Treatment of acute otorrhea in children with tympanostomy tubes

Thijs M.A. van Dongen

Treatment of acute otorrhea in children with tympanostomy tubes
PhD Thesis with a summary in Dutch.
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.

Printing of this thesis was financially supported by: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht; Stichting Kleine kwalen in de Huisartsgeneeskunde; Daleco Pharma B.V. and EmiD audiologische apparatuur.

ISBN: 978-90-8891-864-3

Author: Thijs M.A. van Dongen
Cover design: Jonas Louisse
Layout: Thijs M.A. van Dongen
Printed/published by: Proefschriftmaken.nl || Uitgeverij BOXPress, 's-Hertogenbosch

Treatment of acute otorrhea in children with tympanostomy tubes

Behandeling van een acuut loopoor
bij kinderen met trommelvliesbuisjes
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
vrijdag 23 mei 2014 des middags te 4.15 uur

door

Thijs Marinus Adriaan van Dongen
geboren op 7 mei 1985
te Tilburg

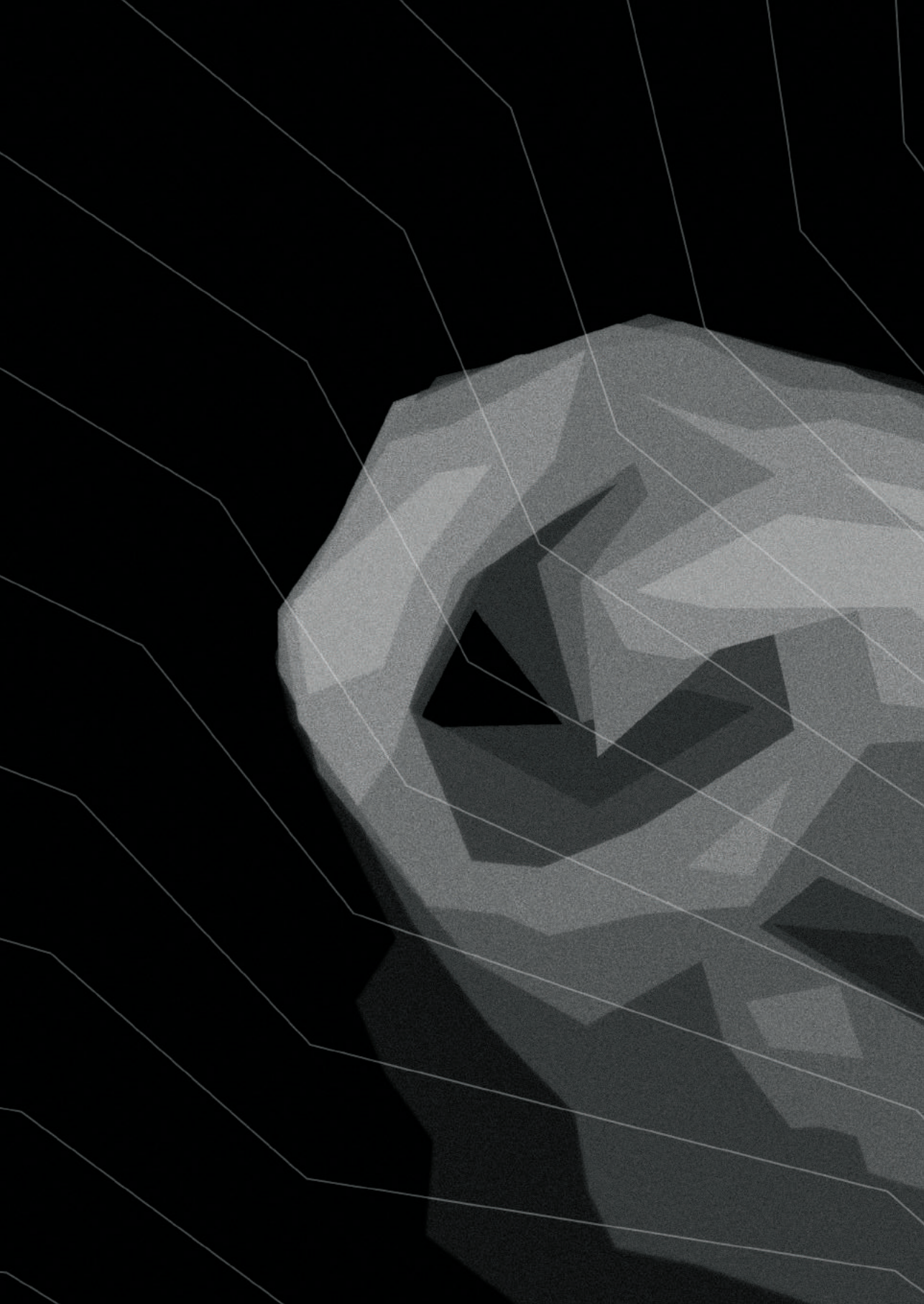
Promotores:	Prof.dr. A.G.M. Schilder Prof.dr. G.J.M.G. van der Heijden
Co-promotor:	Dr. R.P. Venekamp

The studies presented in this thesis were financially supported by the Netherlands Organisation for Health Research and Development (ZonMw, grant no. 170992502).

The microbiologic study presented in this thesis was financially supported by a grant from GlaxoSmithKline Biologicals.

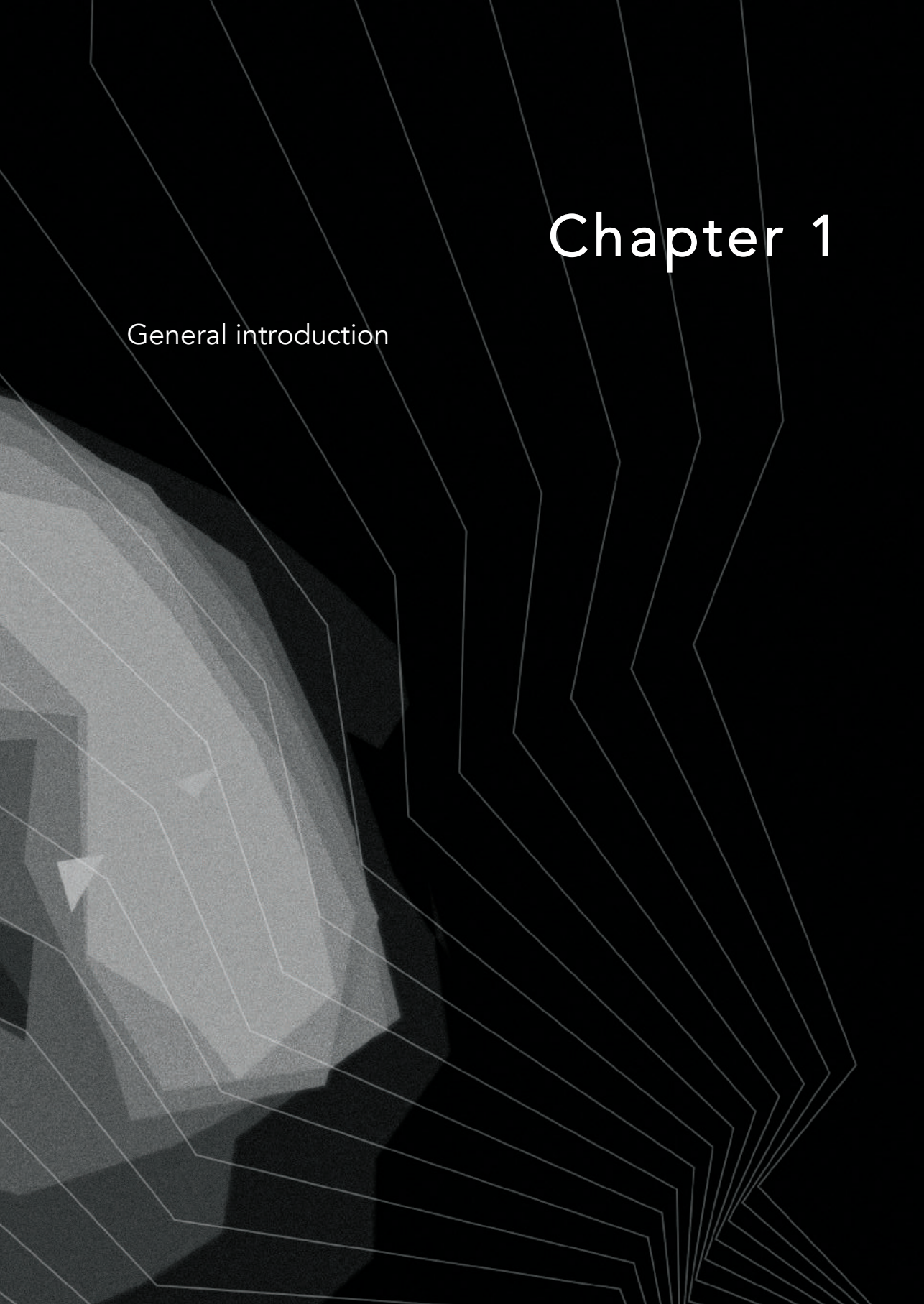
Voor mijn ouders

Contents



Chapter 1

General introduction



Mrs. Van Kempen, mother of 5-year old Lucas who had tympanostomy tubes placed some months ago for his recurrent middle ear infections, has contacted her family physician by phone. For three days Lucas' left ear has been discharging and he seems to be having difficulty hearing. He is a bit irritable but otherwise fine.
The family physician is unsure how best to manage this problem. Usually he would suggest to wait for a week and see if the discharge resolves. On the other hand he feels that oral antibiotics may shorten the condition, while at a recent Continuing Medical Education course an ENT surgeon suggested that antibiotic(-glucocorticoid) eardrops work best in these children.

Acute tympanostomy-tube otorrhea

Definition & incidence

Tympanostomy-tube placement is one of the most common surgical procedures performed in children worldwide with around 50,000 children in the Netherlands and almost 700,000 in the United States receiving tubes each year.[1,2] Otorrhea, or ear discharge, is a frequent problem in children with tubes.[3,4] Tympanostomy-tube otorrhea (TTO) is generally a symptom of a middle ear infection in which discharge from the infection drains through the tube into the ear canal. Definitions of acute TTO (ATTO) vary from a maximum duration of 2 to 8 weeks; from then on it is defined as chronic TTO.[5,6]
Indications for tympanostomy-tube placement in children include persistent bilateral otitis media with effusion or recurrent acute otitis media. Parents of children receiving tubes often have high expectations that this surgical procedure will bring the solution to their child's middle ear problems and may therefore be disappointed when their child develops ATTO.[7] It is therefore important that parents are informed of the probability that their child will develop ATTO when tube placement is discussed. To tailor information to individual children, accurate estimations of ATTO incidence and its predictors are needed. To date, this knowledge is lacking and therefore clinicians cannot provide parents with clear, evidence-based and up-to-date information.

Treatment

ATTO is mostly unpleasant as it can smell bad; the underlying middle ear infection can cause general illness, irritability, pain and fever in the child. A previous study showed that tube otorrhea has a negative impact on children's quality of life when it persists for 3 days or more.[8] Although most TTO episodes are acute and transient, some children develop chronic otorrhea, which may cause considerable morbidity and hearing loss.[9,10] As such, it is important to optimize ATTO treatment.
Similar to acute otitis media, bacterial (super)infection of the middle ear is thought to cause ATTO.[11] Many physicians therefore prescribe antibiotics to children with ATTO. Antibiotics can be administered systemically, in children mostly as syrup, or topically as eardrops. Current evidence for the use of antibiotics in the treatment of ATTO is limited.[12] The few trials assessing the effectiveness of topical and oral antibiotics in this condition included either small numbers of children or suffered from methodological limitations, but suggest that antibiotic(-glucocorticoid) eardrops are as effective as or more effective than oral antibiotics.[12-15] Since ATTO, like acute otitis media, may be self-limiting, initial observation may be an alternative strategy and is often practiced, in particular in primary care.[12,16,17]

Interestingly, no trial so far has compared the effectiveness of oral or topical antibiotics with initial observation, and no studies have yet compared their costs.

Microbiology

Knowledge on the prevalence of microorganisms in the middle ear during middle ear infections as well as their antimicrobial susceptibility is important for selecting the most appropriate antibiotic treatment.

Since obtaining a sample of middle ear fluid during a middle ear infection involves tympanocentesis (or myringotomy) when the tympanic membrane is still intact, many studies on the microbiology of otitis media sample the nasopharynx as a proxy for middle ear fluid to assess the likely presence of microorganisms in the middle ear.[18-21] As such, practical and medical ethical issues are avoided, but it is unclear whether this proxy provides an accurate estimate of the prevalences of the various microorganisms involved in otitis media.

In case of ATTO, middle ear fluid can be easily obtained by sampling the ear discharge from the external ear canal. Nevertheless, recent data on the microorganisms involved in ATTO is lacking. The widespread use of pneumococcal vaccination (PCV) has changed the bacterial prevalence in the upper respiratory tract of children, but its impact on bacterial and viral pathogens causing ATTO is yet unknown.[22-27]

Aims of this thesis

The main aim of this thesis is to study the clinical and cost-effectiveness of three commonly used treatment strategies in children with recent-onset ATTO: antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation.

The following questions will be answered:

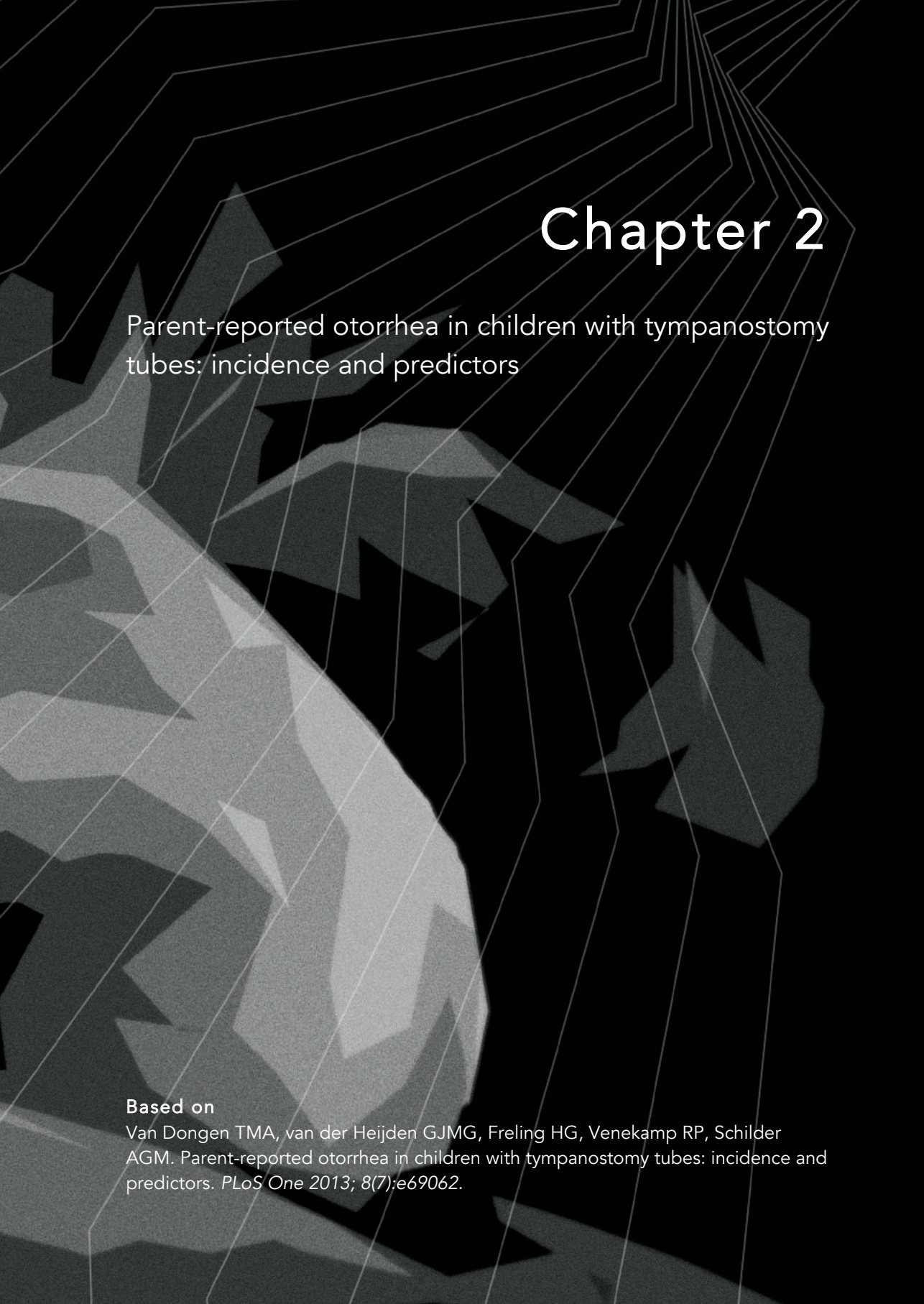
- What is the current incidence of parent-reported otorrhea in children with tympanostomy tubes and what are independent predictors for its occurrence?
- What is the clinical effectiveness of antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation in children with ATTO in terms of otoscopic signs of otorrhea at 2 weeks, duration of the first otorrhea episode, treatment-related adverse events, quality of life and total number of days with otorrhea and otorrhea recurrences during six months follow-up?
- What is the cost-effectiveness of antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation in children with ATTO, in both the short- (2 weeks) and long-term (6 months)?
- What is the interobserver agreement between parents and physicians on the presence of otorrhea after treatment?
- What are the prevalences of bacteria and viruses in samples taken from the otorrhea and nasopharynx of children with ATTO before and after treatment and what is the antimicrobial susceptibility of the bacteria?
- What is the concordance between the presence of bacteria and viruses in middle ear fluid and nasopharynx in children with otitis media?

