the responses and playing with the child who sits on his mother's lap, the second person producing the sound stimuli outside the child's field of vision. If the child fails this test, a second test is performed one month later. After failing the second test, a third, more extensive test takes place again one month later, lasting about 15 minutes. The parents of children who fail the third test are advised to consult their GP. The Ewing test was performed in 2 of the 3 health care centers; in one (rural) center hearing evaluation was not yet integrated into the examination.
To detect the presence of OME, at each visit a tympanogram of each ear was made: a type B-tympanogram was considered as OME.

RESULTS

During the observational period, the 3 child health-care centers were visited 3021 times by all 289 children. Prior to the visit, acute otitis media occurred 251 times, in 120 children; 32 children had recurrent otitis media (3 times or more). Acute otitis media occurred 170 times together with or after a common cold, 52 times without.
In the areas investigated 39 general practitioners were visited 955 x: 452 x because of otitis media and/or upper respiratory tract problems, 503 x for other reasons. 23 children (8%) did not see their physician at all.
Table 2 shows the results of the Ewing test: 11 children (8%) failed the third test. 3 children were referred after failing the hearing test twice, without being subjected to the third test. Another 3 children failed the test once: one of these children received ventilation tubes (afterwards the hearing test, repeated in the hospital, was normal); the mother of the second child did not find it necessary to repeat the hearing test, and the third child was mentally retarded, the test was not repeated.

Table 2. Results of Ewing test

	rural 2 n = 83	urban n = 52	total n = 135	National average '88/'89
failure of first test	31 (37%)	16 (31%)	47 (35%)	33%
failure of second test	12 (14%)	8 (15%)	20 (15%)	13%
failure of third test	8 (10%)	3 (6%)	11 (8%)	7.5%

Ewing test not performed (rural 1) : 102
lost to follow-up : 52

In table 3 and 4 an inventory is made of the occurrence and treatment of upper respiratory tract infections; in table 5 and 6 of the occurrence and treatment of acute otitis media in the three investigated areas.

Table 3 Occurrence and treatment of upper respiratory tract infections (URTI)

		treatment	no treatment	total (no. of visits)
rural 1	URTI +	151 (54.3%)	127 (45.7%)	278 (25.3%)
	URTI -		822 (100 %)	822 (74.7%)
rural 2	URTI +	176 (71.8%)	69 (28.2%)	245 (24.2%)
	URTI -		769 (100 %)	769 (75.8%)
urban	URTI +	128 (56.9%)	97 (43.1%)	225 (24.9%)
	URTI -		677 (100 %)	677 (75.1%)

Table 4. Treatment of upper respiratory tract infections (URTI)

		rural 1	rural 2	urban
salt water nose drops	yes	110 (72.8%)	136 (77.7%)	110 (86.6%)
	no	41 (27.2%)	39 (22.3%)	17 (13.4%)
decongestants	yes	42 (27.8%)	76 (43.3%)	34 (26.8%)
	no	109 (72.2%)	99 (56.6%)	93 (73.2%)
antibiotics	yes	19 (12.6%)	54 (30.9%)	27 (21.3%)
	no	132 (87.4%)	121 (69.1%)	100 (78.7%)
homeopathics	yes	31 (20.5%)	31 (17.7%)	16 (12.6%)
	no	120 (79.5%)	144 (82.3%)	111 (87.4%)

Table 5. Occurrence and treatment of acute otitis media (AOM)

		treatment	no treatment	total (no. of visits)
rural 1	AOM +	84 (90.3%)	9 (9.7%)	93 (8.5%)
	AOM -		1004 (100 %)	1004 (91.5%)
rural 2	AOM +	81 (90.0%)	9 (10.0%)	90 (8.9%)
	AOM -		926 (100 %)	926 (91.1%)
Urban	AOM +	60 (88.2%)	8 (11.8%)	68 (7.5%)
	AOM -		833 (100 %)	833 (92.5%)

Table 6. Treatment of acute otitis media (AOM)

		rural 1	rural 2	urban
nose drops	yes	63 (75.0%)	73 (90.1%)	40 (66.7%)
	no	21 (25.0%)	8 (9.9%)	20 (33.3%)
ear drops	yes	24 (28.6%)	44 (54.3%)	31 (51.7%)
	no	60 (71.4%)	37 (45.7%)	29 (48.3%)
antibiotics	yes	32 (38.1%)	42 (51.9%)	34 (56.7%)
	no	52 (61.9%)	39 (48.1%)	26 (43.3%)
homeopathics	yes	10 (11.9%)	8 (9.9%)	10 (16.7%)
	no	74 (88.1%)	73 (90.1%)	50 (83.3%)
myringotomy	yes	3 (3.6%)	5 (6.2%)	6 (10.0%)
	no	81 (96.4%)	76 (93.8%)	54 (90.0%)

n = no. of visits

Of the 11 children who failed the Ewing test, 8 experienced an acute otitis media during the observational period, of which 2 children recurrently. 9 of

the 11 children received antibiotics at least once, for upper respiratory tract infections and/or otitis media. 4 children were treated surgically, by inserting ventilation tubes (2x) or adenoidectomy (2x). 6 children were referred to the audiologist to perform more extensive observational audiometry, sometimes after treatment of middle ear pathology; no sensorineural hearing losses were found in this subgroup of 11 children. 4 children were not referred for further investigation by their general practitioner, who applied a "wait and see policy"; 3 children were lost to follow-up.
One child had a severe sensorineural hearing loss, detected at the age of 3 months due to the concern of the child's mother and by direct referral to a hearing institute by the investigator. The child received hearing aids and some months later ventilation tubes were inserted because of middle ear effusion.
Surgical treatment for upper respiratory tract infections and otitis media per area is shown in table 7, related to the frequency of recurrent otitis media (3 times or more) and failure of the third Ewing test.

Table 7. Surgical treatment for upper respiratory tract infections and otitis media

	rural 1 (n = 101)	rural 2 (n = 102)	urban (n = 86)	TOTAL (n = 289)
adenotomy	7	9	8	24
adenotonsillectomy	-	1	1	2
ventilation tubes	2	5	2	9
recurrent otitis media	12	11	9	32
failure of third Ewing test	NA	8	3	11

NA = not applicable

DISCUSSION

During the observation period, nearly half of all visits to the general practitioners was made because of middle ear problems and/or upper respiratory tract infections. In another Dutch cohort study following over two thousand children from birth up to their second birthday, it appeared that the parents of 96% of the children contacted their GP at least once; most frequent causes for seeking medical advice were upper respiratory tract problems. Half of the children went to consult a specialist, of which 15% an ENT-surgeon. 19% of the children went to GP or specialist because of otitis media.[15]
The hearing distraction test was failed by 8% of the children investigated; the failing percentages of the three tests are more or less equal to the national average (7.5%); sometimes the third test is not performed, mostly because of organisational problems.
An inventory of medical treatment for upper respiratory tract infections and otitis media in our population is made in table 3 - 6. Table 3 shows that upper respiratory tract infections occurred in the period prior to about 25% of the visits in all three areas. In two of the three centers, about half of these occurrences were medically treated, in the third (rural 2) about 72%. Table 4 shows what kind of treatment has been given: the largest differences in treatment between the three centers were seen in treatment with decongestants and with antibiotics (27% - 43% and 13% - 31% respectively). In table 5 can be seen that acute otitis media occurred in the period prior to about 8% of the visits in all three areas, and was almost always treated (approximately 90% of the occurrences). For acute otitis media also, medical therapy varies considerably (table 6). Although the effect of homeopathic medicines on children with recurrent upper respiratory tract infections has not been proven,[16] these are frequently used (table 4 and 6). Since the publications of van Buchem[17] much less myringotomies are performed in the Netherlands, as is also reflected in our results (table 6).
In spite of the existence of a rationalized, uniform treatment policy,[18,19] there is still inconsistency in antimicrobial therapy. Van der Ven et al.[20] reported that in the Netherlands half of all antimicrobial treatments are prescribed by only 25% of the GP's.
In the group of 11 children who failed the Ewing test, medical consumption was clearly increased; this could be due to the underlying disease (OME), but it could also be a consequence of the test-result, since all these children were referred to their GP. As Baart de la Faille[21] mentioned, probably most of these children had a prolonged period with conductive hearing loss. Moreover, failure of the third Ewing test is a strong indicator for persistent or recurrent bilateral OME at age 2-4 years.[22] Detection of sensorineural hearing losses, not longstanding conductive hearing losses was the initial goal of the Ewing test. After referral to the GP, there exists no uniform policy. A national failure percentage of 7.5 leads to almost 15000 referrals a year, a mean of 2-3 per GP. Several GP's consider this too much and have a wait and see policy. Sometimes this leads to a delay in treatment for children with sensorineural hearing loss.[23] Failure of the test can also be caused by a mixed hearing loss. After surgical treatment of middle ear pathology, the reactions to sound will be improved, both at home and during the screening test.

Evaluation data indicate that parents and testers are often misled by this improvement and as a result the perceptive hearing loss is not detected.[10]
No consensus exists on the causality of detrimental effects of conductive hearing loss; developmental sequelae have not been proven to be permanent.[24] There is a general agreement, that the first year of life is an important developmental phase. In our population, however, failure of the Ewing test seemed to lead to a minor increase in surgical therapy: of the 11 children who failed the test, 2 children had an adenoidectomy and ventilation tubes were inserted in 2 children (see also table 7; since the numbers are very small, percentages are not given). In a previous study we found that surgical treatment of conductive hearing losses mostly takes place when the child is older, with a maximum at the age of 4,[25] probably because at this age the existence of a conductive hearing loss is more easily noticed.