Outline of this thesis

In **chapter 2** we establish the current incidence of parent-reported TTO in a large cohort of children with tympanostomy tubes and identify predictors for its occurrence.
Chapter 3 focuses on treatment of children with ATTO. In **chapter 3.1** we present the clinical results of our randomized controlled trial on the effectiveness of antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation in children with ATTO. In **chapter 3.2** we present the cost-effectiveness of these treatment strategies in children with ATTO. In **chapter 3.3** we study the interobserver agreement between parents and physicians in the assessment of ear discharge in children during follow-up after treatment.
Chapter 4 focuses on the microbiology of children with otitis media and ATTO. In **chapter 4.1** we present the prevalences of bacteria and viruses in the otorrhea and nasopharynx of children with ATTO, both before and after treatment, as well as their antimicrobial susceptibility. In **chapter 4.2** we report the results of a systematic review evaluating the concordance between microorganisms detected in the nasopharynx and middle ear of children with otitis media.
In **chapter 5** we discuss the clinical implications of our main findings, including recommendations for clinical practice and future research.

References

1. Dutch Hospital Data (Landelijke medische registratie). 2010.
2. Cullen K, Hall M, Golosinskiy A. Ambulatory Surgery in the United States, 2006. National health statistics reports; no 11. Revised. In. Hyattsville, MD: National Center for Health Statistics; 2009.
3. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. Otolaryngol Head Neck Surg 2001;124:374-80.
4. Ah-Tye C, Paradise JL, Colborn DK. Otorrhea in young children after tympanostomy-tube placement for persistent middle-ear effusion: prevalence, incidence, and duration. Pediatrics 2001;107:1251-8.
5. Smith AW, Hatcher J, Mackenzie IJ, et al. Randomised controlled trial of treatment of chronic suppurative otitis media in Kenyan schoolchildren. Lancet 1996;348:1128-33.
6. Myer CM, 3rd. Post-tympanostomy tube otorrhea. Ear Nose Throat J 2001;80:4-7.
7. Rosenfeld RM, Isaacson G. Tympanostomy tube care and consequences. In: Rosenfeld RM, Bluestone CD, eds. Evidence-Based Otitis Media. 2 ed. Hamilton, Ontario, Canada: BC Decker Inc.; 2003:466.
8. Rosenfeld RM, Bhaya MH, Bower CM, et al. Impact of tympanostomy tubes on child quality of life. Arch Otolaryngol Head Neck Surg 2000;126:585-92.
9. van der Veen EL, Schilder AG, van Heerbeek N, et al. Predictors of chronic suppurative otitis media in children. Arch Otolaryngol Head Neck Surg 2006;132:1115-8.
10. Acuin J. Chronic suppurative otitis media: burden of illness and management options. Geneva, Switzerland: World Health Organization; 2004.
11. Peters BM, Jabra-Rizk MA, O'May GA, et al. Polymicrobial interactions: impact on pathogenesis and human disease. Clin Microbiol Rev 2012;25:193-213.
12. Vaile L, Williamson T, Waddell A, et al. Interventions for ear discharge associated with grommets (ventilation tubes). Cochrane Database Syst Rev 2006:CD001933.
13. Goldblatt EL, Dohar J, Nozza RJ, et al. Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes. Int J Pediatr Otorhinolaryngol 1998;46:91-101.
14. Dohar J, Giles W, Roland P, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2006;118:e561-9.
15. Heslop A, Lildholdt T, Gammelgaard N, et al. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhea in children: the results of a randomized clinical trial. Laryngoscope 2010;120:2516-20.
16. Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet 2006;368:1429-35.
17. Isaacson G. Why don't those ear drops work for my patients? Pediatrics 2006;118:1252-3.
18. Cohen R, Levy C, Bingen E, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. Pediatr Infect Dis J 2012;31:297-301.
19. Hilty M, Qi W, Brugger SD, et al. Nasopharyngeal microbiota in infants with acute otitis media. J Infect Dis 2012;205:1048-55.
20. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. N Engl J Med 2011;364:105-15.
21. Tahtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011;364:116-26.
22. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. JAMA 2010;304:2161-9.
23. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J 2010;29:304-9.
24. van Gils EJ, Hak E, Veenhoven RH, et al. Effect of seven-valent pneumococcal conjugate vaccine on Staphylococcus aureus colonisation in a randomised controlled trial. PLoS One 2011;6:e20229.
25. Spijkerman J, Prevaes SM, van Gils EJ, et al. Long-term effects of pneumococcal conjugate vaccine on nasopharyngeal carriage of S. pneumoniae, S. aureus, H. influenzae and M. catarrhalis. PLoS One 2012;7:e39730.
26. Pichichero ME. Otitis media. Pediatr Clin North Am 2013;60:391-407.
27. Casey JR, Kaur R, Friedel VC, et al. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. Pediatr Infect Dis J 2013;32:805-9.



Chapter 2

Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors

Based on

Van Dongen TMA, van der Heijden GJMG, Freling HG, Venekamp RP, Schilder AGM. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. *PLoS One 2013; 8(7):e69062.*

Abstract

Background

Although common in children with tympanostomy tubes, the current incidence of tympanostomy-tube otorrhea (TTO) is uncertain. TTO is generally a sign of otitis media, when middle ear fluid drains through the tube. Predictors for otitis media are therefore suggested to have predictive value for the occurrence of TTO.

Objective

To determine the incidence of TTO and its predictors.

Methods

We performed a cohort study, using a parental web-based questionnaire to retrospectively collect data on TTO episodes and its potential predictors from children younger than 10 years of age with tympanostomy tubes.

Results

Of the 1,184 children included in analyses (total duration of time since tube placement was 768 person years with a mean of 7.8 months per child), 616 children (52%) experienced one or more episodes of TTO. 137 children (12%) had TTO within the calendar month of tube placement. 597 (50%) children had one or more acute TTO episodes (duration < 4 weeks) and 46 children (4%) one or more chronic TTO episodes (duration ≥ 4 weeks). 146 children (12%) experienced recurrent TTO episodes. Accounting for time since tube placement, 67% of children developed one or more TTO episodes in the year following tube placement. Young age, recurrent acute otitis media being the indication for tube placement, a recent history of recurrent upper respiratory tract infections and the presence of older siblings were independently associated with the future occurrence of TTO, and can therefore be seen as predictors for TTO.

Conclusions

Our survey confirms that otorrhea is a common sequela in children with tympanostomy tubes, which occurrence can be predicted by age, medical history and presence of older siblings.

Introduction

Tympanostomy-tube placement is one of the most common surgical procedures performed in children worldwide, with around 50,000 children in the Netherlands, and almost 700,000 in the United States receiving tubes each year.[1,2] Indications for tympanostomy tubes include prevention of acute otitis media (AOM) recurrences in children with recurrent AOM and restoration of hearing in children with persistent otitis media with effusion (OME).[3] Tympanostomy-tube otorrhea (TTO) is a well-known and common sequela in children with tympanostomy tubes. It is generally a sign of otitis media (OM), when middle ear fluid drains through the tube. TTO can be accompanied by foul odor, pain, and fever and can reduce the child's quality of life.[4] Moreover it may lead to blockage or early extrusion of the tympanostomy tube and hence impact the child's hearing. As parents generally hope that tympanostomy tubes will solve their child's middle ear problems, they may be disappointed, or anxious, when their child develops TTO.[5]

Published TTO incidences vary widely and the most recent publications on this topic date from 2001. In that year, a meta-analysis reported an average TTO incidence of 26% based on 23 studies with incidences ranging from 4% up to 68%.[6] A subsequent trial reported a TTO incidence of 75% at 12 months after tube placement in children younger than 3 years.[7] Irrespective of the wide range of reported incidences, changes in health care practice over the last decade, such as development of new OM guidelines and the introduction of pneumococcal vaccination in children, may have changed the incidence of TTO.

For OM, many risk factors have been established such as age, gender, day-care attendance and household smoking.[8,9] These factors have also been suggested to have predictive value for the occurrence of TTO, but evidence is limited.[10] In addition, the indication for tympanostomy-tube placement and frequent water exposure of the ear during swimming or bathing, have been considered as predictors specific for TTO occurrence.[10]

The objectives of the current study are to establish the incidence of TTO in children aged up to 10 years of age with tympanostomy tubes, and to identify predictors for TTO in these children.

Methods

We designed a cohort study, using a web-based survey to retrospectively collect data on TTO at one point in time from children with tympanostomy tubes. Approval from the Medical Ethics Committee of the University Medical Center Utrecht was obtained.

Population characteristics

The survey was conducted among a cohort of 3,559 children up to 10 years of age. They had tympanostomy tubes placed between April 2009 and June 2011 in 18 Dutch general hospitals and two academic hospitals. Children were excluded from the current survey if they had Down's syndrome, a known immune disorder, cleft lip or palate or if their questionnaire was filled out incompletely.

Data collection

Between May and October 2011, a letter was sent to the parents of the children asking them to participate in the survey by filling out a web-based questionnaire regarding potential TTO predictors at the time of the most recent tube placement, TTO occurrence

thereafter and time of extrusion of the tympanostomy tube(s) (available as Supporting Information at www.plosone.org: e69062). The standardized questionnaire was piloted in a small group of parents of children with tympanostomy tubes and amended based on their responses. It could be filled out at only one point in time. A reminder was sent to the parents who did not complete the questionnaire within 6 weeks after sending the letter.
All children remained under the care of their own family physician and ENT surgeon throughout our survey. We asked parents if they were willing to fill out a web-based questionnaire and did not attempt to alter local care pathways.

Data-analysis

We used Rothman's Episheet (version October 2012) to calculate the incidences.[11] For all other statistical analyses we used SPSS version 17 (SPSS Inc., Chicago, Ill).

Time since tympanostomy-tube placement

Time since tympanostomy-tube placement was defined as starting at the day of the most recent tube placement and ending at the day the web-based questionnaire was filled out. We censored this time period either at the date of tube extrusion as reported by the parents or, when parents were uncertain about presence of tympanostomy tubes, at the day the tubes were last seen in place by a physician. We included all reported TTO episodes during this time period in our analyses.

Incidence

We calculated the number of children who had developed 1 or more TTO episodes. Moreover, we assessed the number of children with 2 to 3, or 4 or more episodes of TTO, the numbers of children with early TTO (starting within the calendar month of tube placement), acute TTO (duration <4 weeks), chronic TTO (duration ≥4 weeks) and recurrent TTO (≥3 episodes in 6 months or ≥4 episodes in 12 months), and the proportions of TTO episodes managed by antibiotic(-glucocorticoid) eardrops, oral antibiotics or initial observation.
To account for differences in time since tube placement, we assessed incidence densities. We used a Kaplan-Meier curve to depict the time between tube placement and the occurrence of a first TTO episode in the first 12 months after tube placement. We also assessed the median duration between the most recent tube placement and onset of the first TTO episode in children developing TTO, and the TTO incidence rate in all included children.

Predictors

We selected candidate predictors based on their suggested or shown association with OM or TTO in the literature (see table 1 for definitions).[7-10,12-15] First, we assessed the relation between each of the candidate predictors and our main outcome (one or more episodes of TTO in the time period since tympanostomy-tube placement). To account for differences in time since tube placement we used Cox regression analyses using occurrence of the first TTO episode as the outcome. Second, to determine independent predictors, we also performed a multivariable Cox regression analysis. For this analysis, we did not select predictors based on the outcomes of univariable analyses, but included all putative indicators, and used a backward elimination procedure with a cutoff value of $p<0.05$ to

identify independent predictors. In this, we followed the rule of thumb of a minimum of 10 events for each predictor to be included in the multivariable Cox regression analysis.[16] All results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). We dichotomized age (<4 years / ≥4 years) for the univariable analysis, but because of potential loss of information we included age as a continuous variable in the multivariable analysis. Guided by the outcomes of the multivariable Cox regression analysis, we calculated the absolute risk (incidence) of TTO in children grouped according to the presence of the independent predictors.

Results

Parents of 3,559 children who had tympanostomy tubes placed by their local ENT surgeon were approached and between May and December 2011 we received questionnaires of 1,322 (37%) children. Of these 1,322 children, we excluded 138 from analysis: 9 with cleft lip or palate, 4 with a known immunodeficiency, 4 with Down's syndrome, 109 whose questionnaires were not completed and 12 children whose parents had reported incorrect dates making it impossible to calculate the time period since tympanostomy-tube placement.

At tube placement, the mean age of the 1,184 included children was 4.4 years (SD: 2.3) and 58% were boys. The total time between tube placement and the survey was 768 person years with a mean of 7.8 months (SD: 5.7, range: 0.3 to 34.0) and a median of 6.4 months (interquartile range: 7.9) per child. Other baseline characteristics of the included children are presented in table 1.

Incidence

A total of 616 (52.0%) of the children experienced one or more episodes of TTO (table 2). 137 children (11.6%) had otorrhea within the calendar month of tube placement. 597 (50.4%) children had one or more acute TTO episodes with a duration below 4 weeks and 46 (3.9%) one or more chronic TTO episodes (duration ≥ 4 weeks). 146 (12.3%) of the children experienced recurrent episodes of TTO. 60.5% of the reported TTO episodes had been treated with antibiotic(-glucocorticoid) eardrops, 12.9% with oral antibiotics and 36.1% had been managed with initial observation (total exceeds 100% because treatments are not mutually exclusive).

Figure 1 shows the Kaplan-Meier curve of the time between tube placement and the occurrence of a first TTO episode. It demonstrates that at 6 months, 49.1% of the children had developed one or more episodes of TTO. At 12 months this percentage is 67.2%. In the children who experienced TTO, the median time between tube placement and onset of the first episode was 2 months (interquartile range: 3). The TTO incidence rate in our study population was 1.8 (95% CI: 1.7 to 1.9) episodes per person year.

Predictors

The results of the univariable analyses are presented in table 1. When accounted for differences in time since tympanostomy-tube placement and dependency between predictors, age (per year increase: HR = 0.95; 95% CI: 0.91 to 0.98), the indication for tube placement being recurrent acute OM (HR = 1.26; 95% CI: 1.06 to 1.49), a history of 6 or more upper respiratory tract infections in the past year (HR = 1.38; 95% CI: 1.17 to 1.63) and

Table 1. Univariable and multivariable Cox regression analysis of potential predictors for developing otorrhea in children with tympanostomy tubes.

Potential predictors	≥ 1 episode of TTO, n (%)		Univariable	Multivariable[i]	
	Yes (n = 616)	No (n = 568)	HR (95% CI)	HR (95% CI)	Coefficient (SE)
Age					
< 4 years	305 (49.5)	201 (35.4)	1.00	-	-
≥ 4 years	311 (50.5)	367 (64.6)	0.72 (0.62 ; 0.85)	-	-
Age per year increase	-	-	0.91 (0.87 ; 0.94)	0.95 (0.91 ; 0.98)	-0.06 (0.02)
Male gender	360 (58.4)	325 (57.2)	1.08 (0.92 ; 1.27)	NS	NA
Indication for tube placement[ii]					
Recurrent acute otitis media	319 (51.8)	204 (35.9)	1.48 (1.26 ; 1.73)	1.26 (1.06 ; 1.49)	0.23 (0.09)
Chronic otitis media with effusion	291 (47.2)	356 (62.7)	0.69 (0.59 ; 0.80)	NS	NA
Previous tube placement	228 (37.0)	281 (49.5)	0.83 (0.70 ; 0.97)	NS	NA
Previous ENT surgery					
Adenoidectomy	347 (56.3)	279 (49.1)	1.22 (1.04 ; 1.44)	NS	NA
Tonsillectomy	130 (21.1)	121 (21.3)	0.99 (0.81 ; 1.20)	NS	NA
≥6 URTIs in past year	282 (45.8)	183 (32.2)	1.59 (1.35 ; 1.86)	1.38 (1.17 ; 1.63)	0.32 (0.09)
Atopy[iii]	199 (32.3)	152 (26.8)	1.12 (0.95 ; 1.33)	NS	NA
Water exposure	430 (69.8)	415 (73.1)	0.83 (0.70 ; 0.99)	NS	NA
Attending day-care/school[iv]	282 (92.5)	190 (94.5)	0.79 (0.51 ; 1.20)	NS	NA
Smoking in household	32 (5.2)	33 (5.8)	0.91 (0.64 ; 1.30)	NS	NA
Low maternal education level	65 (10.6)	55 (9.7)	1.09 (0.84 ; 1.41)	NS	NA
Overweight[v]	38 (6.2)	36 (6.3)	0.94 (0.68 ; 1.31)	NS	NA
≥ 2 siblings	200 (32.5)	172 (30.3)	1.06 (0.90 ; 1.26)	NS	NA
Older siblings	363 (58.9)	285 (50.2)	1.29 (1.10 ; 1.51)	1.21 (1.03 ; 1.42)	0.19 (0.08)

Family history					
Middle ear infections in parents	303 (49.2)	280 (49.3)	1.10 (0.94 ; 1.29)	NS	NA
Middle ear infections in siblings[vi]	231 (44.0)	241 (46.5)	1.03 (0.86 ; 1.22)	NS	NA
Allergy in parents	324 (52.6)	325 (57.2)	0.92 (0.78 ; 1.07)	NS	NA
Allergy in siblings[vi]	168 (32.0)	152 (29.4)	1.08 (0.90 ; 1.30)	NS	NA
Gestational age <37 weeks	75 (12.2)	68 (12.0)	0.99 (0.78 ; 1.26)	NS	NA
Birth weight <2500 grams	44 (7.1)	41 (7.2)	1.09 (0.80 ; 1.48)	NS	NA
Breastfed for >3 months	305 (49.5)	277 (48.8)	0.97 (0.83 ; 1.13)	NS	NA
Pacifier use in previous year	133 (21.6)	79 (13.9)	1.43 (1.18 ; 1.73)	NS	NA
PCV7-vaccination	339 (55.0)	251 (44.2)	1.42 (1.21 ; 1.67)	NS	NA

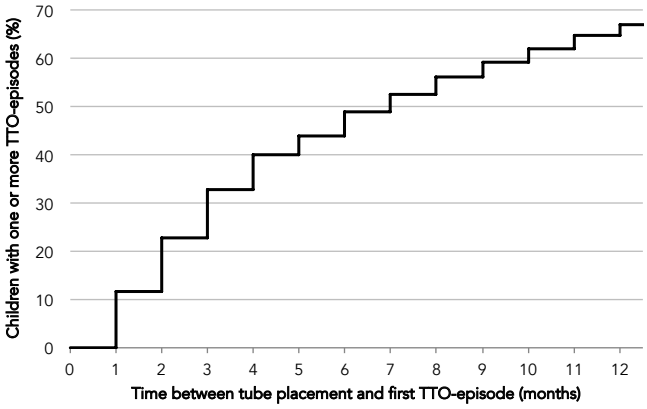
TTO = tympanostomy-tube otorrhea; n = number; HR = hazard ratio; CI = confidence interval; SE = standard error; i = only results presented for independent predictors with $p<0.05$;
NS = not significant; NA = not applicable; ii = 14 children for other indications; ENT = ear, nose and throat; URTI = upper respiratory tract infection; iii = diagnosis of allergic rhinitis, asthma, eczema or food allergy; iv = univariable analysis only including children younger than 4 years, school is mandatory for children 4 years and over; v = BMI was categorized into underweight or normal weight versus overweight according to the World Health Organization standards, corrected for age and gender[24,25]; vi = univariable analysis only including 1045 children with siblings; PCV-7 = 7-valent pneumococcal vaccine

Table 2. Incidence of tympanostomy-tube otorrhea.