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CHAPTER 4

THE COLLABORATIVE PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE INFANTS (POPS) IN THE NETHERLANDS

CHAPTER 4a

OTITIS MEDIA, RESPIRATORY TRACT INFECTIONS AND HEARING LOSS IN PRETERM AND LOW BIRTHWEIGHT INFANTS

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ABSTRACT

In 1983, 1338 liveborn infants with a gestational age of less than 32 weeks and/or a birthweight of less than 1500 g, were enrolled in a national follow-up study in The Netherlands. At the age of 5 years, 966 children were alive. Of these, 927 (96%) were on a home visit 2-6 weeks after their fifth birthday by three specially trained paediatricians. An assessment of ENT morbidity was made and compared with ENT morbidity in full-term children of the same age group. Markedly preterm birth or very low birthweight does not seem to be a risk factor for developing middle ear disease in childhood, however, the rate of ENT problems seems to be higher than in the general population of Dutch pre-school children.

INTRODUCTION

Several authors report that otitis media is a common occurrence in neonatal intensive care units[1-10] and suggest that, during childhood, there is a higher incidence of middle ear disorders in children with low birthweight[4,5,8-10] or preterm birth.[11] In contrast with this, Gravel et al., comparing preterm with term infants reported no difference in frequency or age of onset of otitis media.[12]

In the Netherlands a nation-wide cohort study was started in 1983, involving nearly all paediatric and neonatal departments in the country. This collaborative "Project On Preterm and Small for gestational age infants" (POPS 1983) collected data on virtually all very preterm and very low birthweight infants, liveborn in 1983 in The Netherlands.[13] At 5 years of age these children were re-examined. We used this opportunity to assess ENT morbidity in this population in the first 5 years of life, and compare it with ENT morbidity of full-term children.

PATIENTS AND METHODS

In 1983, 1338 infants, liveborn before 32 completed weeks of gestation and/or with a birthweight of less than 1500 g, were enrolled in the prospective survey (POPS). Between birth and 5 years of age, 372 infants died, most of them (312) during the neonatal period.[14] At 5 years of age, 966 children were alive; 927 (96%) having been examined. Available information about the 39 children, not assessed at 5 years of age indicates that selection bias is improbable.

All 927 children were assessed at home, by three paediatricians, in 10 areas of investigation: congenital malformation, neuro-motor function, mental development, hearing, visual function, language and speech development, musculoskeletal system, respiratory tract and ear nose throat disorders, behaviour and growth. A more detailed description of the methods of assessment used is given in another paper.[15] The results of the study in terms of impairments, disabilities and handicaps have been reported elsewhere.[16]

Otitis media, respiratory tract infections and hearing loss were evaluated by means of history and audiometry. The presence of serous or purulent rhinitis at the time of examination was recorded. Otoscopy was done in case of a middle ear ventilation-tube history to verify if these tubes were still in situ, and whenever audiometry could not be performed.

The frequency of otitis media before 5 years of age was based on the number of times otitis media was diagnosed by a physician. Recurrent otitis media was defined as three or more episodes a year of otitis media; recurrent upper respiratory tract infections as rhinitis more than 10 times a year, and recurrent lower respiratory tract infections as bronchitis three or more times a year and/or pneumonia more than once a year.

Audiometric examination was performed by one of the three paediatricians, trained at our ENT department, with a hand-held pure-tone audiometer (Hortmann DA 323) fitted for air and bone conduction, with Holmberg 8103 BZ and Oticon 60 231 headphones respectively, and the possibility of masking. Calibration: ISO/DP 389-1983. Hearing was tested at 500, 1000, 2000 and 4000 Hz, for each ear separately up to a hearing threshold of 15 dB. The curtains were closed and no other persons or noisy animals were in the same room. An average of the threshold levels of 26 dB or more was considered abnormal.[17] A hearing loss of 26-40 dB was classified as mild, 41-55 dB as moderate, 56-70 dB as moderately severe, 71-91 dB as severe and >91 dB as profound.[17] Four types of hearing loss were distinguished: conductive, sensorineural, mixed and unspecified.

Data were processed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois, USA) and the Statistical Analysis System (SAS Institute, Cary, North Carolina, USA). The relationships between the occurrence of otitis media, hearing loss and several other environmental factors were examined univariately by cross-tabulations. Chi-square tests were applied to assess the statistic significance of these relations.

RESULTS

Nearly half of all children had otitis media at least once (table 1). Seventy children (8%) were reported to have recurrent otitis media. Socio-economic class, race or number of siblings did not seem to influence the occurrence of recurrent otitis media; boys seemed to have a higher risk (47 % versus 42 % in girls), but this was not statistically significant.
Seven children had more than 10 episodes of otitis media in one year, of these children three had recurrent upper respiratory tract infections, three recurrent lower respiratory tract infections, and one both; six of them had middle ear ventilation tubes.

Table 1. Frequency of otitis media, 0 - 5 years of age.

	n	%
< 3 a year	345	37.2
3 - 10 a year	63	6.8
> 10 a year	7	0.8
ever	415	44.8
never	512	55.2
total	927	100.0

No relationship was found between recurrent otitis media and assisted ventilation (IPPV and/or CPAP, in most cases by naso-tracheal tube) during the neonatal period. No relationship was found between recurrent otitis media and gestational age, birthweight, septicaemia and antenatal glucocorticoid administration.

Twenty-three children had a myringotomy before their first birthday; most myringotomies were performed at the age of 4 years (Figure 1). Most of the middle ear ventilation tubes were also inserted at the age of 4 years (Figure 2); six children had middle-ear ventilation tubes before their first birthday.
Recurrent upper respiratory tract infections were reported in 146 children (16%), recurrent lower respiratory tract infections in 81 (9%). Table 2 demonstrates the relation between recurrent upper respiratory tract infections, lower respiratory tract infections and otitis media. Only eight children had all three.

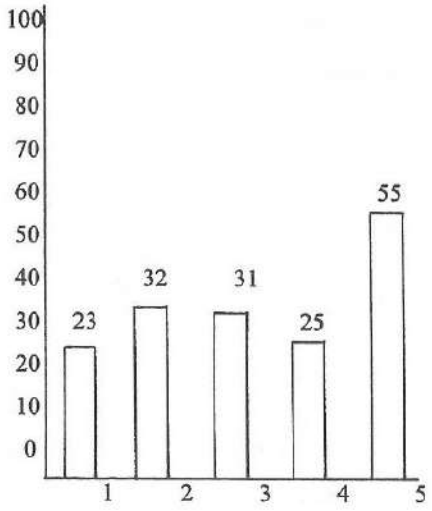

Figure 1. Distribution of myringotomy

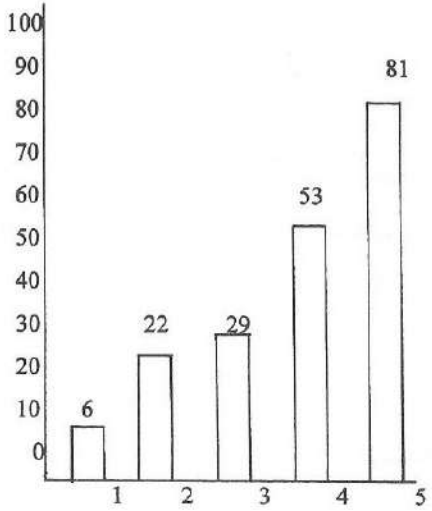

Figure. 2. Distribution of insertion of middle ear ventilation tubes

The statistical test of interaction is not significant (P = 0.11), hence the data observed are still in agreement with a model which assumes an effect of both "lower present" and "upper present" (adjusted OR of 3.0 (P < 0.001) and 2.2 (P = 0.01 - 05), respectively) being the same regardless of the status of the other one. However, the data also seem to suggest the possibility that there exists "interaction" between "lower" and "upper" in such a way that if one of them is present, the additional presence of the other one does not matter very much (clearly seen in the second row of the table where "lower" is present and the additional effect of "upper" is negligible).
Table 3 shows the relation between surgical intervention for upper respiratory tract infections and for otitis media; these interventions were very often exerted at the same time.
Hearing loss was found in 136 (15%) of the 890 children (in three children with severe sensorineural hearing loss the results of recently performed audiometry were used). Table 4 shows the type and severity of the hearing loss. In 37 children audiometry could not be performed because of mental retardation or behavioural disturbances.

Table 2. Prevalence of recurrent otitis media

respiratory tract infections	Upper absent	Upper present	
Lower absent	38/737 5%	15/109 14%	53/846 6%
Lower present	9/ 44 20%	8/ 37 22%	17/ 81 21%
	47/781 6%	23/146 16%	70/927 8%

Table 3. Surgical intervention: adenoidectomy (A), adenotonsillectomy (AT), myringotomy and ventilation tubes

	n	%	Myringotomy n	%	Ventilation tubes n	%	Total n	%
-	586	87.0	43	6.4	45	6.6	674	100
A	41	41.4	21	21.2	37	37.4	99	100
AT	73	47.4	37	24.0	44	28.6	154	100
Total	700	75.5	101	10.9	126	13.6	927	100

The majority of children were recorded to have a mild to moderate conductive hearing loss (13%, if the mixed losses are included and all the unspecified losses, in which the type of hearing loss is unknown, are regarded as purely sensorineural losses and 14.7% if the mixed losses are included and all the unspecified losses are regarded as purely conductive).
Sensorineural hearing loss was found in 13 children (1.5%).
In the total group of 136 children with hearing loss, 18 children had recurrent otitis media; 31 had ventilation tubes inserted, nine children used a hearing aid, all because of bilateral sensorineural hearing loss, and seven children with sensorineural hearing loss had middle ear ventilation tubes.
Of the 70 children with recurrent otitis media, eight children had conductive hearing loss and five children sensorineural loss.
At the time of audiometric examination, 56% of the children with conductive hearing loss had a serous or purulent rhinitis, vs. 21% of the children with normal hearing.