Types of TTO*	Children (n=1,184)	
	n	% (95% CI)
Unspecified		
1 or more episodes	616	52.0 (49.2 ; 54.9)
2 to 3 episodes	213	18.0 (15.9 ; 20.3)
4 or more episodes	102	8.6 (7.1 ; 10.3)
Early	137	11.6 (9.8 ; 13.5)
Acute	597	50.4 (47.6 ; 53.3)
Chronic	46	3.9 (2.9 ; 5.1)
Recurrent	146	12.3 (10.6 ; 14.3)

TTO = tympanostomy-tube otorrhea; * Unspecified = any type of TTO, early = starting within the calendar month of tube placement, acute = duration <4 weeks, chronic = duration ≥4 weeks; recurrent = ≥3 episodes in 6 months or ≥4 episodes in 12 months; n = number; CI = confidence interval.

Figure 1. Kaplan-Meier curve for the duration between tube placement and the occurrence of a first TTO episode.



Children who did not develop TTO (n)	Still at risk	1184	993	780	609	507	439	350	282	234	190	155	122	95
	Censored*	0	54	141	210	248	281	331	374	401	428	451	472	491
Children who developed TTO (n)		0	137	263	365	429	464	503	528	549	566	578	590	598

* = total number of children who did not develop TTO but were no longer at risk due to a shorter time period on which data was available

Table 3. Incidence of tympanostomy-tube otorrhea according to presence of independent predictors.

Independent predictors present, n*	≥ 1 episode of TTO		Total children, n
	n	% (95% CI)	
0	85	38.1 (31.9 ; 44.6)	223
1	210	46.5 (41.9 ; 51.1)	452
2	209	60.9 (55.7 ; 66.0)	343
3	112	67.5 (60.1 ; 74.3)	166

* recurrent acute otitis media as the indication for tube placement; ≥ 6 upper respiratory tract infections in past year; presence of older siblings. The above risks are derived from a study population with a mean age of 4.4 years and will be lower in older children and higher in younger children.

having older siblings (HR = 1.21; 95% CI: 1.03 to 1.42) were found to be independent predictors for the occurrence of otorrhea in children with tympanostomy tubes (see table 1). Table 3 gives an indication of the risk (incidence) of TTO in children according to the presence of these independent predictors (except age): the risk of TTO ranged from 38.1% in children without any of these predictors up to 67.5% in children with all predictors present at tympanostomy-tube placement.

Discussion

In this cohort study of children younger than 10 years of age with tympanostomy tubes, 67% experienced one or more episodes of otorrhea in the year after tube placement. Young age, recurrent acute OM being the indication for tube placement, a recent history of recurrent upper respiratory tract infections and the presence of older siblings are independently associated with the future occurrence of TTO.

This is one of the largest studies on the incidence of TTO. The TTO incidence ascertained in our survey is higher than reported by Kay et al. in 2001.[6] In their meta-analysis they found a wide range of incidences as reported in the different studies, which they explained by differences in study design. In our population 22% of parents contacted the ENT surgeon, and 17% their family physician every time their child developed TTO (data not shown). This indicates that observational studies relying on medical records are likely to underreport TTO incidence. Clinical trials on the other hand report much higher TTO incidences, as they may include asymptomatic and subclinical episodes.[7] We believe that our parent-reported observational study provides a good estimate of the TTO incidence in children with tympanostomy tubes.

To our knowledge, this is the first study establishing the associations between a comprehensive set of potential predictors and future occurrence of TTO. Previous studies on these associations often used univariable analyses or included a small selection of predictors.[7,12-14,17,18] To account for dependencies between predictors, we have performed a multivariable analysis. Because all included children have a history of OM, the absolute hazard ratios, which can also be interpreted as relative risks, are small. The TTO incidence is however considerably higher in children with more independent predictors present at the time of tube placement than those with fewer of these predictors. Our results are consistent with those of Debruyne et al. who labeled age and a history of recurrent acute OM as predictors for TTO, and those of Gates et al. who suggested an association between recurrent upper respiratory tract infections and the occurrence of TTO.[13,14] A potential TTO-specific predictor is frequent water exposure by bathing or swimming; we however did not find any association. Although pneumococcal vaccination was believed to reduce OM incidence, a recent review suggests that its effect on OM incidence is only marginal.[9,10,19] A first glance at our univariable analysis suggests that pneumococcal vaccination may increase the risk of a future occurrence of TTO, however this is easily explained by the fact that all young children in our survey, born since 2006 when pneumococcal vaccination was introduced in The Netherlands, have been vaccinated and the older children have not. Our multivariable analysis revealed no association between pneumococcal vaccination and occurrence of TTO. The surgical rate of tympanostomy-tube placement is high in The Netherlands, suggesting that our results may not be generalizable to countries that have a different study domain through use of more stringent criteria for tube placement.[20]

Some aspects of our study deserve further consideration. First, we relied on parental diagnosis of TTO. We previously showed that during follow-up after a physician diagnosis of otorrhea (n=291 children), there was a high level of agreement between parents and physicians in the assessment of persisting ear discharge.[21] Second, although so far no trials have assessed the long-term effects of treatment for acute TTO, treatment may influence persistence or recurrence of TTO. We therefore provide information on the proportions of TTO episodes treated with antibiotic(-glucocorticoid) eardrops, oral antibiotics and initial observation and emphasize that throughout our survey children remained under the care of their local family physician and ENT surgeon. Third, non-response bias may have affected our results. We explored this by comparing demographics, i.e. age and gender, of responders and non-responders. In addition, we compared TTO incidences as recorded in the medical records of a 10% sample of all responders (n=144) with those of an equal number of non-responders. Although this does not rule out non-response bias, we did not find differences between these groups for both comparisons (data not shown). Fourth, we collected data on previous TTO episodes using survey methods, whereby recall may have contributed to inaccuracy of our incidence estimates. To address this, we asked for the calendar month and year of TTO episodes rather than the actual day of onset. Our study design therefore allows us to approximate the incidence of early TTO, defined as starting within the calendar month of tube placement. It does however not allow us to determine the incidence of early postoperative TTO, defined as starting within 2 weeks after tube placement. Previous studies comparing parental report of OM with diagnoses recorded in medical records have shown that OM frequency is most prone to bias and the longer the time since OM occurrence, the larger the inaccuracy of recall.[22,23] We therefore used presence of one or more episodes of TTO as outcome of our Cox regression analyses and Kaplan-Meier curve, rather than the absolute number of episodes. Also, most children in our survey had their tympanostomy tubes placed in the past year, reducing the time since potential TTO occurrence. In addition, as reported above we compared a random sample of medical records with the completed questionnaires of these children and checked the accuracy of verifiable data. We found a high correspondence between the questionnaires and the medical records with regard to patient characteristics, date and number of tympanostomy-tube placements and previous ENT surgery (data not shown).

Conclusion

Our survey confirms that otorrhea is a common sequela in children with tympanostomy tubes: more than half of these children develop at least one episode, in particular young children with older siblings, a recent history of recurrent upper respiratory tract infections and recurrent acute otitis media being the indication for tube placement.

References

1. Cullen K, Hall M, Golosinskiy A. Ambulatory Surgery in the United States, 2006. National health statistics reports; no 11. Revised. In. Hyattsville, MD: National Center for Health Statistics; 2009.
2. Dutch Hospital Data (Landelijke medische registratie). 2010.
3. Rosenfeld RM, Bluestone CD. Clinical efficacy of surgical therapy. In: Rosenfeld RM, Bluestone CD, eds. Evidence-Based Otitis Media. 2 ed. Hamilton, Ontario, Canada: BC Decker Inc.; 2003:227-40.
4. Rosenfeld RM, Bhaya MH, Bower CM, et al. Impact of tympanostomy tubes on child quality of life. Arch Otolaryngol Head Neck Surg 2000;126:585-92.
5. Rosenfeld RM, Isaacson G. Tympanostomy tube care and consequences. In: Rosenfeld RM, Bluestone CD, eds. Evidence-Based Otitis Media. 2 ed. Hamilton, Ontario, Canada: BC Decker Inc.; 2003:466.
6. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. Otolaryngol Head Neck Surg 2001;124:374-80.
7. Ah-Tye C, Paradise JL, Colborn DK. Otorrhea in young children after tympanostomy-tube placement for persistent middle-ear effusion: prevalence, incidence, and duration. Pediatrics 2001;107:1251-8.
8. Casselbrant ML, Mandel EM. Epidemiology. In: Rosenfeld RM, Bluestone CD, eds. Evidence-Based Otitis Media. 2 ed. Hamilton, Ontario, Canada: BC Decker Inc.; 2003:150–8.
9. Rovers MM, Schilder AG, Zielhuis GA, et al. Otitis media. Lancet 2004;363:465-73.
10. Oberman JP, Derkay CS. Posttympanostomy tube otorrhea. Am J Otolaryngol 2004;25:110-7.
11. Episheet. 2012. (Accessed at http://www.drugepi.org/dope-downloads/ - Episheet)
12. Balkany TJ, Barkin RM, Suzuki BH, et al. A prospective study of infection following tympanostomy and tube insertion. Am J Otol 1983;4:288-91.
13. Debruyne F, Jorissen M, Poelmans J. Otorrhea during transtympanal ventilation. Am J Otol 1988;9:316-7.
14. Gates GA, Avery C, Prihoda TJ, et al. Post-tympanostomy otorrhea. Laryngoscope 1986;96:630-4.
15. Nelson HM, Daly KA, Davey CS, et al. Otitis media and associations with overweight status in toddlers. Physiol Behav 2011;102:511-7.
16. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503-10.
17. Giebink GS, Daly K, Buran DJ, Satz M, Ayre T. Predictors for postoperative otorrhea following tympanostomy tube insertion. Arch Otolaryngol Head Neck Surg 1992;118:491-494.
18. Epstein JS, Beane J, Hubbell R. Prevention of early otorrhea in ventilation tubes. Otolaryngol Head Neck Surg 1992;107:758-762.
19. Taylor S, Marchisio P, Vergison A, et al. Impact of pneumococcal conjugate vaccination on otitis media: a systematic review. Clin Infect Dis 2012;54:1765–1773.
20. Schilder AG, Lok W, Rovers MM. International perspectives on management of acute otitis media: a qualitative review. Int J Pediatr Otorhinolaryngol 2004;68:29-36.
21. van Dongen TM, Schilder AG, Manders LA, et al. Good agreement between parents and physician in the assessment of ear discharge in children. Pediatr Infect Dis J 2012;31:868-9.
22. Daly KA, Lindgren B, Giebink GS. Validity of parental report of a child's medical history in otitis media research. Am J Epidemiol 1994;139:1116-21.
23. Alho OP. The validity of questionnaire reports of a history of acute otitis media. Am J Epidemiol 1990;132:1164-70.
24. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, et al. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660-667.
25. World Health Organization Child growth standards. (Accessed 2011 August 1 at: http://www.who.int/childgrowth/standards/bmi_for_age/en/index.html)

Chapter 3.1

Effectiveness of treatment for acute otorrhea in children with tympanostomy tubes: a pragmatic randomized controlled trial

Based on
Van Dongen TMA, van der Heijden GJMG, Venekamp RP, Rovers MM, Schilder AGM. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med 2014;370:723-33.*

Abstract

Background

Recent guidance for the management of acute otorrhea in children with tympanostomy tubes (ATTO) is based on limited evidence from trials comparing oral with topical antibiotics.

Methods

In this open-label, pragmatic trial, we randomly assigned 230 children, 1 to 10 years of age, who had acute tympanostomy-tube otorrhea to receive hydrocortisone– bacitracin–colistin eardrops (76 children) or oral amoxicillin–clavulanate suspension (77) or to undergo initial observation (77). The primary outcome was the presence of otorrhea, as assessed otoscopically, 2 weeks after study-group assignment. Secondary outcomes were the duration of the initial otorrhea episode, the total number of days of otorrhea and the number of otorrhea recurrences during 6 months of follow-up, quality of life, complications and treatment-related adverse events.

Results

Antibiotic-glucocorticoid eardrops were superior to oral antibiotics and initial observation for all outcomes. At 2 weeks, 5% of children treated with antibiotic-glucocorticoid eardrops had otorrhea as compared with 44% of those treated with oral antibiotics (risk difference [RD]: -39%, 95% confidence interval [CI] - 51% to -26%) and 55% of those managed by initial observation (RD: -49%, 95% CI: - 62% to -37%). The median duration of the initial otorrhea episode was 4 days in children treated with antibiotic-glucocorticoid eardrops versus 5 days in children treated with oral antibiotics ($p<0.001$) and 12 days for those who were assigned to initial observation ($p<0.001$). Treatment-related adverse events were mild and no complications of otitis media were reported at 2 weeks.

Conclusions

Antibiotic-glucocorticoid eardrops are more effective than oral antibiotics and initial observation in children with tympanostomy tubes who had uncomplicated acute otorrhea.

Introduction

Insertion of tympanostomy tubes is one of the most frequently performed surgical procedures in children.[1,2] The main indications for this procedure are restoration of hearing in children with persistent otitis media with effusion (OME) and prevention of recurrences in children who have recurrent acute otitis media (AOM).[3] Acute tympanostomy-tube otorrhea (ATTO) is a common sequela in children with tympanostomy tubes, with reported incidence rates varying from 26% in a meta-analysis of mainly observational studies (involving cases of clinically manifested otorrhea) to 75% in a randomized trial (including asymptomatic and subclinical cases).[4-6] ATTO is unpleasant as it may be accompanied by foul odor, pain, and fever and can reduce the child's quality of life.[7]

ATTO is thought to be the result of AOM, whereby middle ear fluid drains through the tube. Bacterial (super)infection of the middle ear is considered to be the predominant cause of AOM and hence ATTO.[8] Treatment is therefore aimed at eradicating bacterial infection, with the options including broad-spectrum oral antibiotics and antibiotic(-glucocorticoid) eardrops.[9]

The few trials comparing topical and oral antibiotics in this condition included either small samples of children or had methodological limitations.[9-12] The results have indicated that antibiotic(-glucocorticoid) eardrops are as effective as, or more effective than, oral antibiotics. In addition, topical treatment is better tolerated, as it causes little to no systemic side effects, and is less likely to cause microbial resistance of otopathogens.[10,12,13] Since ATTO, like AOM, may be self-limiting, initial observation may also be a good alternative.[9,14,15] No previous trial, however, compared the effectiveness of oral or topical treatment with initial observation.

In this trial, we compare the effectiveness of three treatment strategies in children with ATTO: immediate treatment with antibiotic-glucocorticoid eardrops, immediate treatment with oral antibiotics, and initial observation.

Methods

Trial conduct and oversight

We performed an open-label, pragmatic, randomized controlled trial. All authors vouch for the completeness and accuracy of the data and analyses presented and for the fidelity of the trial to the study protocol. For full details of the study design and statistical analysis plan see the study protocol, which is available at NEJM.org. The study was approved by the medical ethics committee of University Medical Center Utrecht. There was no commercial involvement in the trial.