Table 4. Hearing loss (n=136) in 890 assessed children

			n	n	(%)
normal hearing				754	(84.7)
conductive	unilateral	mild	52		
		moderate	21		
	bilateral	mild	18		
		moderate	17		
		mod. severe	1		
				109	(12.3)
sensori-neural	bilateral	mod. severe	3*		
		profound	2*		
				5	(0.6)
mixed	unilateral	mild	1*		
		severe	1*	4	(0.4)
	bilateral	mod. severe	1*		
		severe	1*		
unspecified	unilateral	mild	5		
		moderate	1		
	bilateral	mild	3		
		moderate	4		
		mod. severe	1#*		
				14	(1.6)
others					
R.cond.,mild /L.unspec.,mod.severe			1#*		
R.sens.,mod.severe/L.unspec.,mod.severe			1#*		
R.mixed,severe /L.unspec.,severe			1#*		
R.cons.,mild /L.unspec.,mild			1		
				4	(0.4)
				136	(15.3)
total				890	(100.0)

* sensorineural hearing loss n = 13 (1.5%)
\# the amount of dB loss and the type of audiogram (high frequency hearing loss) indicates a sensorineural component

No relationship was found between conductive hearing loss and gestational age, birthweight, sex, septicaemia, assisted ventilation and antenatal administration of glucocorticoids. A more detailed description of the 13 children with sensorineural hearing loss has been published elsewhere.[18]
Four children had a congenital malformation related to ENT problems: three children with palatoschisis, all had normal hearing and two had middle ear

ventilation tubes. In one child with Down's syndrome hearing could not be tested because of mental retardation. Of the total study population of 927 children, 36% had been or were still being attended by an ENT specialist. In children with hearing loss this was 47%, with recurrent respiratory tract infections 56%, with recurrent otitis media 74%.
Table 5 shows a comparison of the results of our study with results of the KNOOP-project (Zielhuis 1991, unpublished data). This project was a Dutch cohort study on the occurrence of otitis media with effusion in preschool children of all gestational ages, born between 1 September 1982 and 31 August 1983.[19] A comparison of the results in POPS and KNOOP demonstrates, that otitis media occurred more frequently in the latter, but considerably more medical intervention was given to the first.

Table 5. Comparison of the POPS-data with data from the KNOOP-project in Nijmegen (Zielhuis 1991, unpublished data)

	POPS (0 - 5 years old) n = 927			KNOOP (0 - 4 years old) n = 781		
	n	%	ID	n	%	ID
otitis media	415	44.8	89	568	72.7	182
myringotomy	155	16.7	33	42	5.4	13
vent.tubes	126	13.6	27	40	5.1	13
adenoidectomy	233	25.1	50	68	8.7	22
tonsillectomy	153	16.5	33	26	3.3	8
no. of children who visited an ENT-specialist	330	35.6	71	210	26.9	67

ID = incidence density: n / 1000 person years

DISCUSSION

Previous studies have reported that otitis media is common in children admitted to neonatal intensive care units[1-5,7-11] and suggested that there is a higher incidence of middle ear disorders in children with low birthweight.[4,5,8-10] Several factors have been suggested as being responsible for this higher incidence: infection,[3,7] nasotracheal[1,7] or nasogastric tubes,[2,20] meconium contamination of the middle ear,[21] and supine position for extended periods.[2] Early episodes of otitis media experienced in the neonatal intensive care unit might pre-dispose to recurrent middle ear disease, with persistent or frequently recurring conductive hearing losses during childhood.[5,9,10]
Histopathological studies of petrous bones of premature infants[6] and infants receiving intensive care in the neonatal period[3] seemed to confirm the high incidence of middle ear disease in these populations.
Gravel et al.[12] found no difference in incidence and age of onset of otitis media between a group of 19 full-term and a group of 46 very low birthweight infants, but the numbers of these populations were small.
In the studies mentioned above, the populations differ greatly in number, gestational age, birthweight, and age at the time of examination. Moreover, the period of follow-up varies from 2 weeks to 4 years. In the majority of the studies no control or reference group was described. Diagnostic criteria vary, and exact definitions are lacking. Zielhuis et al. also described the problems one is faced with when studying the literature.[22] Therefore, it is not easy to compare our results with other studies. Moreover, in our population special attention was paid to ENT problems when the children were 5 years old. No information was available about middle ear status of these children in early life, otoscopy not being a routine examination during neonatal intensive care.
From the POPS study it appears that preterm and low birthweight children do not have an increased frequency of middle ear disorders during childhood compared with children in the general population[23-30] (and Table 5); in these studies, the occurrence of acute otitis media varies from 40-85% in the first 5 years of life. Medical consultations as far as ENT is concerned, seem to be higher than in a normal population at all ages from 0 to 4 years (Table 5).
In our study, recurrent upper and lower respiratory tract infections were clearly associated with the occurrence of otitis media. No significant relation with other risk factors, such as gestational age, birthweight, assisted ventilation and septicaemia could be found. The prevalence of sensorineural hearing loss is well described in the literature. Little is known about the prevalence of conductive, often temporary hearing loss in a normal population of full term children. In the POPS-project, a small reference group of 52 volunteer children from 4 nursery schools was examined using the same protocol; in this group, 13% had a conductive hearing loss.
Our finding of 13 - 14,7% conductive hearing loss, compared with other studies[23,31-33] indicates, that preterm birth or low birth weight is probably not a risk factor for this condition. From the information available about the 37 children for whom audiometry was not feasible it is not likely that the prevalence of hearing loss would increase substantially. Straightforward comparison of the results from POPS and KNOOP is methodologically not acceptable, because the study design is not the same: in POPS a questionnaire

is answered at the age of 5 years and in KNOOP multiple questionnaires every 3 months from 2 to 4 years of age. Since at the end of the studies the children from POPS were 5 and those from KNOOP 4 years old, we compared the incidence density.[34] The higher rate of medical consumption, including surgical ENT procedures might be caused by "overconcern" of parents and/or doctors. Another explanation could be the high prevalence of delay in language and speech development,[35] which is often a reason for earlier intervention by the ENT-specialist.

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CHAPTER 4b

HEARING LOSS IN VERY PRETERM AND VERY LOW BIRTHWEIGHT INFANTS AT THE AGE OF 5 YEARS IN A NATIONWIDE COHORT

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ABSTRACT

In a geographically defined population of very preterm and very low birthweight infants (gestational age < 32 weeks and/or birthweight < 1500 g) hearing was evaluated in 890 children by pure-tone audiometry at the age of 5 years. Hearing loss was conductive/unspecified in 123 (13.8%) and sensorineural in 13 (1.5%) children. The prevalence of sensorineural hearing loss was 15 times as high as in 5-7 year old children in the Dutch population at large. The sensorineural hearing loss prevalence in very low birthweight and extremely low birthweight infants was similar. On account of communication disorders 10 (1.1%) children were classified as disabled and 6 (0.7%) as handicapped, following the definitions of the International Classification of Impairments, Disabilities, and Handicaps of the World Health Organization. Children with conductive hearing loss had a higher risk of impairments, disabilities and handicaps of language and speech development, than children with normal hearing, the difference being statistically significant. The same holds for children with sensorineural hearing loss; moreover they had a significantly higher risk of impairments, disabilities and handicaps of mental development. Overall comparison of children with and without sensorineural hearing loss proved that the children with sensorineural hearing loss had a significantly less favourable outcome, based on 15 perinatal factors simultaneously. The age at which sensorineural hearing loss in very preterm and/or very low birthweight infants is detected has to be improved.

INTRODUCTION

The developmental and psychosocial impact of hearing loss can be devastating,[9] particularly if hearing loss is accompanied by other developmental disorders. Early identification and intervention is of the utmost importance.[12,25] The prevalence of hearing loss among very and/or extremely low birthweight survivors of neonatal intensive care, ranges from 0.5 % to 12.3 %.[1,2,4,7,14-17,20,22,24,26-29,31,36] This range is, among others, caused by differences between the populations studied (hospital based versus area based) and differences in intake criteria and methods of assessment (questionnaire, audiometry, brainstem-evoked response). In order to obtain an unbiased prevalence of hearing loss and associated (developmental) disorders, we used data from the Dutch nationwide survey of a year cohort of 1338 very preterm and very low birthweight infants at 5 years of age. Results regarding the pre-, peri- and postnatal period and the follow-up studies at the corrected age of 2 years and at the chronological age of 5 years in this population have been published previously.[38-40,43-48]

PATIENTS AND METHODS

The "Project on Preterm and Small for gestational age infants" (POPS) collected data on 1338 liveborn infants in the Netherlands, from 1 January to 31 December 1983, with a gestational age of less than 32 completed weeks and/or a birthweight of less than 1500 g. The study population included 94% of all infants meeting the intake criteria. At the age of 5 years all 966 survivors were elected for a second follow-up study. The main results have been published previously.[45]

The entire assessment took place during a home visit and was performed by three specially trained paediatricians (S.V., M.H.E-D., A.M.S.). As far as hearing was concerned, the examiners were trained at the ENT department of the Leiden University Hospital. The hearing assessment consisted of history and pure-tone audiometry. The latter was performed with a handheld pure-tone audiometer (Hortman DA 323) fitted for air and bone conduction, with Holmberg 8103 BZ and Oticon 60 231 headphones, respectively, and the possibility of masking. Calibration: ISO/DP 389-1983. Hearing was tested at 500, 1000, 2000 and 4000 Hz, for each ear separately till a hearing threshold of 15 dB. The threshold level was recorded when a tone was heard three times, while the same tone at a 5 dB lower level was not heard. The curtains were closed and no other persons or noisy animals were in the same room. An average of the threshold levels of 26 dB or more was considered abnormal.[49] A hearing loss of 26-40 dB was classified as mild, 41-55 dB as moderate, 56-70 dB as moderately severe, 71-91 dB as severe and > 91 dB as profound.[49] Four types of hearing loss were distinguished: conductive (CDHL), sensorineural (SNHL), mixed and unspecified.

Besides the outcome expressed in dB, the definitions of the International Classification of the World Health Organisation for Impairments, Disabilities and Handicaps were used as an outcome measure:

An impairment is any loss or abnormality of psychological, physiological or anatomical structure or function.

A disability is any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.

A handicap is a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual.

Following this classification hearing loss was coded according to the

better ear, which implies that a child with one normal ear was regarded to have no hearing impairment. Disability or handicap did not just depend on the amount of hearing loss in dB: a child was classified as disabled when the hearing loss was limiting the ability to take part in oral communication. A child was classified as handicapped when this communication disorder resulted in an orientation, physical independence or social integration handicap. Thus the use of hearing aids was not considered to be a handicap per se contrary to the WHO definition.

Besides the audiological evaluation the assessment included the following 9 areas: congenital malformation, neuromotor function, mental development, visual function, speech and language development, musculoskeletal system, respiratory tract and ENT disorders, behaviour and growth.[33]

The Mantel-Haenszel procedure was used to assess and depict the relationship between SNHL ("exposure") and other areas of investigation ("outcome"), stratified by CDHL ("confounding factor"). [As an example, this results in making a simple 2 x 2 table showing the relation between, e.g., SNHL (yes versus no) and congenital malformation (present versus absent) (see Table 6), for both children with and without CDHL; the association in both subgroups, i.e., both 2 x 2 tables, is then combined into one overall assessment of the SNHL versus congenital malformation relation]. The same analysis was carried out with CDHL as "exposure" and SNHL as "confounding" factor. Possible interactions between SNHL and CDHL were tested by incorporating both factors in a simple logistic regression model (which is, in the absence of an interaction term, equivalent to the Mantel-Haenszel approach). Two children with unspecified hearing loss were categorized as sensorineural depending on the amount of hearing loss and the type of audiogram (high frequency hearing loss). When we assume a similar distribution of type of hearing loss in the children who refused cooperation during bone conduction (the remaining unspecified hearing losses) as in those who did co-operate during the whole hearing assessment (air and bone conduction), the expected number of children with SNHL would be 1 and the expected number of children with CDHL would be 12. Exclusion of these 12 children from the analyses would result in a larger bias, than the 1 or probably 2 children misclassified as having no SNHL. Therefore these 13 children with unspecified hearing losses were included in the analyses as CDHL. The children with mixed hearing loss were categorized in the CDHL as well as in the SNHL category. In the area language and speech development 66 children with another native language were excluded from the analysis. Fisher's exact test and the Student's t-test were used to assess the relationship between SNHL and several perinatal factors. A P value of < 0.05 was considered significant. Group comparison in a multiple-endpoint situation was performed according to the approach suggested by O'Brien[21] and Pocock.[23]

The test statistic is a weighted sum over individual test statistics comparing the means of a number of outcome variables in two groups. The test procedure evaluates whether the two groups differ consistently in the same "direction": even if all individual tests would be non-significant (for example due to small numbers) a consistent direction of the effect - assuming the coding of all variables being consistent as far as the direction of a clinically favourable situation is concerned - would be highly unlikely if all individual outcomes were not too highly correlated. The weights applied in the overall test statistic are based upon the correlations between the outcome variables in such a way that highly correlated variables contribute less to the overall statistic than uncorrelated ones. In other words, if the outcome to be compared between two groups can be expressed in a number of clinically different aspects (here 15 perinatal factors), this test can detect whether one group performs significantly worse in the majority of those aspects, even if each aspect individually can not be shown to be significantly different (due to a small sample size).

Data were processed with use of the Statistical Package for the Social Sciences (SPSS-X 2.1) [35], the Statistical Analysis System[32] and EGRET.[10]

RESULTS

Three hundred and seventy-two infants out of 1338 died between birth and 5 years of age. Of the 966 children alive, 927 were assessed (loss to follow-up 4%) with respect to the 10 areas of investigation. In 37 of these children it was not possible to perform audiometry as a result of behavioural disturbances and/or mental retardation; thus 890 children had a complete hearing assessment (in 3 children with severe SNHL the results of recently performed audiometry were used).

Of the assessed children 15.3% had some type of uni- or bilateral hearing loss (Table 1). In 13.8% (13.0% if the mixed losses are included and all the unspecified losses are regarded purely sensorineural and 14.7% if the mixed losses are included and all unspecified losses are regarded as purely conductive) the hearing loss was of conductive/unspecified origin, mostly unilateral and classified as mild or moderate. SNHL was present in 13 children (1.5%), mostly bilateral and in all but one classified in a range from moderately severe to profound.

Table 1. Hearing in 890 assessed 5 year old children in dB categories (bilateral according to the worst ear)

			n	n	(%)	n	(%)
Normal						754	(84.7)
Conductive/unspecified							
Conductive	unilateral	mild	52				
		moderate	21				
	bilateral	mild	18				
		moderate	17				
		moderately severe	1				
				109	(12.2)		
Unspecified	unilateral	mild	5				
		moderate	1				
	bilateral	mild	3				
		moderate	4				
				13	(1.5)		
Right conductive mild left unspecified mild			1				
				1	(0.1)		
						123	(13.8)
Sensorineural							
Sensorineural	bilateral	moderately severe	3				
		profound	2				
				5	(0.6)		
Mixed	unilateral	mild	1				
		severe	1				
	bilateral	moderately severe	1				
		severe	1				
				4	(0.5)		
Unspecified	bilateral	moderately severe	1#				
				1	(0.1)		
Right sensorineural moderately severe left unspecified moderately severe			1#				
			1#				
Right mixed severe left unspecified severe			1#				
				3	(0.3)		
Right conductive mild left unspecified moderately severe						13	(1.5)
Total				136	(15.3)	890	(100.0)

\# The amount of dB loss and the type of audiogram (high frequency hearing loss) indicates a sensorineural component.

Table 2. Conductive and sensorineural hearing loss at 5 years of age in the total cohort and in subgroups of infants with gestational age < 32 weeks, VLBW infants (< 1500 g) and ELBW infants (< 1000 g)

Present study POPS	Study sample	Dead	Surviving	Lost	Audiometry not possible *	FU $	Total HL		SNHL		CDHL/ Unspecified HI	
	n	n	n	n	n	n	n	(%)	n	(%)	n	(%)
< 1500 g and/or < 32 wks	1338	372	966	39	37	890	136	(15.3)	13	(1.5)	123	(13.8)
< 32 wks	1010	332	678	30	24	622#	84	(13.5)	11	(1.8)	73	(11.7)
< 1500 g	1097	330	767	31	29	707	121	(17.1)	11	(1.6)	110	(15.6)
< 1000 g	292	162	130	2	5	123	17	(13.8)	2	(1.6)	15	(12.2)

* Audiometry not possible because of behavioural disturbances and/or mental retardation; $ FU = Follow-up; # n = 2 gestational age unknown

The subgroups of infants with a gestational age < 32 weeks, the VLBW infants (birthweight <1500 g) and the ELBW infants (birthweight < 1000 g), showed similar results (Table 2).

Six children with SNHL visited special schools for the deaf or special schools for children with less severe hearing loss, 3 had other forms of special education because of additional developmental disorders and 4 children were attending regular schools. Nine children had hearing aids, all because of bilateral SNHL. There were no indications of congenital hearing disorders in the first and second degree of the children's relatives. Socioeconomic status was low in 7 and middle and high in 3 children each. The distribution of socioeconomic status in the children with and without SNHL was similar. Most children had a hearing screening test (distraction test, Ewing) at about 9 months of age according to the Dutch Child Health Care prevention program[5] and the majority visited an ENT-specialist (Table 3). In only one child, the Ewing test had not been performed; in one other case no information on this issue could be obtained. At 2 years of corrected age the SNHL had been diagnosed in 6 of the 13 children.

Table 3. Screening, detection and associated disorders in 13 children with SNHL

Patient	Ewing test at 9 months of age	Age at detection#	ENT-specialist since	Associated middle ear disorders	Associated impairments disabilities and handicaps
1	-	3 months	3 months	yes	neuro,lang,vis,res
2	-	3 months	3 months	no	neuro,md,lang
3	yes	1 year	1 year	yes	neuro,md,lang,res
4	yes	1 year	2 years	no	lang
5	yes	2 years	1 year	yes	neuro,lang,vis
6	yes	2 years	2 years	yes	lang,vis,res
7	yes	3 years	no	no	lang,res
8	yes	4 years	2 years	yes	cgm,neuro,md,lang
9	yes	4 years	3 months	yes	neuro,md,lang, vis,musc skel
10	yes	4 years	3 months	yes	cgm,md,lang,vis, musc skel
11*	yes	5 years	no	no	no
12	unknown	5 years	1 year yes 2 years no	no	res
13*	no	5 years	2 years	yes	neuro,md,lang,vis

\# 0 - 2 years of age: corrected for prematurity
* Unilateral SNHL
Abbreviations: cgm, congenital malformation; neuro, neuromotor function; md, mental development; vis, visual function; lang, language and speech development; musc skel, musculoskeletal system; res, respiratory tract.

The hearing outcome, based on hearing in the better ear and expressed as impairment, disability or handicap, and the type of hearing loss are shown in Table 4. In 6.2% the outcome was abnormal; 4.4 % had an impairment, 1.1 % a disability and 0.7% a handicap. The children with CDHL were mostly classified as impaired; there was no handicap in this group of children. On the other hand, almost half of the children with SNHL were handicapped in this area of examination.