Patients

Children 1 to 10 years of age with symptoms of tympanostomy-tube otorrhea for up to 7 days were eligible for trial participation. We excluded children with a body temperature of more than 38.5°C, those who had received antibiotics during the previous 2 weeks, those who had had tympanostomy tubes placed within the previous 2 weeks, and those who had had an episode of otorrhea in the previous 4 weeks, three or more otorrhea episodes in the previous 6 months or four or more episodes in the previous year. We also excluded children with Down's syndrome, a craniofacial anomaly, a known immunodeficiency, and children with an allergy to medications used in this study.

Patient recruitment

From June 2009 through May 2012, ear, nose, and throat (ENT) surgeons and family physicians approached parents of children with tympanostomy tubes for study participation. Our research team contacted by telephone parents who expressed interest in participation. We informed them about the trial, and checked in- and exclusion criteria. If a child had otorrhea at time of the telephone call and was eligible for participation, a home visit was planned. If there were no current symptoms of otorrhea, parents were asked to contact the study center as soon as otorrhea would occur, so that a home visit by the study physician could be arranged.

Baseline assessments

At the home visit, the study physician obtained written informed consent from parents, confirmed the presence of otorrhea otoscopically, took otorrhea samples for bacterial culture, and collected demographic and disease specific data. Parents completed the Child Health Questionnaire (CHQ),[16,17] which measures generic health-related quality of life (HRQoL), and the Otitis Media-6 (OM-6) questionnaire,[18] which measures disease specific HRQoL. Scores on the CHQ range from 1 to 35 across the four CHQ domains, with higher scores indicating better quality of life. Scores on the OM-6 questionnaire range from 6 to 42, with lower scores indicating better quality of life.

Study-group assignments

An independent data manager generated a block (n=6) randomization sequence with stratification according to age (younger than 4 years of age and 4 years and older). The study physician accessed the trial randomization website at the conclusion of the home visit to obtain the study-group assignment. The randomization assignment was concealed and could not be predicted in advance of or during enrollment. The assignments were balanced (1:1:1) for the three treatments: hydrocortisone-bacitracin-colistin eardrops (Bacicoline-B) (administered as five drops, three times daily in the discharging ear(s) for 7 days), oral amoxicillin-clavulanate suspension (30 milligram amoxicillin and 7.5 milligram clavulanate suspension per kilogram of body weight per day, divided into three daily doses administered orally for 7 days) or initial observation for 14 days (no assigned medication prescription to fulfill).

The study physician did not clean the ear canal, either at the baseline visit or at follow-up visits during the trial. Parents of children assigned to topical antibiotics were instructed to clean the outer ear of any discharge that could easily be removed from the outer ear with a tissue before applying the drops. In addition, they were instructed to tilt their child's head to one side (to an angle of approximately to 90 degrees) when applying the eardrops and have the child maintain this tilt for a few minutes to allow the drops to enter the ear canal. No other instructions, such as tragal pumping, were given. After the first follow-up visit at 2 weeks, further management of otorrhea was left to the discretion of the child's ENT surgeon or family physician.

Follow-up

Parents kept a daily diary of treatment adherence, adverse events and complications for 2 weeks and of ear-related symptoms for 6 months. At 2 weeks and at 6 months, the study physician visited the children at home, performed otoscopy and checked and collected the parental diaries, and parents completed generic and disease specific HRQoL questionnaires.

Primary and secondary outcomes

The primary outcome, treatment failure, was defined as the presence of otorrhea in one or both ears, as observed otoscopically by the study physician, 2 weeks after study-group assignment. Secondary outcomes were based on parental diaries and included duration of the initial otorrhea episode (interval from study-group assignment up to the first day of otorrhea that was followed by 7 or more days without otorrhea), total number of days with otorrhea and number of recurrent otorrhea episodes (1 or more days with otorrhea after 7 or more days without otorrhea) during 6 months of follow-up, complications and treatment-related adverse events in the first 2 weeks. In addition, generic and disease specific HRQoL was assessed at 2 weeks follow-up.

Statistical analysis

Using SPSS version 20 (SPSS, Chicago, IL) and Episheet (version of October 2012)[19], we performed all analyses according to the intention-to-treat principle and, except for treatment-related adverse events, blinded with respect to study-group assignment. We imputed missing baseline data using unconditional medians.[20]

Primary analysis and sample size

The main comparisons in our study were antibiotic-glucocorticoid eardrops versus oral antibiotics and antibiotic-glucocorticoid eardrops versus initial observation. For these comparisons we calculated absolute risk differences (RD) with 95% confidence intervals (CIs) and numbers needed to treat (NNT) in order to prevent one case of otorrhea at 2 weeks as assessed otoscopically. To control for multiple testing, topical treatment had to be superior in both comparisons. Assuming a conservative effect of about 60%[4,10,12,21], with a two-sided 5% threshold for statistical significance and 90% statistical power, we estimated that 105 children would need to be enrolled in each study-group to demonstrate a clinically relevant absolute difference of at least 20% between groups for this primary outcome.

Secondary analyses

We also calculated the RD and 95% CI for the comparison of oral antibiotics with initial observation for our primary outcome, as well as relative risks (RRs) and 95% CIs for all treatment comparisons. Using log-binomial regression analyses we adjusted RRs for possible confounding by a-priori-defined clinically relevant and statistically significant differences in baseline characteristics.

For the secondary outcomes, we plotted Kaplan-Meier curves to determine the duration of the initial otorrhea episode in the three treatment groups, and used log rank tests to test for differences between groups. We calculated medians for total number of days with otorrhea and number of recurrent otorrhea episodes during 6 months of follow-up, and HRQoL change scores at 2 weeks follow-up. A change in the mean OM-6 score of 1.0 to 1.4

indicates a moderate and 1.5 or greater a large change.[7,18] We evaluated differences between groups using Mann-Whitney U tests.

Interim analysis

After 2 years of recruitment, 150 children with ATTO were randomized. This number was considerably lower than our target of 315 children. After consultation with the funder of our trial, ZonMw (The Netherlands Organisation for Health Research and Development), we opted for an (not planned a priori) interim analysis, to be performed by an independent data review committee. Committee members were blinded for study-group assignment. The end point was defined a priori as a RD exceeding 20%. The end point was tested using the Haybittle-Peto approach ($p<0.01$). Since safety (risk of harm) was not the reason for performing this interim analysis, patient inclusion continued. The interim analysis showed that the smallest RD for the primary outcome between the superior treatment and the other treatments was -32% (95% CI: -48% to -17%, $p<0.001$). On May 21, 2012, the committee therefore recommended to discontinue further recruitment to the trial, to complete follow-up of all 230 children included thus far, to maintain blinding during data analyses and to report results according to accepted standards.[22,23]

Results

Enrollment

In total, 1133 potentially eligible children with tympanostomy tubes were registered for the trial; their parents were willing for them to participate in the trial in case ATTO developed. Parents of 886 children did not contact us or reported an otorrhea episode that did not fulfill the trial inclusion criteria (e.g. symptoms present for more than 7 days, otorrhea within 2 weeks after tympanostomy-tube insertion).

Home visits were scheduled for 247 children with ATTO. Among these children, 17 had a body temperature of 38.5°C or higher or the tympanostomy tubes were no longer present (Figure 1). 230 children with ATTO were randomly assigned to receive antibiotic-glucocorticoid eardrops (76 children) or oral antibiotics (77 children), or to undergo initial observation (77 children). In the first 2 weeks, 71 (93%), 68 (88%) and 61 children (79%) in the three groups, respectively, fully adhered to the allocated treatment strategy (Figure 1).

Completeness of data

The primary outcome was assessed in 228 children (99%). Parental diaries of 221 children (96%) were available. In these diaries, information on the presence of otorrhea was available for 94% of all follow-up days (Figure 1).

Study population

Demographic and clinical characteristics of the participants are reported in Table 1. No clinically significant differences in baseline characteristics among the three study groups were observed. The indication for tube insertion (recurrent AOM versus persistent OME) and the bacteria cultured from otorrhea differed slightly among the groups (Table 1). The mean age of the children was 4.5 years, the median duration of otorrhea before study entry was 3 days and 38 children (17%) had bilateral otorrhea at baseline.

Figure 1. Flow of participants through trial of treatment of acute tympanostomy-tube otorrhea in children.

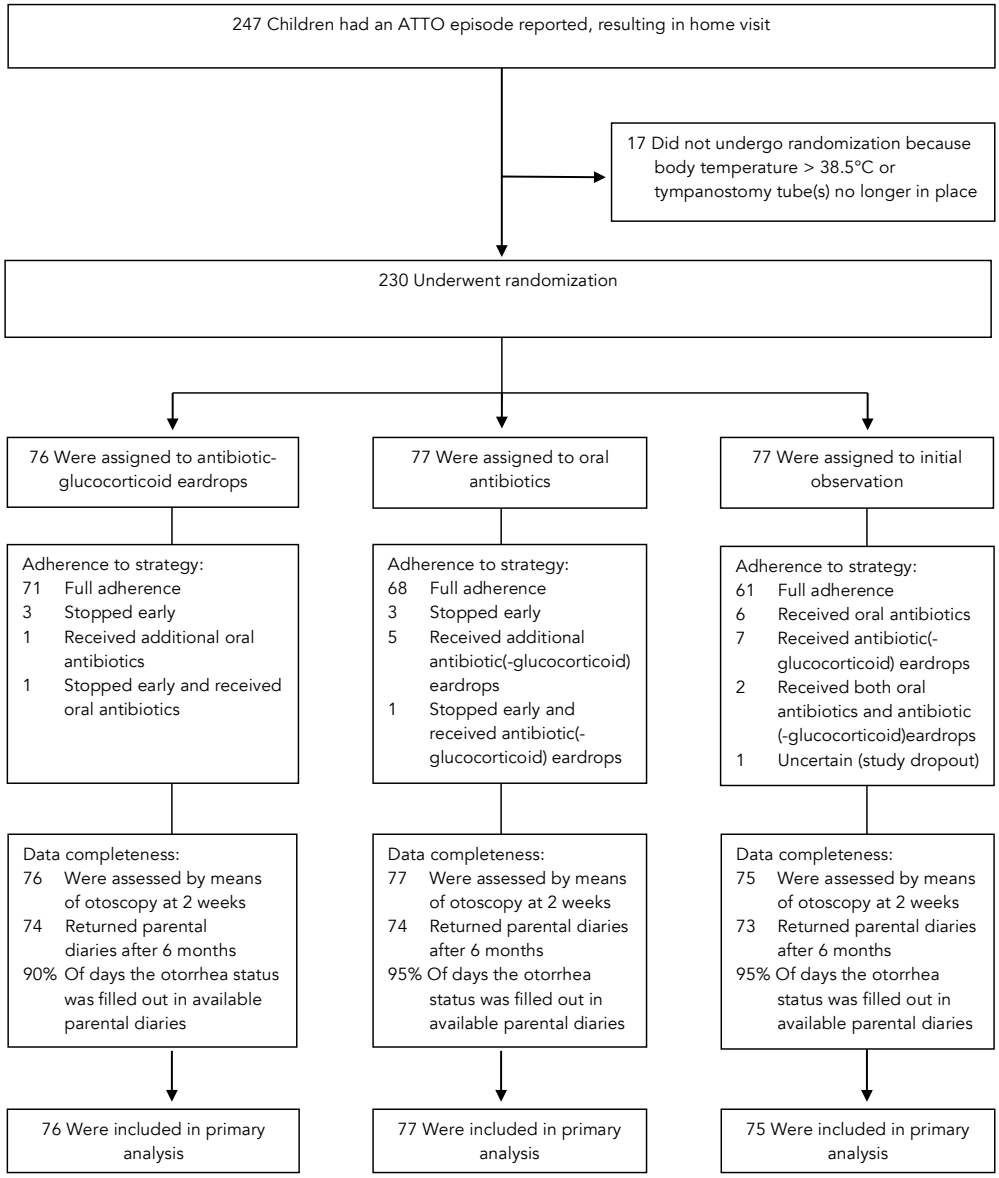


Table 1. Baseline characteristics of 230 children with acute tympanostomy-tube otorrhea according to assigned management strategy.

Patients' characteristics	Antibiotic-glucocorticoid eardrops (n=76)	Oral antibiotics (n=77)	Initial observation (n=77)	All children (n=230)
Age in years, mean (SD)	4.6 (2.1)	4.4 (2.0)	4.4 (2.0)	4.5 (2.0)
Male sex/gender, n (%)	50 (66)	40 (52)	43 (56)	133 (58)
Duration of otorrhea in days before enrollment, median (Range)	3 (0 to 7)	2 (0 to 7)	2 (0 to 7)	3 (0 to 7)
Bilateral otorrhea, n (%)	14 (18)	11 (14)	13 (17)	38 (17)
Upper respiratory tract infection in the week before study entry, n (%)	47 (62)	52 (68)	49 (64)	148 (64)
Swimming in week before study entry, n (%)	39 (51)	38 (49)	36 (47)	113 (49)
Number of tympanostomy-tube insertions, median (Range)[i]	1 (1 to 7)	1 (1 to 3)	1 (1 to 5)	1 (1 to 7)
Number of previous episodes of tympanostomy-tube otorrhea, median (Range)[ii]	0 (0 to 5)	0 (0 to 5)	0 (0 to 3)	0 (0 to 5)
Indication for tube insertion, n (%)				
Recurrent acute otitis media	36 (47)	27 (35)	36 (47)	99 (43)
Persistent otitis media with effusion	40 (53)	50 (65)	41 (53)	131 (57)
≥6 upper respiratory tract infections in past year, n (%)	39 (51)	43 (56)	46 (60)	128 (56)
Previous ENT-surgery, n (%)				
Adenoidectomy	44 (58)	41 (53)	48 (62)	133 (58)
Tonsillectomy	13 (17)	13 (17)	22 (29)	48 (21)
Atopy, n(%)	38 (50)	35 (46)	38 (49)	111 (48)
Daycare attendance in those aged younger than 4 years, n(%)	29 (91)	27 (82)	25 (81)	81 (84)
Older siblings, n (%)	43 (57)	42 (55)	41 (53)	126 (55)
Family history of otitis media, n (%)	52 (68)	47 (61)	56 (73)	155 (67)
Educational level of mother, n (%)				
Low	15 (20)	11 (14)	10 (13)	36 (16)
Average	31 (41)	24 (31)	33 (43)	88 (38)
High	30 (40)	42 (55)	34 (44)	106 (46)
Household smoking, n (%)	13 (17)	4 (5)	9 (12)	26 (11)
Gestational age <37 weeks, n (%)	13 (17)	8 (10)	7 (9)	28 (12)
Birth weight <2500 grams, n (%)	5 (7)	4 (5)	4 (5)	13 (6)
Breastfeeding > 3 months, n (%)	36 (47)	37 (48)	31 (40)	104 (45)
Pacifier use in past year, n (%)	17 (22)	16 (21)	13 (17)	46 (20)
Positive otorrhea cultures, any pathogen, n (%)[iii]	69 (91)	72 (94)	71 (92)	212 (92)
Haemophilus influenzae	31 (41)	32 (42)	31 (40)	94 (40)
Staphylococcus aureus	25 (33)	27 (35)	39 (51)	91 (40)
Pseudomonas aeruginosa	16 (21)	16 (21)	10 (13)	42 (18)
Streptococcus pneumoniae	5 (7)	5 (6)	5 (6)	15 (7)
Moraxella catarrhalis	3 (4)	2 (3)	3 (4)	8 (3)

n=number; SD = standard deviation; i = including current tympanostomy tubes; ii = for current tympanostomy tubes; ENT = ear, nose and throat; iii = multiple bacteria can be present in one sample so percentages do not add up to 100. In 9 (4%) children information for one or two, and in 1 (0.4%) child three or more, baseline characteristics were missing, which we imputed by the unconditional median.

Primary analysis

At 2 weeks, 5% of children treated with eardrops had otorrhea versus 44% of those who received oral antibiotics (RD: -39%, 95% CI: -51% to -26%; NNT: 3) and 55% who were assigned to initial observation (RD: -49%, 95% CI: -62% to -37%; NNT: 2) (Table 2).

Secondary analyses

At 2 weeks, children treated with oral antibiotics were less likely to have otorrhea than those managed by initial observation, but this difference was not statistically significant (RD: -11%, 95% CI: -27% to 5%). The RRs adjusted for small baseline differences were not substantially different from the crude RRs, which consistently favored antibiotic-glucocorticoid eardrops (Table 2). The median duration of the initial otorrhea episode was 4 days in children treated with eardrops versus 5 days for those treated with oral antibiotics ($p<0.001$) and 12 days for those managed by initial observation ($p<0.001$) (Table 2 and Figure 2). The median total number of days with otorrhea during 6 months of follow-up was 5 days in children receiving eardrops versus 13.5 days for those receiving oral antibiotics ($p<0.001$) and 18 days for those managed by initial observation ($p<0.001$). The median number of recurrent episodes of otorrhea during 6 months of follow-up was 0 for children treated with antibiotic eardrops versus 1 for those treated with oral antibiotics ($p=0.03$) and 1 for those managed by initial observation ($p=0.26$).

At baseline, the generic and disease-specific HRQoL scores indicated good quality of life and were similar across the groups. At 2 weeks follow-up, the change in generic HRQoL scores did not significantly differ between groups. The changes in disease specific HRQoL scores at 2 weeks were small but consistently favored eardrops (Appendix tables 1 and 2).

Complications and treatment-related adverse events

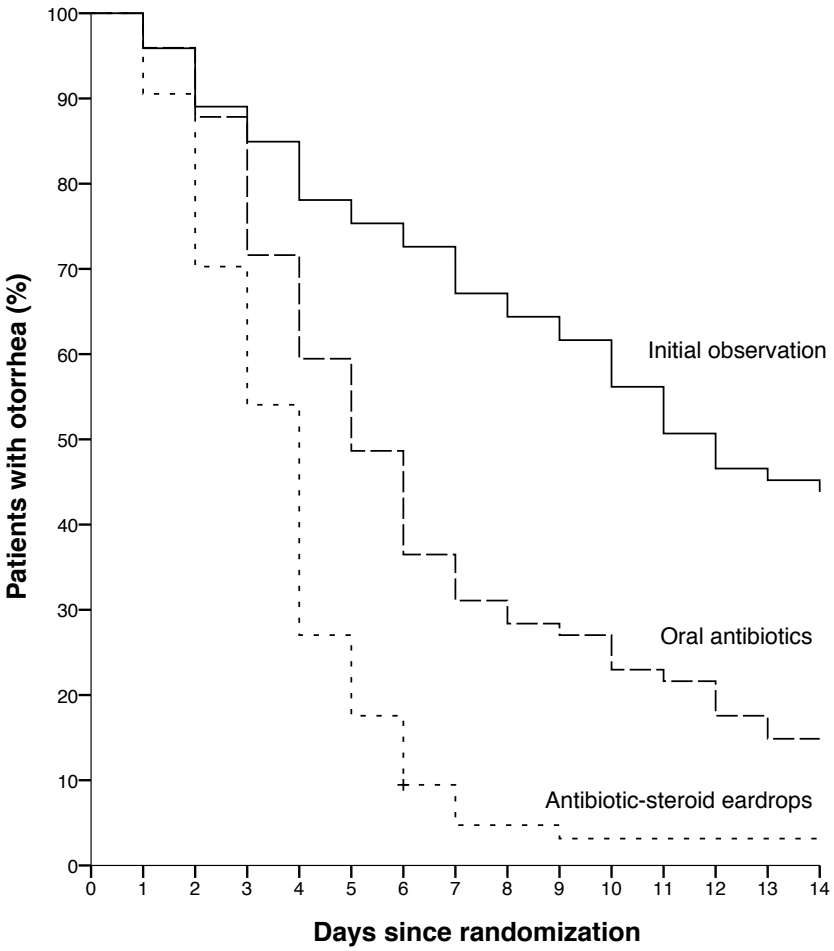
No complications of otitis media including local cellulitis, perichondritis, mastoiditis or intracranial complications were reported during the first 2 weeks of follow-up (Table 3). Treatment-related adverse events were mild. A total of 16 (21%) children who received eardrops experienced pain or discomfort when drops were administered and 2 (3%) children developed a local rash. A total of 18 (23%) children who received oral antibiotics developed gastrointestinal symptoms and 3 (4%) developed a rash. During 6 months of follow-up, fewer children treated with eardrops had otorrhea episodes that persisted for more than 4 weeks as compared with those treated with oral antibiotics or initial observation (Table 3).

Table 2. Outcomes in children with acute tympanostomy-tube otorrhea according to study-group assignment.

Outcomes	Antibiotic-glucocorticoid eardrops (n=76)	Oral antibiotics (n=77)	Initial observation (n=77)	Antibiotic-glucocorticoid eardrops versus initial observation	Oral antibiotics versus initial observation	Oral antibiotics versus initial observation
Otoscopy[i]						
Number of children	76	77	75			
Otorrhea at 2 weeks follow-up, n (%)	4 (5)	34 (44)	41 (55)			
Risk difference, % (95% CI)				-49 (-62 to -37)	-39 (-51 to -26)	-11 (-27 to 5)
Relative risk (95% CI)						
Unadjusted				0.10 (0.04 to 0.26)	0.12 (0.04 to 0.32)	0.81 (0.58 to 1.12)
Adjusted[ii]				0.09 (0.03 to 0.24)	0.12 (0.05 to 0.33)	0.75 (0.54 to 1.03)
Parental diary						
Number of children	74	74	73			
Duration of the initial otorrhea episode, days[iii]						
Median (Range)	4 (1 to 28)	5 (1 to 36)	12 (1 to 159)			
Difference in median[iv]				-8 (p<0.001)	-1 (p<0.001)	-7 (p<0.001)
Total number of days with otorrhea during 6 months follow-up						
Median (Range)	5 (1 to 62)	13.5 (1 to 61)	18 (1 to 159)			
Differences in median[v]				-13 (p<0.001)	-8.5 (p<0.001)	-4.5 (p=0.04)
Number of otorrhea recurrences during 6 months follow up[vi]						
Median (Range)	0 (0 to 9)	1 (0 to 6)	1 (0 to 5)			
Differences in median[v]				-1 (p=0.26)	-1 (p=0.03)	0 (p=0.21)

i = assessed by physician; ii = adjusted for duration of otorrhea before enrollment, indication for tympanostomy-tube insertion and presence or absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in otorrhea samples; iii = interval from study-group assignment up to the first day of otorrhea that was followed by 7 or more days without otorrhea, median from Kaplan-Meier analysis; iv= Log rank test; v = Mann-Whitney-U test; vi = 1 or more days of otorrhea after an otorrhea free interval of 7 or more days. No rounding was used in the difference calculations.

Figure 2. Kaplan-Meier curve for the duration of otorrhea after randomization as reported by parents in a diary.



Appendix for figure 2. Data from Kaplan-Meier analysis.

	Study day														
Number of children	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Antibiotic-glucocorticoid eardrops															
Otorrhea	74	67	52	40	20	13	7[i]	3	3	2	2	2	2	2	2
No otorrhea	0	7	22	34	54	61	67	70	70	71	71	71	71	71	71
Oral antibiotics															
Otorrhea	74	71	65	53	44	36	27	23	21	20	17	16	13	11	11
No otorrhea	0	3	9	21	30	38	47	51	53	54	57	58	61	63	63
Initial observation															
Otorrhea	73	70	65	62	57	55	53	49	47	45	41	37	34	33	32
No otorrhea	0	3	8	11	16	18	20	24	26	28	32	36	39	40	41

i = data censoring took place

Table 3. Treatment-related and serious adverse events in children with acute tympanostomy-tube otorrhea according to study-group assignment

	Children, n/total n (%)			Risk difference, % (95% CI)		
	Antibiotic-glucocorticoid eardrops	Oral antibiotics	Initial observation	Antibiotic-glucocorticoid eardrops versus initial observation	Oral antibiotics versus initial observation	
Short-term adverse events (2 weeks)[i]						
Local discomfort/pain during administration	16/75 (21)	0/77 (0)	-	-	21 (12 to 30)	-
Gastrointestinal complaints	0/75 (0)	18/77 (23)	-	-	-23 (-33 to -14)	-
(Local) rash	2/75 (3)	3/77 (4)	-	-	-1 (7 to -4)	-
Oral candidiasis	0/75 (0)	0/77 (0)	-	-	0 (-)	-
Long-term adverse events (6 months)[i]						
Chronic otorrhea episode(s)						
Duration ≥4 weeks	1/74 (1)	5/74 (7)	12/73 (16)	-15 (-24 to -6)	-5 (-12 to 1)	-10 (-20 to 1)
Duration ≥ 12 weeks	0/74 (0)	0/74 (0)	1/73 (1)	-1 (-4 to 1)	0 (-)	-1 (-4 to 1)
Serious adverse events (2 weeks)[i]						
Complications of otitis media[ii]	0/75 (0)	0/77 (0)	0/75 (0)	0 (-)	0 (-)	0 (-)

n = number, CI = confidence interval; i = Adverse events and serious adverse events occurring within 2 weeks after study-group assignment were reported by parents in a diary in which data related to the treatment strategy and complications of otitis media were collected, whereas those occurring within 6 months after study- group assignment were derived from the parental diary on ear-related symptoms. No rounding was used in the difference calculations; ii = e.g. local cellulitis, perichondritis, mastoiditis or intracranial complications

Discussion

In this pragmatic, randomized controlled trial we found that antibiotic-glucocorticoid eardrops are superior to oral antibiotics (NNT=3) and to initial observation (NNT=2) with respect to the primary outcome of otorrhea at 2 weeks, as assessed otoscopically, in children with tympanostomy tubes and acute otorrhea. Our secondary analyses support these findings. Approximately one in two children managed by initial observation still had otorrhea at 2 weeks and initial observation resulted in more days with otorrhea in the following months than did topical or oral antibiotics. This suggests that initial observation may not be an adequate management strategy in such children.

One previous trial compared the same treatment strategies - antibiotic–glucocorticoid eardrops, oral antibiotics, and observation - but as a prophylaxis for infection following tympanostomy-tube insertion.[24] Three previous trials compared eardrops with oral antibiotics in the treatment of children with tympanostomy-tube otorrhea.[10-12] Two of these trials were performed in a slightly different study population, i.e. children with otorrhea persisting for up to 3 weeks (the exact duration of otorrhea at baseline was not reported upon), some of whom had received treatment prior to study entry.[10,12] Both studies excluded children with positive cultures for group A streptococci or *Pseudomonas aeruginosa* from the analyses, which affected the applicability of these results to daily practice. The third trial, which had a study population more similar than ours, 68 children with ATTO were randomly assigned to either oral amoxicillin, ciprofloxacin eardrops or saline rinsing of the ear canal.[11] These investigators also found topical treatment to be superior over the other treatments with comparable between study-group differences, but reported higher failure rates than we observed. The higher failure rates may be explained by us assessing the treatment effect at 2 weeks rather than at one week and, specifically for topical treatment, our use of eardrops containing both antibiotics and glucocorticoids.[25]

A Finnish trial comparing the effectiveness of oral antibiotics with placebo in children with ATTO, showed a shorter duration of otorrhea in children treated with oral antibiotics.[21] During the study, the ear canal of participating children was cleaned by daily suction. Apart from uncertainty about the benefits of this additional daily intervention, the study results may not be applicable to daily clinical practice, in which it is neither accepted nor feasible to perform daily suction. We did not find a greater benefit of oral antibiotics over initial observation for presence of otorrhea at 2 weeks' otoscopy, but did also find a shorter duration of the initial otorrhea episode in children treated with oral antibiotics.

Some aspects of our trial deserve further attention. First, the antibiotic-glucocorticoid eardrops we used are not routinely available outside the Netherlands and France. We chose hydrocortisone-bacitracin-colistin eardrops because they were the most widely used commercially available eardrops for ATTO in the Netherlands that did not contain a potentially ototoxic aminoglycoside [Unpublished data]. The eardrops are active against most isolates of bacteria that cause ATTO (i.e. *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus* and *P. aeruginosa*). It is likely that any combination of antibiotic-glucocorticoid eardrops with a similar antimicrobial activity, such as ciprofloxacin-dexamethasone, would show similar results.[26] Second, the dose of amoxicillin-clavulanate suspension that we used in our trial (30 mg of amoxicillin and 7.5 mg of clavulanate per kilogram per day) is the recommended dose in the Netherlands and other European countries where antimicrobial resistance rates are low.[11,21,27,28] Third, we used a

pragmatic non-blinded trial design to enhance the applicability of our findings to daily practice.[29] Nevertheless, the outcomes assessed by the study physician were highly consistent with those reported by the parents in the diaries. Fourth, we believe that these diary data are accurate. We collected diaries, including information on the presence of otorrhea per follow-up day, for nearly all children. Furthermore, in a study that was parallel to this trial we found high agreement between parents and physicians in the assessment of ear discharge in children after management of ATTO.[30] Fifth, at the design stage of this trial we assumed a 20% absolute reduction of otorrhea after 2 weeks for one treatment strategy as compared to the others to be clinically relevant. The observed risk difference was actually twice as large, illustrating the importance of our findings for clinical practice. Finally, in a comparison of the children who were included in the trial with those who were not, we found similarities with regard to age, gender and number of previous tympanostomy-tube insertions. Since the design of our trial allowed inclusion of children who would be managed across health care settings, our findings are likely applicable to children with uncomplicated ATTO both in primary and secondary care.

Conclusions

Antibiotic-glucocorticoid eardrops are more effective than oral antibiotics and initial observation in children with tympanostomy tubes suffering from uncomplicated acute otorrhea.

References

1. Cullen K, Hall M, Golosinskiy A. Ambulatory Surgery in the United States, 2006. National health statistics reports; no 11. Revised. In. Hyattsville, MD: National Center for Health Statistics; 2009.
2. Dutch Hospital Data (Landelijke medische registratie). 2010.
3. Rosenfeld RM, Bluestone CD. Clinical efficacy of surgical therapy. In: Rosenfeld RM, Bluestone CD, eds. Evidence-Based Otitis Media. 2 ed. Hamilton, Ontario, Canada: BC Decker Inc.; 2003:227-40.
4. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. Otolaryngol Head Neck Surg 2001;124:374-80.
5. van Dongen TM, van der Heijden GJ, Freling HG, et al. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. PLoS One 2013;8:e69062.
6. Ah-Tye C, Paradise JL, Colborn DK. Otorrhea in young children after tympanostomy-tube placement for persistent middle-ear effusion: prevalence, incidence, and duration. Pediatrics 2001;107:1251-8.
7. Rosenfeld RM, Bhaya MH, Bower CM, et al. Impact of tympanostomy tubes on child quality of life. Arch Otolaryngol Head Neck Surg 2000;126:585-92.
8. Peters BM, Jabra-Rizk MA, O'May GA, et al. Polymicrobial interactions: impact on pathogenesis and human disease. Clin Microbiol Rev 2012;25:193-213.
9. Vaile L, Williamson T, Waddell A, et al. Interventions for ear discharge associated with grommets (ventilation tubes). Cochrane Database Syst Rev 2006:CD001933.
10. Dohar J, Giles W, Roland P, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2006;118:e561-9.
11. Heslop A, Lildholdt T, Gammelgaard N, et al. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhea in children: the results of a randomized clinical trial. Laryngoscope 2010;120:2516-20.
12. Goldblatt EL, Dohar J, Nozza RJ, et al. Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes. Int J Pediatr Otorhinolaryngol 1998;46:91-101.
13. Weber PC, Roland PS, Hannley M, et al. The development of antibiotic resistant organisms with the use of ototopical medications. Otolaryngol Head Neck Surg 2004;130:S89-94.
14. Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet 2006;368:1429-35.
15. Isaacson G. Why don't those ear drops work for my patients? Pediatrics 2006;118:1252-3.
16. Raat H, Botterweck AM, Landgraf JM, et al. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. J Epidemiol Community Health 2005;59:75-82.
17. Hullmann SE, Ryan JL, Ramsey RR, et al. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S420-30.
18. Rosenfeld RM, Goldsmith AJ, Tetlus L, et al. Quality of life for children with otitis media. Arch Otolaryngol Head Neck Surg 1997;123:1049-54.
19. Episheet. 2011. (Accessed at http://www.drugepi.org/dope-downloads/ - Episheet.)
20. Donders AR, van der Heijden GJ, Stijnen T, et al. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-91.
21. Ruohola A, Heikkinen T, Meurman O, et al. Antibiotic treatment of acute otorrhea through tympanostomy tube: randomized double-blind placebo-controlled study with daily follow-up. Pediatrics 2003;111:1061-7.
22. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63:834-40.
23. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63:e1-37.
24. Balkany TJ, Barkin RM, Suzuki BH, et al. A prospective study of infection following tympanostomy and tube insertion. Am J Otol 1983;4:288-91.
25. Roland PS, Anon JB, Moe RD, et al. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tubes. Laryngoscope 2003;113:2116-22.

26. U.S. National Library of Medicine: Daily Med. (Accessed at http://dailymed.nlm.nih.gov.)
27. Easton J, Noble S, Perry CM. Amoxicillin/clavulanic acid: a review of its use in the management of paediatric patients with acute otitis media. Drugs 2003;63:311-40.
28. Tahtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011;364:116-26.
29. Scott IA, Glasziou PP. Improving the effectiveness of clinical medicine: the need for better science. Med J Aust 2012;196:304-8.
30. van Dongen TM, Schilder AG, Manders LA, et al. Good agreement between parents and physician in the assessment of ear discharge in children. Pediatr Infect Dis J 2012;31:868-9.

Appendix table 1. Generic quality of life assessed with the child health questionnaire (CHQ-PF28)[16,17] at baseline and at 2 weeks follow up.