Table 4. Hearing loss based on hearing in the better ear, expressed in impairment, disability and handicap and type of hearing loss

		No	No	(%)
Normal			835	(93.8)
Conductive/unspecified				
Impairment	conductive	29		
	unspecified	7		
	right conductive left unspecified	1		
			37	(4.2)
Disability	conductive	7		
Handicap	-	-		
			7	(0.8)
Sensorineural*				
Impairment	mixed	1		
	right conductive left unspecified	1#		
			2	(0.2)
Disability	sensorineural	1		
	mixed	1		
	unspecified	1#		
			3	(0.3)
Handicap	sensorineural	4		
	right mixed left unspecified	1#		
	right sensorineural left unspecified	1#		
			6	(0.7)
Total		55 (6.2)	890	(100.0)

* Two children with a unilateral sensorineural hearing loss are not represented in this classification
\# The amount of unspecified dB loss and the type of audiogram (high frequency hearing loss) indicate a sensorineural component

Table 5. Comparison of children with and without sensorineural hearing loss in relation to perinatal factors

	Sensorineural Hearing Loss Absent No	(%)	Present No	(%)	P - value	
Gestational age	875		13			
Mean gestational age (wks)	31.1 ± 2.5		29.9 ± 2.9		0.09	NS#
Birthweight	877		13			
Mean birthweight (g)	1325 ± 287		1255 ± 267		0.46	NS#
Highest bilirubin	849		13			
Mean highest bilirubin (micromol/l)	177.84 ± 43.84		189.38 ± 50.04		0.35	NS#
Male	442/877	(50)	7/13	(54)	1.00	NS*
Apgar score at 5 min < 7	89/822	(11)	3/13	(23)	0.16	NS*
PH within 30 minutes of birth < 7.10	54/637	(8)	2/9	(22)	0.18	NS*
Hypothermia temperature on first day of life < 35.5 °C	265/863	(31)	5/13	(38)	0.55	NS*
Apnoea during minimal 15 sec. or with bradycardia < 100/min	473/877	(54)	8/13	(61)	0.78	NS*
Bradycardia < 100/min without apnoea	268/877	(31)	6/13	(46)	0.24	NS*
IRDS clinical diagnosis based on extra O2 > 24 h, expiratory grunting, tachypnoea, sternal and intercostal retractions and nasal flaring and/or typical X-ray	337/877	(38)	7/13	(54)	0.27	NS*
IPPV and/or CPAP	419/875	(48)	11/13	(85)	0.01	-*
Intra cranial haemorrhage clinical diagnosis based on rapid or saltatory deterioration, fall in haematocrit and/or ultrasound or computed tomography	143/877	(16)	6/13	(46)	0.01	-*
Bilirubin > 200 micromol/l	223/849	(26)	5/13	(38)	0.35	NS*
Congenital infections haem strepto, hepatitis B, herpes, CMV, listeria, rubella, toxoplasmosis, lues	30/877	(3)	1/13	(8)	0.37	NS*
Sepsis haematological findings typical white blood cell count and/or positive blood culture	285/875	(33)	9/13	(69)	< 0.01	-*
Overall comparison of children with and without SNHL with respect to all endpoints simultaneously, corrected for interdependence [21,23]					0.002	

Student-t test; * Fischer exact test

Table 6. Adjusted odds ratios, 95% confidence intervals of impairments, disabilities and handicaps in 7 other areas of investigation, in children with CDHL and in children with SNHL

Congenital Malformation	CDHL no -	CDHL no +	CDHL yes -	CDHL yes +	OR CDHL/ Stratum	Overall OR CDHL
SNHL no	660	94	115	8	.49	.51 [.22,1.05] P = 0.07
SNHL yes	5	1	6	1	.85	
OR SNHL/stratum	1.40		2.37			
Overall OR SNHL	1.77 [.18,8.37] P = 0.71					

Neuromotor Function	CDHL no -	CDHL no +	CDHL yes -	CDHL yes +	OR CDHL/ Stratum	Overall OR CDHL
SNHL no	533	211	83	40	1.22	1.22 [.80, 1.85] P = 0.38
SNHL yes	3	3	3	4	1.30	
OR SNHL/stratum	2.52		2.74			
Overall OR SNHL	2.64 [.74, 9.70] P = 0.15					

Mental Development	CDHL no -	CDHL no +	CDHL yes -	CDHL yes +	OR CDHL/ Stratum	Overall OR CDHL
SNHL no	633	91	102	20	1.43	1.28 [.72, 2.20] P = 0.42
SNHL yes	2	4	5	2	.23	
OR SNHL/stratum	14.47		2.03			
Overall OR SNHL	5.29 [1.41, 19.13] P = 0.01					

Visuel function	CDHL no -	CDHL no +	CDHL yes -	CDHL yes +	OR CDHL/ Stratum	Overall OR CDHL
SNHL no	544	190	89	31	1.00	1.01 [.63, 1.57] P = 1.00
SNHL yes	2	2	3	4	1.30	
OR SNHL/stratum	2.86		3.78			
Overall OR SNHL	3.40 [.84, 14.49] P = 0.09					

Table 6. (Continued)

Language and Speech Development	CDHL no		CDHL yes		OR CDHL/ Stratum	Overall OR CDHL
	-	+	-	+		
SNHL no	479	233	56	60	2.30	2.23 [1.47, 3.38] P<0.001
SNHL yes	0	6	1	4	.00	
OR SNHL/stratum	inf		3.70			
Overall OR SNHL	15.70 [2.16, 693] P = 0.002					

Musculoskelatal System	CDHL no		CDHL yes		OR CDHL/ Stratum	Overall OR CDHL
	-	+	-	+		
SNHL no	655	94	111	12	.75	.68 [.33, 1.31] P = 0.30
SNHL yes	4	2	7	0	.00	
OR SNHL/stratum	3.48		.00			
Overall OR SNHL	1.52 [.16, 7.33] P = 0.84					

Respiratory Tract	CDHL no		CDHL yes		OR CDHL/ Stratum	Overall OR CDHL
	-	+	-	+		
SNHL no	566	188	82	41	1.50	1.50 [.98, 2.28] P = 0.06
SNHL yes	4	2	4	3	1.45	
OR SNHL/stratum	1.50		1.50			
Overall OR SNHL	1.50 [.38, 5.35] P = 0.67					

Table 5 shows 15 perinatal risk factors in relation to SNHL. Univariate analyses resulted in a significant relationship between SNHL and intermittent positive pressure ventilation (IPPV) and/or continuous positive airwaypressure (CPAP) ($P = 0.01$), intra cranial haemorrhage ($P = 0.01$) and sepsis ($P < 0.01$), respectively. Overall comparison of children with and without SNHL with respect to all endpoints simultaneously, corrected for interdependence[21,23] resulted in a P-value of 0.002. Note that all perinatal factors are less favourable in the SNHL subgroup; this test merely qualifies the probability that such a phenomenon would occur by chance, considering how these factors are clinically interrelated. The odds ratios per stratum and the overall odds ratios for children with CDHL and for children with SNHL, describing the risk of impairment, disability or handicap in 7 other areas of investigation (behaviour and growth excluded) are summarized in Table 6. In each area homogeneity of odds ratios was tested before calculating an overall odds ratio. None of them reached a significance level of 10%. CDHL was associated with a higher risk of impairments, disabilities and handicaps of language and speech development ($P < 0.001$) and respiratory tract (borderline significance $P = 0.06$). SNHL was associated with a higher risk of impairments, disabilities and handicaps in the areas mental development ($P = 0.01$) and language and speech development ($P = 0.002$).

DISCUSSION

In this nationwide long-term follow-up study we followed the outcome definitions of the International Classification of Impairments, Disabilities, and Handicaps of the World Health Organization. This was done to standardize outcome as much as possible.[11] Hearing loss was measured in dB. Regarding hearing loss and the outcome definitions we used two approaches: one is based on any hearing loss, and expressed in dB categories with respect to the worst ear. The other approach refers to hearing loss in the better ear and is expressed as impairment disability or handicap (following the WHO definitions). This implies that only the children with bilateral hearing loss can be classified as impaired, disabled or handicapped (one normal ear results per definition in a normal outcome). For the classification of handicap we used three dimensions, orientation, physical independence and social integration. Unlike Stephens et al.,[37] occupation and economic self-sufficiency were not taken into account, because they are not applicable for five year old children. Because pure-tone audiometry was performed at the children's home we chose a hearing threshold of 15 dB. Testing at lower levels seemed to be of pseudo-accuracy.

The prevalence of any hearing loss in this cohort of very preterm and/or very low birthweight infants was 15.3%. In 1977 the prevalence of childhood deafness (defined as an average hearing loss of 50 dB or worse in the better ear) in 8 year old children in the Netherlands as well as in 9 countries of the European Community as a whole, was 0.9/1000.[18] Adjusting our data to this study, using the same definition of hearing loss and the same pure tone frequencies, we found an almost ten times higher prevalence of 0.8/100 (7/890, all sensorineural) in our cohort of high risk infants.

Comparison of CDHL (13.8%) with the Dutch population at large is not possible, because the prevalence of this disorder in children aged 5 years is not well known. A more detailed description of the relation of CDHL,

otitis media and respiratory tract infections will be published separately.

In a minority (1.5%) of the assessed children the hearing loss was sensorineural. However, this SNHL prevalence in very preterm and/or very low birthweight infants is 15 times higher than the SNHL prevalence of 1.0/1000 in 5-7 year old Dutch children of the population at large.[41] ELBW infants did not show a higher prevalence of SNHL as compared to the total cohort.

Comparison with other geographically defined studies on very preterm and VLBW infants is difficult because of differences in study design. Table 7 summarizes those studies that may nevertheless be used for comparison.
The SNHL prevalence of 1.5% in infants born in the sixties [36] is similar to our results; medical intervention in the newborn period had been avoided in these children. In the study of infants born in the seventies[17] the SNHL frequency was 6.0%; all these surviving infants were treated in a general hospital with facilities for neonatal intensive care.