Questionnaire	Age of participants (years)	Range of scores	Antibiotic-glucocorticoid eardrops (n=76)		Oral antibiotics (n=77)		Initial observation (n=77)		Differences in median Δ 2 weeks[i]		
			Baseline	Δ 2 weeks	Baseline	Δ 2 weeks	Baseline	Δ 2 weeks	Antibiotic-glucocorticoid eardrops versus initial observation	Antibiotic-glucocorticoid eardrops versus oral antibiotics	Oral antibiotics versus initial observation
Parental emotional impact,	1 - 4	7 to 35	34 (21 to 35)	0 (-2 to 4)	33 (15 to 35)	1 (-9 to 9)	33 (7 to 35)	0 (-11 to 27)	0 (p=0.06)	-1 (p=0.85)	1 (p=0.10)
Median (range)	5 - 9	3 to 15	15 (10 to 15)	0 (-2 to 5)	14 (9 to 15)	0 (-3 to 4)	14 (9 to 15)	0 (-4 to 3)	0 (p=0.20)	0 (p=0.32)	0 (p=0.82)
Parental time impact,	1 - 4	7 to 28	28 (8 to 28)	0 (-6 to 19)	27 (11 to 28)	0 (-6 to 5)	27.5 (12 to 28)	0 (-7 to 6)	0 (p=0.90)	0 (p=0.40)	0 (p=0.68)
Median (range)	5 - 9	3 to 12	12 (9 to 12)	0 (-9 to 3)	12 (8 to 12)	0 (-2 to 4)	12 (3 to 12)	0 (-3 to 9)	0 (p=0.79)	0 (p=0.80)	0 (p=0.60)
Family activities,	1 - 4	6 to 30	29 (18 to 30)	0 (-6 to 7)	28 (17 to 30)	0 (-14 to 10)	29 (13 to 30)	0 (-10 to 15)	0 (p=0.27)	0 (p=0.67)	0 (p=0.60)
Median (range),	5 - 9	6 to 30	29 (19 to 30)	0 (-8 to 5)	29 (18 to 30)	0 (-7 to 10)	29 (20 to 30)	0 (-13 to 5)	0 (p=0.86)	0 (p=0.94)	0 (p=0.71)
Family cohesion,	1 - 4	1 to 5	4 (3 to 5)	0 (-1 to 2)	4 (2 to 5)	0 (-2 to 2)	4 (2 to 5)	0 (-1 to 2)	0 (p=0.85)	0 (p=0.95)	0 (p=0.89)
Median (range)	5 - 9	1 to 5	3 (3 to 5)	0 (-1 to 1)	4 (2 to 5)	0 (-2 to 1)	4 (2 to 5)	0 (-1 to 1)	0 (p=0.84)	0 (p=0.98)	0 (p=0.86)

n = number; Δ = difference; i = Mann-Whitney-U test

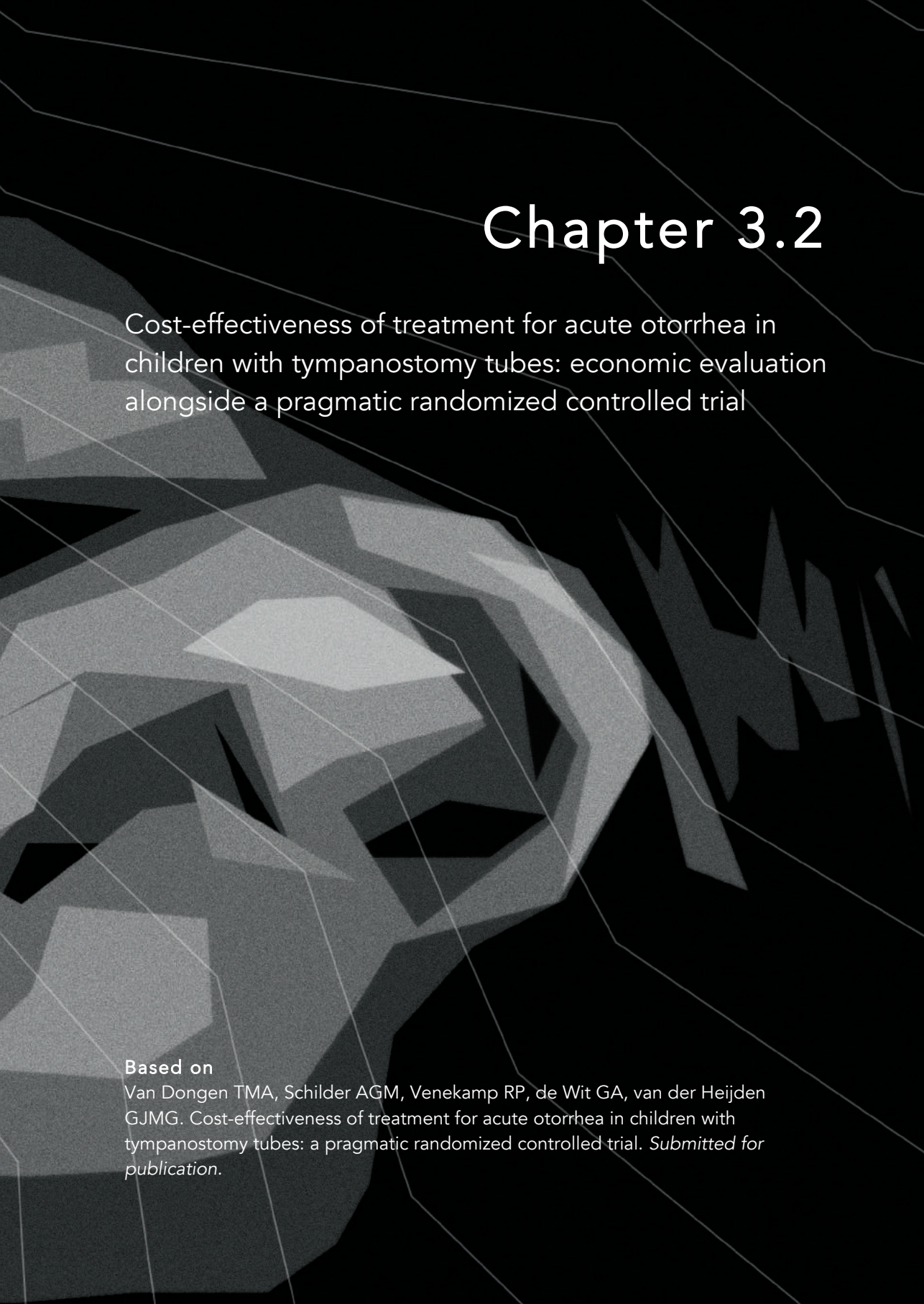
Appendix table 2. Disease specific quality of life assessed with the otitis media-6 questionnaire[18] at baseline and at 2 weeks follow up.

Questionnaire	Age of participants (years)	Range of scores	Antibiotic-glucocorticoid eardrops (n=76)		Oral antibiotics (n=77)		Initial observation (n=77)		Differences in median Δ 2 weeks[i]		
			Baseline	Δ 2 weeks	Baseline	Δ 2 weeks	Baseline	Δ 2 weeks	Antibiotic-glucocorticoid eardrops versus initial observation	Antibiotic-glucocorticoid eardrops versus oral antibiotics	Oral antibiotics versus initial observation
Physical suffering, Median (range) [ii]	1 – 9	1 to 7	3 (1 to 6)	0 (-4 to 3)	3 (1 to 6)	0 (-4 to 5)	3 (1 to 7)	0 (-5 to 4)	0 (p=0.16)	0 (p=0.77)	0 (p=0.43)
Hearing loss, Median (range) [ii]	1 – 9	1 to 7	3 (1 to 7)	0 (-5 to 3)	3 (1 to 6)	0 (-3 to 3)	3 (1 to 7)	0 (-3 to 5)	0 (p=0.02)*	0 (p=0.04)*	0 (p=0.69)
Speech impairment, Median (range) [ii]	1 – 9	1 to 7	1 (1 to 7)	0 (-4 to 3)	1 (1 to 6)	0 (-4 to 3)	1 (1 to 7)	0 (-4 to 5)	0 (p=0.04)*	0 (p=0.20)	0 (p=0.35)
Emotional distress, Median (range) [ii]	1 – 9	1 to 7	2 (1 to 6)	0 (-3 to 2)	2 (1 to 5)	0 (-3 to 3)	2 (1 to 6)	0 (-4 to 4)	0 (p=0.04)*	0 (p<0.01)*	0 (p=0.30)
Activity limitations, Median (range) [ii]	1 – 9	1 to 7	2 (1 to 6)	0 (-4 to 3)	2 (1 to 6)	0 (-3 to 5)	2 (1 to 5)	0 (-4 to 4)	0 (p=0.11)	0 (p=0.03)*	0 (p=0.69)
Caregivers concern, Median (range) [ii]	1 – 9	1 to 7	2 (1 to 7)	0 (-4 to 3)	2 (1 to 6)	0 (-5 to 4)	2 (1 to 6)	0 (-3 to 4)	0 (p<0.01)*	0 (p<0.01)*	0 (p=0.69)
Total score, Median (range) [ii]	1 – 9	6 to 42	15.5 (6 to 29)	-1 (-14 to 11)	15.5 (6 to 28)	1 (-11 to 18)	14 (5 to 33)	0.5 (-15 to 26)	-1.5 (p<0.01)*	-2 (p<0.01)*	0.5 (p=0.81)
Visual analog score, Median (range)	1 – 9	1 to 10	7 (3 to 10)	0 (-4 to 6)	7 (2 to 10)	0 (-5 to 5)	7 (3 to 10)	0 (-4 to 6)	0 (p=0.33)	0 (p=0.50)	0 (p=0.75)

n = number; Δ = difference; i = Mann-Whitney-U test; ii = lower scores indicate better quality of life; * = favoring antibiotic-glucocorticoid eardrops

Chapter 3.2

Cost-effectiveness of treatment for acute otorrhea in children with tympanostomy tubes: economic evaluation alongside a pragmatic randomized controlled trial



Based on

Van Dongen TMA, Schilder AGM, Venekamp RP, de Wit GA, van der Heijden GJMG. Cost-effectiveness of treatment for acute otorrhea in children with tympanostomy tubes: a pragmatic randomized controlled trial. *Submitted for publication*.

Abstract

Objective
To assess the cost-effectiveness of antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation for children with tympanostomy tubes who develop acute otorrhea.

Design
Cost-effectiveness analyses carried out alongside a pragmatic randomized controlled trial with 6 months follow-up.

Setting
Dutch family physicians and ENT surgeons approached parents of children with tympanostomy tubes for trial participation. Parents interested in trial participation contacted our research team when their child developed otorrhea. During the 6 months follow-up, parents of trial participants kept a daily diary of ear-related symptoms and resource use.

Participants
Between June 2009 and May 2012, 230 children aged between 1 and 10 years with uncomplicated acute tympanostomy-tube otorrhea were included.

Interventions
Hydrocortisone-bacitracin-colistin eardrops for 7 days (n=76), oral amoxicillin-clavulanate suspension for 7 days (n=77) or initial observation for 14 days (n=77).

Main outcome measures
Cost-effectiveness was determined at 2 weeks and 6 months. Using a societal perspective, the clinical outcomes otoscopic presence of otorrhea at 2 weeks and mean total number of days with otorrhea during 6 months follow-up were balanced against both healthcare and non-healthcare costs.

Results
Antibiotic-glucocorticoid eardrops were clinically superior to oral antibiotics and initial observation both at 2 weeks and 6 months. At 2 weeks, mean total cost per patient was €29.45 (SE: 3.42) for antibiotic-glucocorticoid eardrops, €49.01 (SE: 13.38) for oral antibiotics and €56.94 (SE: 12.92) for initial observation. At 6 months mean total cost per patient was €255.59 (SE: 354.07), €292.05 (SE: 470.14) and €444.56 (SE: 644.91), respectively.

Conclusion
Antibiotic-glucocorticoid eardrops are clinically superior and have economic benefits over oral antibiotics and initial observation in children who develop acute tympanostomy-tube otorrhea.

Introduction

With around 50,000 procedures in the Netherlands, more than 20,000 in the UK and almost 700,000 in the United States each year, insertion of tympanostomy tubes (also known as ventilation tubes or grommets) is one of the most frequently performed surgical procedures in children.[1-3] Acute otorrhea is the most common sequela in these children with 67% developing at least one episode in the year after tube insertion.[4] The otorrhea is caused by an acute middle ear infection, whereby middle ear fluid drains through the tube.

The societal costs of middle ear infections are considerable.[5-7] Roland et al. showed, using decision-analytic modeling, that the direct healthcare costs of a single episode of tube otorrhea approximated 250 US dollars (US$) in 2004.[8] They did not include non-healthcare costs (e.g. parental time off work) that are suggested to contribute to 50% or more of societal costs of middle ear infections.[9-11]

Our recent pragmatic randomized trial demonstrated that antibiotic-glucocorticoid eardrops are more effective than oral antibiotics and initial observation in children with acute tympanostomy-tube otorrhea in terms of clinical outcomes at 2 weeks and 6 months.[12] The objective of the current study is to establish the cost-effectiveness of these treatments from a societal perspective.

Methods

Design and study population

This cost-effectiveness study was performed alongside a pragmatic, randomized controlled trial in the Netherlands. Its design, methods and clinical outcomes are reported in more detail elsewhere.[12]

Family physicians and ENT surgeons approached parents of children with tympanostomy tubes for trial participation. Parents interested in trial participation contacted our research team when their child developed otorrhea. Children aged between 1 and 10 years with otorrhea for up to 7 days were eligible for trial participation. We excluded children with a body temperature of above 38.5°C, those who had used antibiotics in the previous 14 days, those who had tubes inserted within the previous 14 days, and those who had experienced another episode of otorrhea in the previous 28 days, three or more episodes of otorrhea in the previous 6 months or four or more episodes in the previous year. We also excluded children with Down's syndrome, craniofacial anomalies, a known immunodeficiency, and children with a known allergy to the medications used in this study.

Randomization and interventions

After obtaining informed consent, children were randomized to one of three management strategies: hydrocortisone-bacitracin-colistin eardrops (Bacicoline-B) (administered as five drops, three times daily in the discharging ear(s) for 7 days), oral amoxicillin-clavulanate suspension (30 milligram amoxicillin and 7.5 milligram clavulanate suspension per kilogram of body weight per day, divided into three daily doses administered orally for 7 days) or initial observation for 14 days (no assigned medication prescription to fulfill). After the first follow-up visit, further management of otorrhea was left to the discretion of the child's family physician or ENT surgeon.

Follow-up measurements

Parents kept a daily diary capturing ear related symptoms, direct healthcare resource use (prescriptions, healthcare visits, surgical procedures and hospitalizations) and direct (over-the-counter drugs, travel costs, costs for childcare) and indirect non-healthcare costs (parental time of work) for 6 months. We used monthly telephone reminders to optimize compliance to the daily diary.

At 2 weeks and 6 months, the study physician visited the children at home, performed otoscopy, and checked diaries for completeness. Data quality was monitored by an independent third party, including close-in and close-out visits and regular on-site visits for source data verification.

Clinical outcomes

Clinical effectiveness of antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation was assessed by:

1. otoscopy by the study physician at weeks, i.e. presence of otorrhea;
2. parental diaries at 6 months, i.e. mean number of days with otorrhea.

Resource use and valuation

All costs were estimated at patient level for the year 2009 when the trial started. Older prices were adjusted to the price level of 2009, using the Dutch consumer price index published by Statistics Netherlands.[13]

Costs of medication were retrieved from the Dutch formulary, a pharmacist's fee was added for every prescription.[14,15] We used the cost estimates as presented in the Dutch Formulary, which are based on the defined daily dose system. Use of oral and topical antibiotics with or without glucocorticoids was calculated per course of 3, 5 or 7 days, unless stated otherwise. We used the current cost estimate if medication prices for 2009 were not available. Costs of OTC and complementary medicines were calculated per day, based on current average retail prices. Healthcare visits, telephone consultations and hospitalizations (per day) were valued according to the Dutch guideline for pharmacoeconomic evaluation.[14] We did not include home visits or phone calls by the trial team in resource use and cost estimates. Costs of surgical procedures were retrieved from a previous Dutch costing study that calculated costs for the different components of surgical procedures, which were then added to reach a reliable cost estimate.[16]

Parental time off work was calculated per hour, averaging hourly production losses for men and women, assuming parents to be between 25 and 35 years of age. Hourly estimates were derived from the Dutch guideline for pharmacoeconomic evaluation and are corrected for the elasticity of labor productivity.[14] The hourly cost estimate for childcare was derived from the Dutch National Institute for Family Finance Information (NIBUD).[17] Travel expenses were calculated for healthcare visits, surgical procedures and hospitalizations following the Dutch guideline for pharmacoeconomic evaluation.[14]

The most relevant cost estimates are given in Table 1; a comprehensive overview can be found in Appendix Table.

Statistical analysis

We used a short time horizon for all analyses and therefore took no discount rate into account. First, we compared the clinical effectiveness of the study groups by 1) calculating

the risk differences (RD), with 95% confidence intervals (CI) and numbers needed to treat (NNT), for otoscopic presence of otorrhea at 2 weeks (short-term clinical outcome), and by 2) calculating the differences in mean number of days with otorrhea, with 95% CIs, at 6 months follow-up (long-term clinical outcome).
Second, we compared the costs within the 3 study-groups by calculating mean costs per patient, with standard errors (SE), in both the short- (2 weeks) and long-term (6 months).
Third, we compared differences in costs between groups to differences in clinical effects between groups, by calculating incremental cost-effectiveness ratios (iCERs) from a societal perspective. Short-term cost-effectiveness was expressed as the costs to treat the number of patients needed to prevent one case of otorrhea at 2 weeks as assessed otoscopically. Long-term cost-effectiveness was expressed as cost per day with otorrhea avoided at 6 months follow-up as reported by parents in the diary. Uncertainty for long-term costs and effects was addressed in probabilistic sensitivity analysis using bootstrapping techniques with 2000 replicates. Results of this analysis were plotted in a cost-effectiveness plane. All analyses were performed on an intention-to-treat basis, for which we used SPSS version 20 (SPSS, Chicago, IL) and R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Cost estimates used in this study, in Euros, Pounds Sterling and US Dollars for 2009.