Table 7. Hearing loss in VLBW or ELBW infants in area based studies

Author year of publication	Intake criteria	Method	Study sample		Surviving	Lost	Follow-up		SNHL		CDHL/Unspec	
			No	Year	No	No	No	Years	No	(%)	No	(%)
Steiner[36] 1980	501-1500 g	screening audiometry pure-tone audiometry when indicated	293	1963-71	137	6	131	6-16	2	(1.5)	1	(0.8)
Lloyd[17] 1984	<1501 g	screening audiometry pure-tone audiometry when indicated	159	1975-79	68	1	67	3-7	4	(6.0)	-	(-)
Johnson[15] 1987	500-1499 g	pure-tone audiometry	143	1980-81	82	3	79	1.5-3	0	(0.0)	-	(-)
Saigal[29] 1990	501-1000 g	pure-tone audiometry air conduction	184	1980-82	90	6	73*	5-6	-	(-)	9	(12.3)
Present study 1993	< 1500 g and/or <32 wks	pure-tone audiometry air and bone conduction	1338	1983	966	39	890$	5	13	(1.5)	123	(13.8)

* n = 7 audiometry not possible, n = 4 audiometry not attempted
$ n = 37 audiometry not possible because of behavioural disturbances and/or mental retardation

In a study in the early eighties[15] no hearing loss was found in infants who were delivered at or referred to a tertiary care centre; however these children were rather young (1.5-3 years) for assessment by pure-tone audiometry. In the study of Saigal[29] on ELBW infants also born in the early eighties, the results of air conduction audiometry resemble our results assuming that these hearing losses had no sensorineural component. In our nationwide study all levels of care were represented;[48] thus a prevalence of 1.5% is a reliable measure for SNHL in the eighties in very preterm and/or VLBW infants in the Netherlands. The age at which SNHL was confirmed is rather disappointing (Table 3). Only 2 children were diagnosed very early (before 3 months of corrected age), but 7 of the remaining 11 children were diagnosed only after 2 years of corrected age, despite a routine screening test at approximately 9 months of age in most children. Possible explanations for this late detection could be difficulties in testing the children because of the high frequency of associated disorders, 2 of the 7 children had unilateral SNHL which is more difficult to detect, and in case of middle ear problems the SNHL component might be neglected, especially when the ENT-specialist is unaware of the premature birth. When we use the same definition of hearing loss and the same pure-tone frequencies as the study of Martin et al.,[19] our data seem to show a better detection frequency: at 2 years of corrected age the diagnosis had been confirmed in 6 of the 7 children versus 84 of the 216 (39%) in the Netherlands[42] (Table 8 and Fig. 1).

Table 8. Age of confirmation of the diagnosis sensorineural hearing loss

	1 year		2 years		3 years		4 years		5 years	
	No	(%)	No	(%)	No	(%)	No	(%)	No	(%)
Present study uni- and bilateral (n=13)	4/13	(31)	6/13	(46)	7/13	(54)	10/13	(77)	13/13	(100)
Present study data adjusted to the intake criteria of Martin et al.[18] (n=7)	4/7	(57)	6/7	(86)	6/7	(86)	7/7	(100)	7/7	(100)
Martin et al.[19] results from the Netherlands[42] 50 dB or worse in the better ear (n=216)	30/216	(14)	84/216	(39)	131/216	(61)	161/216	(75)	191/216	(88)

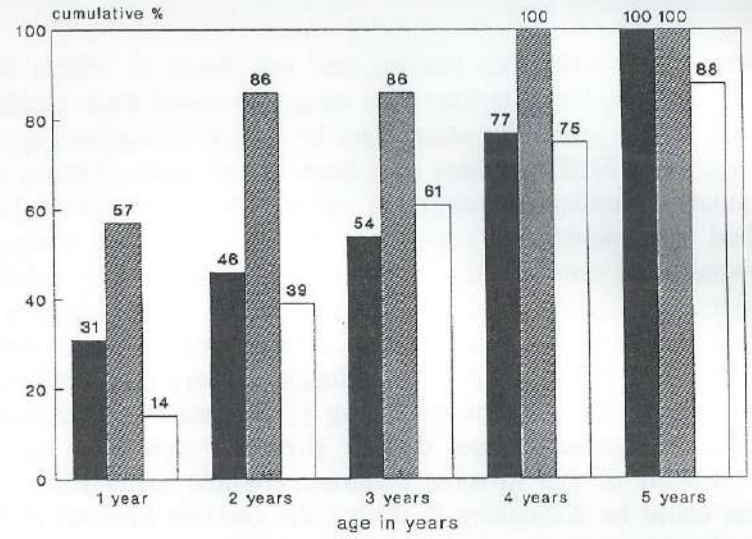

Fig 1. Age of detection of hearing loss in a Dutch year cohort of very preterm and/or very low birthweight infants. Comparison (after adjustment for the intake criteria) with the results from the Netherlands[42] of the study on Childhood Deafness in the European Community.[19]

Legend:
black bars = present study: crude results
lined bars = present study: results adjusted for intake criteria of the CEC study
dotted bars = CEC study : results restricted to the Netherlands

This difference can be caused by the fact that, contrary to the Dutch children in the study of Martin et al.,[19] all children in the present study group were seen by a paediatrician at 3, 6, 12 and 24 months of corrected age and all 7 children were screened by a Ewing-distraction test at the age of 9 months.

The outcome based on hearing in the better ear and expressed in impairment, disability and handicap was rather favourable specially concerning the communication disorders expressed in disability and handicap, respectively 1.1% and 0.7%. This implies that a majority of the children with auditory disorders are neither disabled nor handicapped in this respect at 5 years of age. However as the children grow older the disability and handicap frequencies may increase as a result of the more complicated skills required. As might be expected all children who were classified as hearing handicapped had SNHL.

To prevent bias, inquiries were made from ENT departments and other health services, on the hearing function of the 37 children in whom audiometry was not feasible. Together with the opinion of the assessing paediatricians an estimation of hearing outcome was made. This estimation resulted in 32 children with "normal" hearing. The remaining 5 children had mild communication disorders possibly due to hearing loss. This would mean

an increase of the hearing disability frequency from 1.1% to 1.6%; the estimation did not result in a change of the handicap frequency.

Children with SNHL have a higher risk of coexisting impairments, disabilities and handicaps in all areas of investigation, especially and not surprisingly in language and speech development. In children with CDHL, the risk of language and speech developmental disorders was significantly increased. This association is also mentioned by other authors.[6,8,30] There is also a higher risk of respiratory tract impairments, disabilities and handicaps in the presence of CDHL (although only borderline significant).

Univariate analysis reveals that IPPV and/or CPAP, intra cranial haemorrhage and sepsis may be risk factors for SNHL (Table 5). Due to the small number of children with SNHL it was not feasible to analyse our data in a multivariate (logistic) regression model, correcting for possible confounding factors. Therefore we applied group comparison in a multiple-endpoint situation.[21,23] Suppose there are n different outcome measures (15 perinatal factors), coded in such a way that a higher value indicates an unfavourable situation for all of them. The null hypothesis tested is that all differences in mean outcome (perinatal factors) between the groups to be compared (children with and without SNHL) are zero. A significant value of P (< 0.05) indicates such a consistent effect over all outcome measures (perinatal factors) in one specific direction (favouring one group over the other) that chance fluctuations are not a probable explanation for the effects observed. This analysis resulted in a significant P-value of 0.002.

This means that the null hypothesis must be rejected and the consistently worse outcomes in the SNHL group (compared to the non-SNHL group) can not be attributed to chance.

The Joint Committee on Infant Hearing[3] recommended that the diagnostic process of hearing loss should be completed by the age of 6 months in order to start rehabilitation as soon as possible. In the present study only 2 of the 13 children with SNHL were recognised within this time limit. The age of the diagnosis of SNHL in these high risk children seems disappointing. Sufficient trial data have not accumulated yet on neonatal at risk screening programs.[13] However we would recommend an immediate extensive hearing investigation with sensitive physiological tests[13,34] of very preterm and very low birthweight infants, whenever there is any suspicion of hearing loss or if the distraction test at 9 months of age is unsatisfactory. Difficulties in applying the test or unreliable results because of limited concentration span or associated disorders such as mental retardation and disorders of neuromotor function must not delay further investigation. A policy of "expectant surveillance" in these high risk children is not justified, particularly if they have accompanying developmental disorders.

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CHAPTER 5

SUMMARY AND CONCLUSIONS

The present thesis was designed to study the occurrence and risk factors of acute otitis media and otitis media with effusion, especially in young children.

Otitis media in its various forms is a common childhood disease, especially prevalent in children under 2 years of age; it appears that the prevalence of the disease follows a bimodal curve with the largest peak at around 2 years of age and a second peak some years later, varying in relation to timing of day-care, nursery schooling, and school entry.

Many factors which may place children at risk for having otitis media have been described. Partly, these risk factors are age-related.

In **Chapter 1**, risk factors for otitis media are described, especially for children under 2 years of age. Generally accepted risk factors, according to the more recent literature are: Down's syndrome, cleft palate, race, large adenoids, family history of otitis media, early onset of AOM (for AOM), recurrent AOM (for OME), tympanogram type B (for AOM), season, family size, bottle feeding, day care, upper respiratory tract infections, socio-economic status and passive smoking. In studies investigating very young children, it seems that seasonal variability is less obvious in this age group.

The design of three different studies, used for this thesis, is outlined: a validity study for the diagnosis of otitis media with effusion by tympanometry in different age groups; a study in a population of children aged between 0-2 years visiting three health care centers, to investigate the occurrence and risk factors of otitis media; and a third study in which the influence of prematurity and low birthweight on otitis media and hearing was evaluated in a population of children, liveborn before 32 completed weeks of gestation and/or with a birthweight of less than 1500 g.

In **Chapter 2** the validity of tympanometry, used in two different age groups: 5 months to 2 years and 2-12 years was tested. A group of 266 children (515 ears) admitted into two hospitals was studied. These children were candidates for the insertion of ventilation tubes, or adenoidectomy and/or tonsillectomy with myringotomy. Before surgery, tympanometry was performed. The surgical and tympanometric findings were compared afterwards.

Two different tympanometers were used (GSI-27A and TYMP-85TT). This study showed a comparable validity of these two tympanometers. The sensitivity and specificity of tympanometry in the age group of five months to two years did not show a significant difference from that in the age group of two to twelve years. We found a small difference in validity of tympanometry between the two hospitals that participated in the study, probably due to the fact that the selection criteria for the study population in the two hospitals were not exactly the same. Otoscopy had a limited value for the diagnosis of middle ear effusion in this age group.

Chapter 3 describes the results of an observational cohort study on the occurrence and risk factors of otitis media in a healthy population of infants: two hundred eighty-nine children born between July 1987 and October 1988, were studied up to the age of 24 months. The enrolment of the children took place during their regular check-up visits at three different health care centers. Epidemiological data were collected by questionnaires and evaluated together with data from the medical records, tympanometry and the results of a hearing distraction test (Ewing test) at approximately 9 months of age.

In Chapter 3a possible risk factors associated with the occurrence of otitis media with effusion (OME) were determined. At approximately 9 months of age, 50% of the children already had experienced a period with OME; in nearly all (91.8%) children OME was diagnosed at least once during the observation period. Having older siblings was the most important risk factor, for both the time elapsed until the first occurrence and for the probability of otitis media with effusion at each visit. Other significant risk factors for the probability at each visit were: having had acute otitis media prior to the visit or prior to the previous visit, age, a positive family history of otitis media, and upper respiratory tract infections. The risk of occurrence of OME was significantly influenced by the month of the year the visit took place, but we did not find a clear summer-winter pattern. The probability of acute otitis media increased with deterioration of the tympanogram.

In Chapter 3b the risk of acute otitis media (AOM) was estimated as a function of a number of covariates, with special emphasis on changes to this risk after discontinuing breast-feeding. Nearly half (44%) of the children had acute otitis media at least once during the follow-up period, with the highest risk at approximately 20 months of age. In children who were breast-fed the risk of AOM was significantly decreased until 4 months after quitting breast-feeding, then suddenly the "protective" effect of breast-feeding weared out and with increasing months the child approached the level estimated in the group of children that never received breast-feeding. About 12 months after quitting the risk was virtually the same as if the child had never received breast-feeding at all. The risk of AOM was also significantly associated with the number of siblings and with socio-economic status.

In Chapter 3c an inventory was made of medical consumption related to otitis media and upper respiratory tract infections, and of differences in medical treatment in the three areas investigated. The impact of hearing screening on medical consumption was observed. Nearly half of all visits to the general practitioners were made because of middle ear problems and/or upper respiratory tract infections. The occurrence of otitis media and upper respiratory tract infections was quite equally distributed among the three areas but considerable variations in treatment were found, despite the existence of uniform treatment policies. The hearing distraction test was failed by 8% of the children investigated; in this group medical consumption was increased.

In **Chapter 4** the prevalence of upper respiratory tract infections, otitis media and hearing loss in a population of preterm and small for gestational age infants was described. The Project On Preterm and Small for gestational age infants (POPS) collected data on 1338 infants born alive in the Netherlands between January 1 and December 31, 1983 with a gestational age of less than 32 completed weeks and/or a birthweight <1500 g. A total of 966 children were alive at five years of age, of whom 927 (96%) were assessed during a home visit 2 to 6 weeks after their fifth birthday by three specially trained paediatricians. Otitis media and respiratory tract infections were evaluated by means of history. Hearing was evaluated in 890 children by pure-tone audiometry for each ear separately.

In Chapter 4a an inventory of ENT-morbidity was made and compared to ENT-morbidity in full term children of the same age-group.
Very preterm birth or very low birth weight did not seem to be a risk factor in developing middle ear disease in childhood; however, medical consumption for ENT-problems seemed to be higher than in the general population of Dutch pre-school children.

In Chapter 4b the hearing disorders found in these children are described. Hearing loss was conductive/unspecified in 123 (13.8%) and sensorineural in 13 (1.5%) children. The prevalence of sensorineural hearing loss was 15 times as high as in 5-7 year old children in the Dutch population at large. Children with conductive hearing loss had a higher risk of impairments, disabilities and handicaps of language and speech development, following the definitions of the International Classification of Impairments, Disabilities, and Handicaps of the World Health Organization. The same holds for children with sensorineural hearing loss; moreover they had a significantly higher risk of impairments, disabilities and handicaps of mental development. Overall comparison of children with and without sensorineural hearing loss proved that the children with sensorineural hearing loss had a significantly less favourable outcome, adjusted for 15 perinatal factors simultaneously. The age at which sensorineural hearing loss in very preterm and/or very low birthweight infants is detected has to be lowered, in order to start rehabilitation as early as possible in case of severe hearing loss.

CONCLUSIONS

Studying environmental risk factors for otitis media is necessary to increase the knowledge of the nature of this disease. The exposition to these factors is not the same for preschool children; when risk factors are analysed, this should be done for preschool and school children separately. There is less seasonal variability in preschool children; family size has more influence in this age group. In school children, analysing the effect of bottle feeding and day care attendance is irrelevant.
It is also necessary to make distinctions between the forms of otitis media: (recurrent) acute otitis media and (persistent) otitis media with effusion. Low socio-economic status seems to be associated with augmented prevalence of purulent, but not of secretory otitis media. Being breast-fed did not have the same protective effect for the risk of occurrence of OME, as it had for AOM in our study. The occurrences of upper respiratory tract infections, acute otitis media and otitis media with effusion are very much correlated. No statistical analysis in itself can possibly distinguish what the primary causal factor is; this can only be postulated on clinical grounds. Very preterm birth or very low birth weight does not seem to be a risk factor for otitis media.
The risk factors found do not lead to a clear definition of high-risk groups; therefore it is impossible to reduce the incidence of otitis media substantially by means of primary prevention. However - especially when there is a family history of otitis media - smoking by parents or other householdmembers should be discouraged and breastfeeding of the child should be encouraged.
It was not possible to describe the natural history of otitis media with effusion in this study population. This requires a different study design in which measurements are taken at fixed, prescribed points in time. Because otoscopy has limited value in this age group, and tympanometry is often not interpretable due to a lack of cooperation, studying the natural history of otitis media with effusion will remain difficult. During follow-up, bias may occur due to treatment of the more severe cases, but this can be incorporated in an adequate statistical design.

SAMENVATTING

De studies in dit proefschrift werden opgezet om het optreden en de risico-factoren van acute otitis media en otitis media met effusie bij jonge kinderen te bestuderen.
Otitis media komt zeer veel voor bij kinderen, met name bij kinderen onder de leeftijd van 2 jaar; gebleken is dat de prevalentie van deze aandoening verloopt volgens een bimodale curve met de hoogste piek op ongeveer 2-jarige leeftijd en een tweede piek enkele jaren later, afhankelijk van eventueel creche-bezoek, en het moment van naar school gaan.
Er zijn veel predisponerende factoren beschreven voor het optreden van otitis media bij kinderen. Deze factoren zijn voor een deel gerelateerd aan de leeftijd van het kind.

In **Hoofdstuk 1** worden de risico-factoren voor otitis media beschreven, in het bijzonder voor kinderen onder de leeftijd van 2 jaar. Algemeen geaccepteerde risico-factoren in de meest recente literatuur zijn: het syndroom van Down, palatoschizis, ras, hypertrofisch adenoid, familie-anamnese belast met otitis media, op zeer jonge leeftijd al AOM (voor AOM), recidiverende AOM (voor OME), tympanogram type B (voor AOM), seizoen, gezinsgrootte, flesvoeding, creche, bovenste luchtweginfecties, socio-economische status en passief roken. In studies waar zeer jonge kinderen werden onderzocht, lijkt otitis media minder seizoensafhankelijk te zijn.

Voor dit proefschrift werden 3 verschillende studies uitgevoerd: een studie over de validiteit van tympanometrie als diagnosticum van otitis media met effusie in verschillende leeftijdsgroepen; een studie over het optreden en de risico-factoren van otitis media in een groep kinderen die drie verschillende consultatie-bureau's bezochten; en een derde studie waarin werd onderzocht wat de invloed is van prematuriteit en laag geboorte-gewicht op het voorkomen van otitis media en op het gehoor. Dit onderzoek werd uitgevoerd in een populatie van kinderen die levend werden geboren voor de 32e zwangerschapsweek of met een geboortegewicht van minder dan 1500 gram.

In **Hoofdstuk 2** werd de validiteit onderzocht van tympanometrisch onderzoek in twee leeftijdsgroepen: 5 maanden tot 2 jaar en 2-12 jaar. Onderzocht werd een groep van 266 kinderen (515 oren) die in twee verschillende ziekenhuizen waren opgenomen voor het plaatsen van trommelvliesbuisjes, of adenotomie en/of tonsillectomie met paracentese. Vlak voor de ingreep werd tympanometrisch onderzoek verricht. De bevindingen bij operatie werden vergeleken met de resultaten van het tympanometrisch onderzoek.

Er werden twee verschillende tympanometers gebruikt (GSI-27A en TYMP-85TT). De betrouwbaarheid van de twee tympanometers was gelijkwaardig; de sensitiviteit en specificiteit van het tympanometrisch onderzoek in de leeftijdsgroep van 5 maanden tot 2 jaar verschilde niet significant van ditzelfde onderzoek in de leeftijdsgroep van 2-12 jaar. Er werd wel een klein verschil gevonden in de validiteit van tympanometrie tussen de twee ziekenhuizen die aan het onderzoek deelnamen, vermoedelijk doordat de selectie-criteria voor de studie-populaties in beide ziekenhuizen niet helemaal gelijk waren. Otoscopie had slechts een beperkte waarde bij de diagnostiek van middenoor-effusie in deze leeftijdsgroep.

In **Hoofdstuk 3** worden de resultaten beschreven van een cohort studie naar het voorkomen en de risico-factoren van otitis media in een gezonde groep zeer jonge kinderen: 289 kinderen geboren tussen juli 1987 en oktober 1988 werden gedurende 24 maanden, vanaf de geboorte vervolgd. Deze kinderen bezochten drie verschillende consultatie-bureau's. Epidemiologische gegevens werden verzameld door middel van vragenlijsten, deze werden tezamen met relevante gegevens uit de status van het consultatie-bureau, de tympanogrammen en de resultaten van het gehooronderzoek rond de leeftijd van 9 maanden (Ewing test) bewerkt.

In Hoofdstuk 3a werd onderzocht wat risico-factoren voor het optreden van otitis media met effusie (OME) zijn. Rond de leeftijd van 9 maanden had 50% van de kinderen al eens een periode met OME doorgemaakt; bij bijna alle kinderen (91.8%) werd minstens eenmaal OME gediagnostiseerd tijdens de observatie-periode. Het hebben van oudere broers of zussen was de belangrijkste risico-factor, zowel voor het eerste moment van optreden als voor de kans op OME bij ieder bezoek. Andere significante risico-factoren voor de kans op OME per bezoek waren: het doormaken van acute otitis media in de periode voorafgaand aan het bezoek aan het consultatie-bureau, of voorafgaand aan het vorige bezoek, leeftijd, otitis media in de familie anamnese, en bovenste luchteginfecties. De kans op het optreden van OME werd significant beinvloed door de maand waarin het bezoek plaats vond, maar een duidelijke schommeling in zomer en winter vonden we niet. De kans op acute otitis media nam toe bij verslechtering van het tympanogram.