Resources	Cost estimate			Source
	€	UK£[i]	US$[i]	
Tube removal/reinsertion	380.47	337.90	548.11	Cost study
Tube insertion and adenoidectomy	717.02	636.79	1032.94	
Tube insertion and tonsillectomy	738.25	655.64	1063.52	
Adenotonsillectomy	379.01	336.60	546.00	
Hospitalization (per day)				Guideline
Short stay (1 day)	251.00	222.91	361.59	
Long stay (>1 day)	457.00	405.86	658.35	
Healthcare visit				Guideline
ENT surgeon	72.00	63.94	103.72	
Family physician	28.00	24.87	40.34	
Other medical professional	See appendix			
Healthcare telephone consultation				Guideline
ENT surgeon	36.00	31.97	51.86	
Family physician	14.00	12.43	20.17	
Other healthcare professional	See appendix			
Medication				Dutch formulary
Hydrocortisone-bacitracin-colistin eardrops	9.88	8.77	14.23	
Oral amoxicillin-clavulanate suspension	2.47	2.19	3.56	
Other medication	See appendix			
Pharmacist fee (per prescription)	5.50	4.88	7.92	Guideline
Over-the-counter and complementary and alternative medicines	See appendix			Retail prices
Travel expenses (per hospital visit)	5.80	5.15	8.36	Guideline
Parental time off work (per hour)[ii]	26.37	23.42	37.99	Guideline
Childcare (per hour)	5.00	4.44	7.20	NIBUD

i = the exchange rate of December 31, 2009, was used to convert cost estimates in Euros to UK Pound Sterling (€1 = £0.8881) and US Dollars (€1 = US$1.4406)[18]; ENT = ear, nose and throat; ii = mean productivity loss employee aged 25-35 years.

Results

Study population

Between June 2009 and May 2012, 230 children with acute tympanostomy-tube otorrhea were randomly assigned to either antibiotic-glucocorticoid eardrops (76 children), oral antibiotics (77 children) or initial observation (77 children). Their mean age was 4.5 years (SD: 2.0). Demographic and clinical characteristics of the three study-groups at baseline were comparable and are described in more detail elsewhere.[12]

Completeness of data

At 2 weeks clinical outcomes and parental diaries including resource use data were available for 227 of the 230 children (99%) (Appendix Figure). At 6 months, 221 parental diaries (96%) were available.

Clinical outcomes

Antibiotic-glucocorticoid eardrops were superior to oral antibiotics and initial observation both at 2 weeks and 6 months (Table 2). At 2 weeks, 5% of children treated with eardrops had otorrhea versus 44% of those treated with oral antibiotics (absolute risk difference [RD]: -39%, 95% confidence interval [CI] -51% to -26%) and 55% of those allocated to initial observation (RD: -49%, 95% CI: -62% to -37%). At 6 months, the mean number of days with otorrhea was 10 in children treated with eardrops versus 16 in those treated with oral antibiotics (mean difference: -6.5, 95% CI: -10.4 to -2.6) and 24 in those allocated to initial observation (mean difference: -14.2, 95% CI: -20.4 to -8.1).

Costs

Mean costs per patient were lower in children treated with antibiotic-glucocorticoid eardrops than in those receiving oral antibiotics or initial observation in both the short- and long-term (Tables 3 and 4). At 2 weeks, the mean total costs per patient were €29.45 (SE: 3.42) for antibiotic-glucocorticoid eardrops, €49.01 (SE: 13.38) for oral antibiotics and €56.94 (SE: 12.92) for initial observation (Table 3). Mean total healthcare costs were €25.57 (SE: 2.97), €22.79 (SE: 3.60) and €30.42 (SE: 4.61), respectively. Non-healthcare costs constituted almost half of the total costs in children treated with oral antibiotics and initial observation.

At 6 months, the mean total costs per patient were €255.59 (SE: 354.07) for antibiotic-glucocorticoid eardrops, €292.05 (SE: 470.14) for oral antibiotics and €444.56 (SE: 644.91) for initial observation (Table 4). Mean total healthcare costs were €203.16 (SE: 275.23), €204.66 (SE: 296.59) and €349.93 (SE: 586.09), respectively. Non-healthcare costs contributed to 20% to 30% of the total costs.

Balancing effects and costs

Treatment with antibiotic-glucocorticoid eardrops is both clinically superior and has economic benefits over oral antibiotics and initial observation. Because of this dominance, calculating iCERs is redundant.

The cost-effectiveness plane resulting from the probabilistic sensitivity analyses over 6 months show eardrops to be superior in terms of clinical effectiveness in 100% of the

Table 2. Clinical effectiveness of treatment strategies.

Clinical outcome measures	Antibiotic-glucocorticoid eardrops (n=76)	Oral antibiotics (n=77)	Initial observation (n=77)	Antibiotic-glucocorticoid eardrops versus initial observation	Antibiotic-glucocorticoid eardrops versus oral antibiotics	Oral antibiotics versus initial observation
At 2 weeks follow-up[i]						
Number of children	75	77	75			
Children with otorrhea, n/total (%)	4 (5)	34 (44)	41 (55)			
Absolute risk difference, % (95% CI)				49 (37 to 62)	39 (26 to 51)	11 (-6 to 27)[ii]
NNT				2	3	10
During 6 months follow-up[iii]						
Number of children	74	74	73			
Total number of days with otorrhea, mean (95% CI)	9.9 (7.4 to 12.3)	16.4 (13.3 to 19.4)	24.1 (18.4 to 29.8)			
Differences in mean (95% CI)				14.2 (8.1 to 20.4)	6.5 (2.6 to 10.4)	7.7 (1.3 to 14.2)

n = number; i = assessed by physician; CI = confidence interval; ii = short-term diary of one child was missing for whom we did have a primary outcome assessment, so results are slightly different from our previous publication[12]; NNT = number needed to treat; iii = as reported in parental diary. No rounding was used in the difference calculations.

Table 3. Use of resources and mean costs (in Euros) per child during 2 weeks follow-up.

Resources	Treatment					
	Antibiotic-glucocorticoid eardrops (n=75)		Oral antibiotics (n=77)		Initial observation (n=76)	
	Mean number used (SE)	Mean costs € (SE)	Mean number used (SE)	Mean costs € (SE)	Mean number used (SE)	Mean costs € (SE)
Intervention costs		**15.38 (0)**		**7.97 (0)**		**0.00 (0)**
Study medication	1.0 (0)	9.88 (0)	1.0 (0)	2.47 (0)	0.00 (0)	0.00 (0)
Pharmacist fee	1.0 (0)	5.50 (0)	1.0 (0)	5.50 (0)	0.00 (0)	0.00 (0)
Direct healthcare costs		**10.18 (2.97)**		**14.82 (3.60)**		**30.42 (4.61)**
Tube removal/reinsertion	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Tube insertion and adenoidectomy	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Tube insertion and tonsillectomy	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Adenotonsillectomy	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Hospitalization (days)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Healthcare visit						
ENT surgeon	0.04 (0.02)	2.88 (1.64)	0.04 (0.02)	2.81 (1.60)	0.13 (0.04)	9.47 (2.81)
Family physician	0.11 (0.04)	3.84 (1.43)	0.14 (0.04)	5.42 (1.83)	0.34 (0.07)	10.62 (2.15)
Other healthcare professional	0.01 (0.01)	2.01 (2.01)	0.03 (0.03)	1.87 (1.87)	0.00 (0)	0.00 (0)
Healthcare telephone consultation						
ENT surgeon	0.00 (0)	0.00 (0)	0.05 (0.03)	1.87 (1.13)	0.16 (0.05)	5.68 (1.79)
Family physician	0.03 (0.02)	0.37 (0.26)	0.08 (0.03)	1.09 (0.43)	0.13 (0.04)	1.84 (0.55)
Other healthcare professional	0.01 (0.01)	0.24 (0.24)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Medication						
Antibiotic(-glucocorticoid) eardrops (weeks prescribed)	0.00 (0)	0.00 (0)	0.08 (0.03)	0.64 (0.26)	0.12 (0.04)	1.03 (0.33)
Oral antibiotics (weeks prescribed)	0.03 (0.02)	0.05 (0.03)	0.00 (0)	0.00 (0)	0.12 (0.04)	0.20 (0.07)
Other medication	-	0.50 (0.50)	-	0.48 (0.37)	-	0.12 (0.06)
Pharmacist fee	0.05 (0.03)	0.29 (0.18)	0.12 (0.04)	0.64 (0.23)	0.26 (0.06)	1.45 (0.33)

Direct non-healthcare costs		**0.72 (0.19)**		**2.93 (1.07)**		**6.75 (2.71)**
Over-the-counter medicines						
Analgesics (days used)	0.61 (0.15)	0.09 (0.02)	1.05 (0.20)	0.19 (0.05)	1.59 (0.33)	0.20 (0.04)
Nasal sprays (bottles)	0.13 (0.04)	0.27 (0.09)	0.25 (0.06)	0.56 (0.13)	0.26 (0.06)	0.57 (0.13)
Cough medicines (days used)	0.21 (0.09)	0.06 (0.03)	0.26 (0.10)	0.05 (0.02)	0.63 (0.23)	0.12 (0.04)
Complementary and alternative medicines (days used)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.16 (0.10)	0.03 (0.02)
Childcare (hours)	0.00 (0)	0.00 (0)	0.35 (0.21)	1.75 (1.04)	1.01 (0.54)	5.07 (2.71)
Travel expenses (hospital visits)	0.05 (0.03)	0.31 (0.15)	0.06 (0.03)	0.38 (0.20)	0.13 (0.04)	0.76 (0.23)
Indirect non-healthcare costs		**3.16 (1.73)**		**23.29 (12.36)**		**19.78 (9.44)**
Parental time off work (hours)	0.12 (0.07)	3.16 (1.73)	0.88 (0.47)	23.29 (12.36)	0.75 (0.36)	19.78 (9.44)
Total costs		**29.45 (3.42)**		**49.01 (13.38)**		**56.94 (12.92)**
Total healthcare costs		25.57 (2.97)		22.79 (3.60)		30.42 (4.61)
Total non-healthcare costs		3.88 (1.74)		26.22 (12.75)		26.52 (10.44)

n = number, SE = standard error; ENT = ear, nose and throat

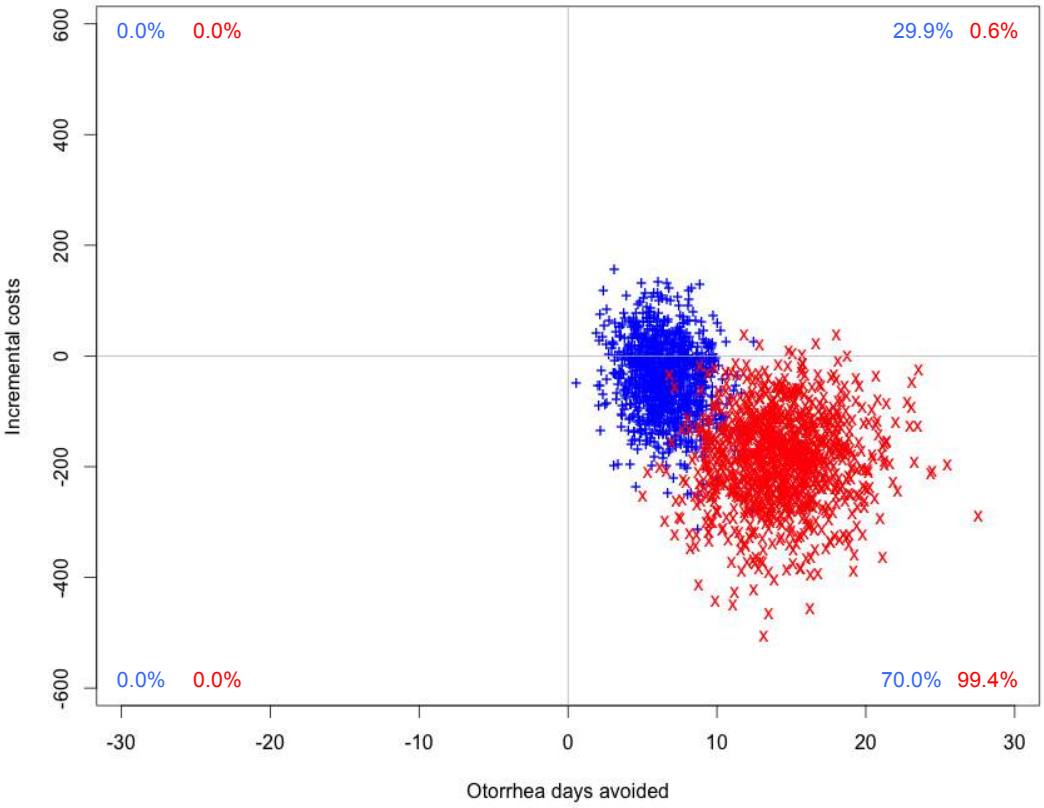
Table 4. Use of resources and mean costs (in Euros) per child during 6 months follow-up.

Resources	Treatment					
	Antibiotic-glucocorticoid eardrops (n=74)		Oral antibiotics (n=74)		Initial observation (n=73)	
	Mean number used (SE)	Mean costs € (SE)	Mean number used (SE)	Mean costs € (SE)	Mean number used (SE)	Mean costs € (SE)
Intervention costs		**15.38 (0)**		**7.97 (0)**		**0.00 (0)**
Study medication	1.0 (0)	9.88 (0)	1.0 (0)	2.47 (0)	0.00 (0)	0.00 (0)
Pharmacist fee	1.0 (0)	5.50 (0)	1.0 (0)	5.50 (0)	0.00 (0)	0.00 (0)
Direct healthcare costs		**187.78 (275.23)**		**196.69 (296.59)**		**349.93 (586.09)**
Tube removal/reinsertion	0.11 (0.04)	41.13 (118.95)	0.09 (0.04)	35.99 (128.58)	0.15 (0.05)	57.33 (151.01)
Tube insertion and adenoidectomy	0.03 (0.02)	19.38 (117.07)	0 (0)	0 (0)	0 (0)	0 (0)
Tube insertion and tonsillectomy	0.01 (0.01)	9.98 (85.82)	0 (0)	0 (0)	0 (0)	0 (0)
Adenotonsillectomy	0.01 (0.01)	5.12 (44.06)	0 (0)	0 (0)	0.01 (0.01)	5.19 (44.36)
Hospitalization (days)	0.04 (0.04)	18.53 (159.38)	0.07 (0.05)	30.88 (190.33)	0.18 (0.13)	70.10 (488.59)
Healthcare visit						
ENT surgeon	0.55 (0.09)	39.89 (54.80)	0.80 (0.12)	57.41 (72.47)	1.11 (0.15)	79.89 (89.45)
Family physician	0.64 (0.12)	22.31 (35.48)	0.81 (0.12)	28.82 (47.68)	1.55 (0.23)	55.47 (77.05)
Other healthcare professional	0.16 (0.05)	10.41 (33.18)	0.22 (0.08)	11.15 (34.51)	0.44 (0.18)	23.66 (83.33)
Healthcare telephone consultation						
ENT surgeon	0.16 (0.06)	5.84 (17.90)	0.31 (0.07)	11.19 (21.42)	0.62 (0.11)	22.19 (33.74)
Family physician	0.26 (0.06)	4.04 (9.24)	0.43 (0.08)	6.35 (11.06)	0.53 (0.11)	8.23 (13.75)
Other healthcare professional	0.01 (0.01)	0.24 (2.09)	0 (0)	0 (0)	0.04 (0.03)	0.96 (5.76)
Medication						
Antibiotic(-glucocorticoid) eardrops (weeks prescribed)	0.50 (0.10)	3.93 (7.47)	0.99 (0.16)	7.08 (9.35)	1.37 (0.18)	11.71 (13.91)
Oral antibiotics (weeks prescribed)	0.45 (0.26)	0.66 (2.69)	0.27 (0.12)	0.46 (1.64)	1.15 (0.31)	1.85 (3.33)
Other medication	-	1.26 (4.87)	-	0.45 (1.47)	-	1.08 (5.00)
Pharmacist fee	0.92 (0.15)	5.05 (6.98)	1.26 (0.18)	6.91 (8.40)	2.23 (0.25)	12.28 (11.61)

Direct non-healthcare costs		**10.03 (19.49)**		**17.19 (33.39)**		**25.64 (38.05)**
Over-the-counter medicines						
Analgesics (days used)	3.19 (0.57)	0.46 (0.65)	4.12 (0.88)	0.51 (0.85)	5.74 (1.10)	0.80 (1.38)
Nasal sprays (bottles)	0.68 (0.17)	1.44 (3.01)	0.82 (0.17)	1.86 (3.46)	1.55 (0.39)	3.32 (7.18)
Cough medicines (days used)	1.77 (0.41)	0.29 (0.61)	0.84 (0.27)	0.14 (0.39)	2.49 (0.65)	0.54 (1.34)
Complementary and alternative medicines (days used)	0.24 (0.13)	0.03 (0.19)	0.15 (0.09)	0.02 (0.13)	0.82 (0.34)	0.14 (0.58)
Childcare (hours)	0.53 (0.35)	2.64 (14.99)	1.57 (0.66)	7.84 (28.21)	1.97 (0.79)	9.86 (33.73)
Travel expenses (hospital visits)	0.89 (0.13)	5.17 (6.55)	1.18 (0.20)	6.82 (9.90)	1.89 (0.32)	10.96 (15.99)
Indirect non-healthcare costs		**42.41 (140.88)**		**70.20 (227.94)**		**69.00 (179.42)**
Parental time off work (hours)	1.61 (0.62)	42.41 (140.88)	2.66 (1.00)	70.20 (227.94)	2.62 (0.80)	69.00 (179.42)
Total costs		**255.59 (354.07)**		**292.05 (470.14)**		**444.56 (644.91)**
Total healthcare costs		203.16 (275.23)		204.66 (296.59)		349.93 (586.09)
Total non-healthcare costs		52.43 (152.71)		87.39 (249.41)		94.63 (188.41)

N = number, SE = standard error; ENT = ear, nose and throat

Figure 1. Cost-effectiveness plane, showing incremental costs (in Euros) and effects (in otorrhea days avoided) of antibiotic-glucocorticoid eardrops versus oral antibiotics (blue) and versus initial observation (red) during 6 months follow-up, with percentages of bootstrap samples per quadrant.



bootstrap samples, with lower costs as compared to oral antibiotics and initial observation in 71% and 99% of the bootstrap samples, respectively (Figure 1).