In Hoofdstuk 3b wordt de kans op acute otitis media (AOM) geschat aan de hand van een aantal mogelijke risicofactoren, met speciale aandacht voor de verandering van deze kans na het staken van borstvoeding. Bijna de helft van het aantal kinderen (44%) maakte minstens eenmaal acute otitis media door tijdens de observatie-periode; het risico was het hoogst rond de 20e levensmaand. Bij kinderen die borstvoeding kregen was de kans op AOM significant verlaagd tot 4 maanden na het staken van de borstvoeding, daarna verminderde het beschermende effect van de borstvoeding vrij snel, en 12

maanden na staken was de kans op AOM weer gelijk aan de kans bij kinderen die nooit borstvoeding hadden gekregen. Andere significante risico-factoren voor het optreden van AOM waren het aantal oudere broers of zussen en de socio-economische status.

In Hoofdstuk 3c wordt een inventarisatie gemaakt van de medische consumptie in verband met otitis media en bovenste luchtweginfecties, en van eventuele verschillen in behandeling in de drie onderzochte regio's. De invloed van het gehooronderzoek op de medische consumptie werd eveneens bestudeerd. Bijna de helft van het aantal bezoeken dat aan de huisarts werd gebracht was vanwege otitis media of bovenste luchtweginfecties. Otitis media en bovenste luchtweginfecties kwamen in de drie onderzochte regio's vrijwel evenveel voor, maar de behandeling verschilde nogal per regio, ondanks het bestaan van algemene richtlijnen. Het gehooronderzoek bleek bij 8% van de kinderen uiteindelijk onvoldoende; in deze groep was de medische consumptie verhoogd.

In **Hoofdstuk 4** wordt de prevalentie van bovenste luchtweginfecties, otitis media en gehoorverlies beschreven in een populatie kinderen die prematuur of met een laag geboortegewicht waren geboren. Het "Project Onderzoek Praematuritas en Small-for-gestational age" (POPS) verzamelde gegevens van 1338 kinderen die in 1983 in Nederland geboren werden na een zwangerschapsduur van minder dan 32 voltooide weken en/of met een geboortegewicht van minder dan 1500 gram. Van de in leven zijnde kinderen kon 96% (927 kinderen) worden onderzocht tijdens een huisbezoek 2 tot 6 weken na hun 5e verjaardag, door drie speciaal getrainde kinderartsen. Gegevens over otitis media en luchtweginfecties werden verkregen uit de anamnese. Het gehoor werd bij 890 kinderen onderzocht door middel van toondrempel-audiometrie, voor ieder oor apart.

In Hoofdstuk 4a wordt een inventarisatie gemaakt van KNO-aandoeningen, deze wordt vergeleken met een normale populatie kinderen met dezelfde leeftijd. Prematuriteit en een zeer laag geboortegewicht lijken geen risico-factoren te zijn voor de ontwikkeling van middenoor-problemen in de jeugd; de medische consumptie voor KNO-aandoeningen blijkt echter wel hoger te zijn dan in het algemeen bij Nederlandse kinderen van deze leeftijdsgroep.

In Hoofstuk 4b worden de gehoorverliezen die bij deze kinderen werden gevonden beschreven. Een geleidings- of ongespecificeerd gehoorverlies werd bij 123 kinderen (13.8%) gevonden; 13 kinderen (1.5%) hadden een perceptief gehoorverlies. De frequentie van perceptief gehoorverlies in de studiegroep is vijftien maal zo hoog als in de normale populatie. Kinderen met geleidingsgehoorverlies hadden een grotere kans op impairments, disabilities en handicaps in de taal- en spraakontwikkeling, volgens de definities van de Internationale Classificatie van Impairments,

Disabilitie en Handicaps van de Wereld Gezondheids Organisatie (WHO). Hetzelfde gold voor kinderen met perceptief gehoorverlies; bij deze kinderen was ook vaak sprake van mentale retardatie. Bij een vergelijking van kinderen met en zonder perceptief gehoorverlies, gelijktijdig gebaseerd op vijftien perinatale factoren, bleek dat kinderen met een perceptief verlies een significant minder gunstige uitkomst hadden op de leeftijd van vijf jaar, dan kinderen zonder een perceptief gehoorverlies. De leeftijd waarop perceptief gehoorverlies bij premature kinderen en kinderen met een zeer laag geboortegewicht wordt gediagnostiseerd dient verder omlaag te worden gebracht, zodat bij ernstig gehoorverlies zo vroeg mogelijk kan worden begonnen met begeleiding.

CONCLUSIES

Het is noodzakelijk om predisponerende omgevingsfactoren voor otitis media te bestuderen om de kennis over de aard van deze aandoening te vergroten. De blootstelling aan deze factoren is voor kinderen die nog niet naar school gaan niet hetzelfde als voor oudere kinderen; als risicofactoren worden geanalyseerd, dient dit voor beide groepen kinderen afzonderlijk te gebeuren. Bij de kinderen die nog niet naar school gaan is er minder seizoensvariatie, en de gezinsgrootte heeft bij deze kinderen meer invloed op het optreden van otitis media. Bij schoolkinderen is het niet relevant om het effect van flesvoeding en van creche-bezoek te bestuderen.
Het is ook noodzakelijk om onderscheid te maken tussen de verschillende vormen van otitis media: (recidiverende) acute otitis media en (persisterende) otitis media met effusie. Een lage socio-economische klasse lijkt samen te hangen met een verhoogde prevalentie van purulente, en niet van secretoire otitis media. Het beschermende effect van borstvoeding op het optreden van acute otitis media in onze studie vonden wij niet voor otitis media met effusie. Het optreden van bovenste luchtweginfecties, acute otitis media en otitis media met effusie hangt zeer nauw samen, maar het is niet mogelijk om met behulp van een statistische analyse te onderscheiden wat de primair oorzakelijke factor is; dit kan alleen op klinische gronden worden vermoed. Prematuriteit en laag geboortegewicht lijken geen predisponerende factoren voor het optreden van otitis media te zijn.
Het is niet mogelijk om op grond van deze resultaten een vastomlijnde definitie te maken van een groep kinderen met verhoogd risico voor otitis media; het is derhalve ook onmogelijk om de incidentie van otitis media door middel van preventie aanzienlijk te verlagen. Het is echter verstandig - vooral als otitis media veel in de familie voorkomt - om roken door ouders of andere huisgenoten af te raden en het geven van borstvoeding te stimuleren.
Het natuurlijk beloop van otitis media kon in deze studie-populatie niet worden beschreven. Hiervoor is een andere studie-opzet vereist, waarbij de metingen op vaste, van tevoren vastgestelde tijdstippen worden verricht. Omdat otoscopie slechts beperkte waarde heeft in deze leeftijdsgroep, en het tympanogram vaak niet goed is te beoordelen door onvoldoende cooperatie, zal het bestuderen van het natuurlijk beloop in deze leeftijdsgroep lastig blijven. Tijdens de observatie-periode kan bovendien bias ontstaan doordat de ernstiger gevallen worden behandeld, echter hiermee kan rekening worden gehouden bij de statistische analyse.

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CURRICULUM VITAE

The author of this thesis was born on the 17th of January 1957, in Dordrecht. After completing her secondary education (Gymnasium B) at the Johan de Witt Gymnasium in Dordrecht, she started her medical studies in 1976 at the School of Medicine of the University of Leiden, after a year's delay due to oversubscription of Dutch medical faculties; in this year she studied biology. She obtained medical qualification in January 1984; from January till November she received training in internal medicine under the supervision of Dr. A. Haak at the Bronovo Hospital in The Hague. In November 1984 she became resident in Otolaryngology at the Leiden University Hospital (head: Prof.dr. P.H. Schmidt). Since November 1988 she has been practising as an otolaryngologist in the Rijnland Hospital in Alphen aan den Rijn.

STELLINGEN

1. De kans op het optreden van acute otitis media bij het zeer jonge kind hangt af van het aantal maanden dat het kind borstvoeding heeft gehad en van het aantal maanden dat deze borstvoeding is gestopt.

2. Het is het overwegen waard om, naast de oppasmoeder, ook de min weer in ere te herstellen.

3. Vermoedelijk zijn schoolvakanties voor een belangrijk deel verantwoordelijk voor de seizoensvariatie in het optreden van otitis media.

4. Alhoewel KNO-aandoeningen niet veelvuldiger voorkomen bij prematuur geboren kinderen, ondergaan zij wel meer KNO-ingrepen, vermoedelijk mede doordat zij reeds in het medisch "circuit" zitten.

5. Ewing onderzoek leidt niet tot het massaal plaatsen van buisjes.

6. OME is nearly a "physiological" event from which virtually every child will suffer at some time in early life. (Zielhuis GA et al., Clinical Otolaryngology, 1990)

7. Bij chirurgie van het ethmoid dient de CT-scan in de eerste plaats ter beoordeling van de anatomie en in veel mindere mate van de pathologie.

8. Bij ethmoidchirurgie verdient lokaal anaesthesie de voorkeur.

9. Bij globusklachten kan men overwegen om ambulante intraluminale 24 uurs pH-metrie van de slokdarm te verrichten.

10. Stakend streekvervoer en gefuseerde ziekenhuizen maken de gezondheidszorg vrijwel onbereikbaar.

11. All scientific thinking is in terms of probability. The old eternal verities are merely a high degree of likeliness; the immutable laws of nature are just statistical averages. (Aldous Huxley in "Island")

12. De piepers moeten op tijd op tafel, en in het rek.

Stellingen behorende bij het proefschrift "*Risk factors for otitis media in infancy*"

M.L. Sassen

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