Discussion

In children developing acute tympanostomy-tube otorrhea, antibiotic-glucocorticoid eardrops are clinically superior and have economic benefits over oral antibiotics and initial observation in both the short- and long-term. Non-healthcare costs constitute a substantial proportion of the total costs of tube otorrhea

We are the first to present cost-effectiveness of common treatment strategies in children with tube otorrhea. This economic evaluation was conducted alongside a pragmatic randomized trial, which is considered the best approach for economic evaluations.[19] Adherence to the allocated treatment strategies in the first 2 weeks was high and we were able to include almost all (99% of randomized children in the short-term and 97% in the long-term) of included children in the cost-effectiveness analysis.

Some aspects of our study deserve further attention. First, hydrocortisone-bacitracin-colistin eardrops are not routinely available in most countries. We believe that the clinical effectiveness of any combination of antibiotic-glucocorticoid eardrops with a similar antimicrobial activity profile would have been alike.[12] Second, the healthcare costs of all treatment strategies may be somewhat higher than reported because we did not include data on diagnostic procedures (e.g. otorrhea cultures, audiometry) during follow-up. As the number of diagnostic procedures will be related to persistence of symptoms, the true difference in costs between the groups may be even larger than currently reported. Third, we chose to balance the societal costs with clinical outcomes instead of quality adjusted life years. Usually the EQ-5D is used in economic evaluations to assess HRQoL, but it was originally designed for use in adult populations aged 18 and over.[20] When our trial started, no suitable questionnaire was available for children to self-report their generic HRQoL. Other available questionnaires, such as the child health questionnaire and otitis media-6 questionnaire, as well as the recently developed EQ-5D Youth require collection by proxy in children below 8 years of age and therefore do not provide direct HRQoL outcomes, but observational assessment of a child's functioning.[21,22] Still, such indirect HRQoL outcomes would not have changed our conclusions since these also favored antibiotic-glucocorticoid eardrops in children with tube otorrhea.[12] Lastly, as recommended in economic evaluations, we included all health care resource use, including surgery and hospitalization, although these may not be directly related to the initial treatment strategies. Since these costs were higher in the children treated with eardrops than in those treated with oral antibiotics, and comparable to those allocated to initial observation, a different approach would not have altered our conclusions.

Conclusion

Antibiotic-glucocorticoid eardrops are clinically superior and have economic benefits over oral antibiotics and initial observation in children with acute tympanostomy-tube otorrhea.

References

1. Dutch Hospital Data (Landelijke medische registratie). 2010.
2. Health & Social Care Information Centre, United Kingdom. (Accessed at http://www.hscic.gov.uk)
3. Cullen K, Hall M, Golosinskiy A. Ambulatory Surgery in the United States, 2006. National health statistics reports; no 11. Revised. In. Hyattsville, MD: National Center for Health Statistics; 2009.
4. van Dongen TM, van der Heijden GJ, Freling HG, et al. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. PLoS One 2013;8:e69062.
5. Gates GA. Cost-effectiveness considerations in otitis media treatment. Otolaryngol Head Neck Surg 1996;114:525-30.
6. Bondy J, Berman S, Glazner J, et al. Direct expenditures related to otitis media diagnoses: extrapolations from a pediatric medicaid cohort. Pediatrics 2000;105:E72.
7. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization and costs for acute otitis media in children. Laryngoscope 2014;124:301-5.
8. Roland PS, Waycaster CR, Wall GM, et al. An economic evaluation of two ototopical treatments for acute otitis media in tympanostomy tube patients. Value Health 2006;9:219-26.
9. Alsarraf R, Jung CJ, Perkins J, et al. Measuring the indirect and direct costs of acute otitis media. Arch Otolaryngol Head Neck Surg 1999;125:12-8.
10. Capra AM, Lieu TA, Black SB, et al. Costs of otitis media in a managed care population. Pediatr Infect Dis J 2000;19:354-5.
11. Niemela M, Uhari M, Mottonen M, et al. Costs arising from otitis media. Acta Paediatr 1999;88:553-6.
12. van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med 2014;370:723-33.
13. Statistics Netherlands. (Accessed at http://statline.cbs.nl.)
14. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg [in Dutch]. Diemen, the Netherlands: College voor zorgverzekeringen. ; 2010.
15. College voor Zorgverzekeringen (CVZ). Farmacotherapeutisch Kompas; 2009.
16. Buskens E, van Staaij B, van den Akker J, et al. Adenotonsillectomy or watchful waiting in patients with mild to moderate symptoms of throat infections or adenotonsillar hypertrophy: a randomized comparison of costs and effects. Arch Otolaryngol Head Neck Surg 2007;133:1083-8.
17. National Institute for Family Finance Information (NIBUD) web site [in Dutch]. (Accessed February, 2013, at http://www.nibud.nl/uitgaven/kinderen/oppas.html.)
18. European Central Bank. Euro Exchange Rates USD. (Accessed February, 2013, at http://www.ecb.int/stats/exchange/eurofxref/html/index.en.html.)
19. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health 2005;8:521-33.
20. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
21. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res 2010;19:875-86.
22. Brouwer CN, Maille AR, Rovers MM, et al. Health-related quality of life in children with otitis media. Int J Pediatr Otorhinolaryngol 2005;69:1031-41.

Appendix chapter 3.2

Appendix Table [Part 1/2]. All cost estimates used in this study, in Euros, British Pounds and US Dollars for 2009.

Resources	Cost estimate			Source
	€	£[i]	US$[i]	
Tube removal/reinsertion	380.47	337.90	548.11	Cost study
Tube insertion and adenoidectomy	717.02	636.79	1032.94	
Tube insertion and tonsillectomy	738.25	655.64	1063.52	
Adenotonsillectomy	379.01	336.60	546.00	
Hospitalization per day				Guideline
Short stay (1 day)	251.00	222.91	361.59	
Long stay (>1 day)	457.00	405.86	658.35	
Healthcare visit				Guideline
Specialist	72.00	63.94	103.72	
Family physician	28.00	24.87	40.34	
Family physician out of office hours	77.20	68.56	111.21	
Audiologist	36.00	31.97	51.86	
Dietician	27.00	23.98	38.90	
Medical psychologist	80.00	71.05	115.25	
Speech therapist	33.00	29.31	47.54	
Emergency room	151.00	134.10	217.53	
Healthcare telephone consultation				Guideline
Specialist	36.00	31.97	51.86	
Family physician	14.00	12.43	20.17	
Family physician out of office hours	38.60	34.28	55.61	
Audiologist	18.00	15.99	25.93	
Dietician	14.00	12.43	20.17	
Medical psychologist	40.00	35.52	57.62	
Speech therapist	17.00	15.10	24.49	
Emergency room	76.00	67.50	109.49	
Medication[ii, iii]				Dutch formulary
Oral antibiotics, estimate per course				
Amoxicillin-clavulanate suspension	2.47	2.19	3.56	
Trimethoprim/sulfamethoxazole suspension	1.05	0.93	1.51	
Amoxicillin suspension	1.76	1.56	2.54	
Claritromycin suspension	2.54	2.26	3.66	
Azitromycin suspension (per 3 days)	2.54	2.26	3.66	
Nitrofurantoin suspension	4.62	4.10	6.66	
Erythromycin suspension	6.71	5.96	9.67	
Oral antibiotics, not specified	1.76	1.56	2.54	
Antibiotic(-glucocorticoid) drops, estimate per course				
Hydrocortisone-bacitracin-colistin eardrops	9.88	8.77	14.23	
Dexamethasone-framycetin-gramicidin eardrops	7.74	6.87	11.15	
Neomycin-hydrocortisone-polymyxin B eardrops	4.72	4.19	6.80	
Dexamethasone-chloramphenicol-polymyxin B eardrops	1.55	1.38	2.23	
Neomycin-fludrocortisone-polymyxin B eardrops	2.85	2.53	4.11	
Oxytetracycline-hydrocortisone-polymyxin B eardrops	4.69	4.17	6.76	
Tobramycin-dexamethasone drops	4.55	4.04	6.55	
Ofloxacin eye-drops	3.01	2.67	4.34	
Chloramphenicol eye-drops	1.92	1.71	2.77	
Trimethoprim-polymyxin B drops	4.11	3.65	5.92	

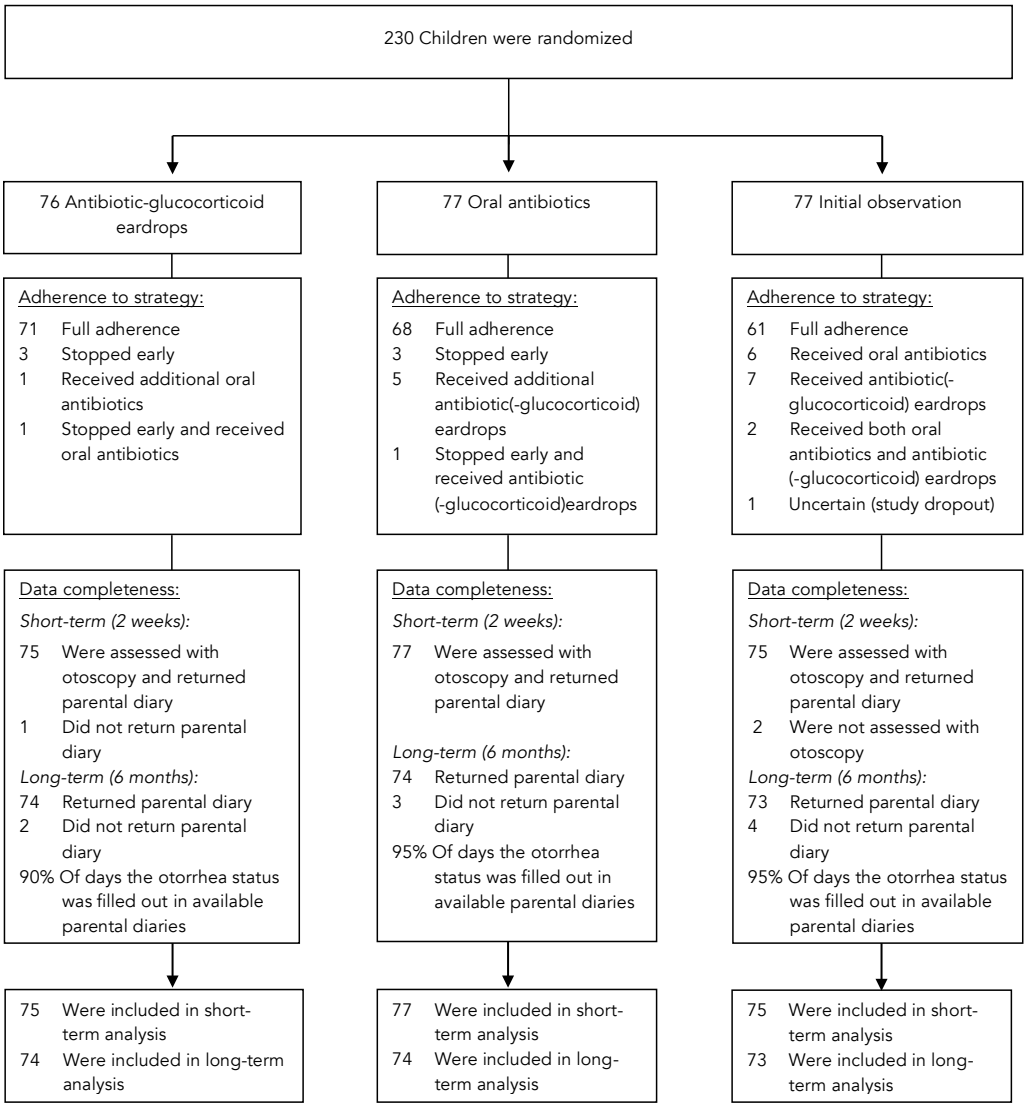
i = the exchange rate of December 31, 2009, was used to convert cost estimates in Euros to Pounds Sterling (€1 = £0.8881) and US Dollars (€1 = US$1.4406)[18]; ii = dosages were estimated by using the mean age and/or weight of the trial participants (4.5 years; 18 kilograms); iii = costs including 6% taxes.

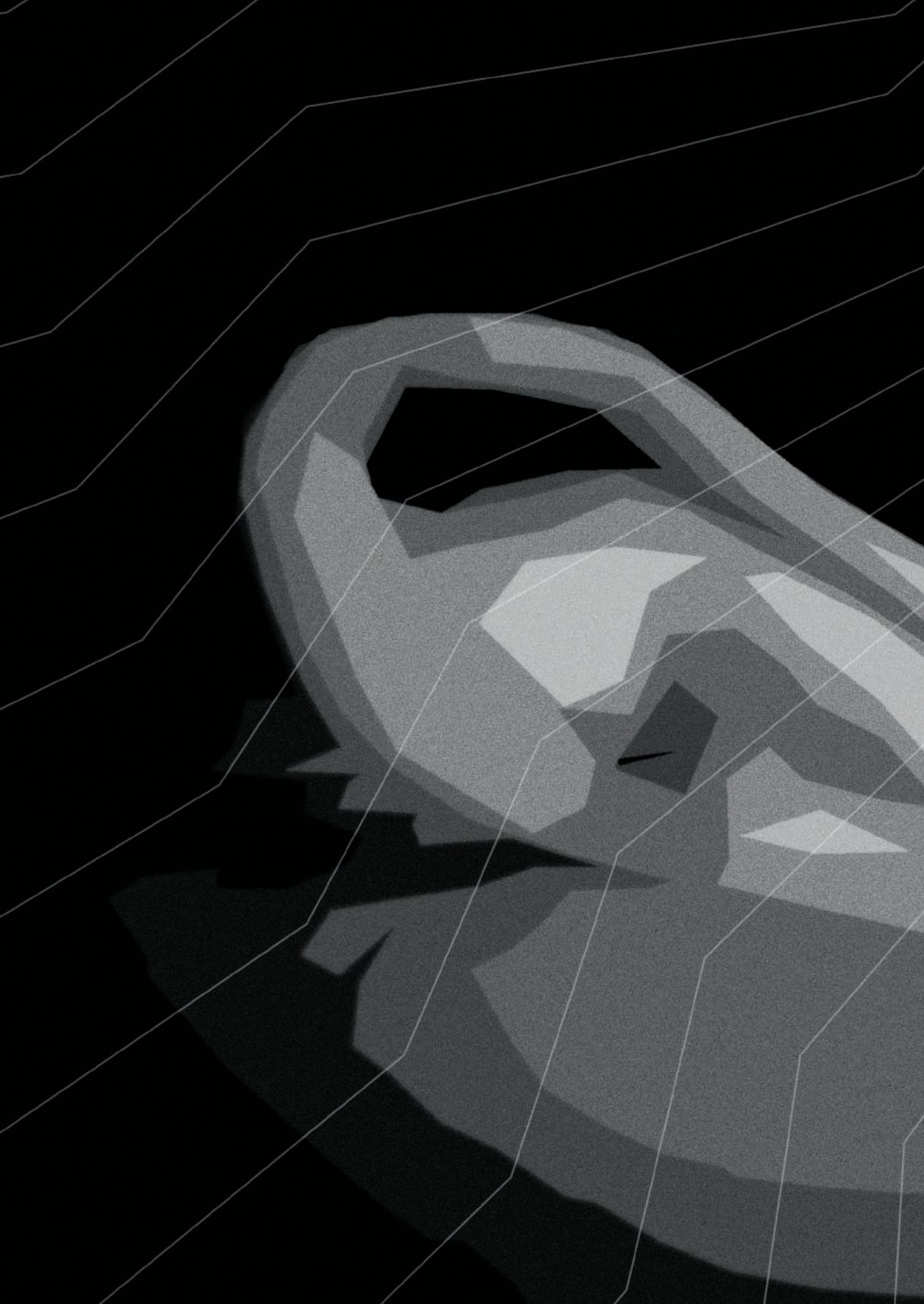
Appendix Table [Part 2/2]. All cost estimates used in this study, in Euros, British Pounds and US Dollars for 2009.

Resources	Cost estimate			Source
	€	£[i]	US$[i]	
Antibiotic(-glucocorticoid) drops, estimate per course [continued]				Dutch formulary
Fusidic acid eye-drops	4.04	3.59	5.82	
Antibiotic(-glucocorticoid) eardrops, not specified	8.81	7.82	12.69	
Other topical treatments, estimate per course				
Acetic acid eardrops	0.61	0.54	1.21	
Aluminium acetotartrate eardrops	3.95	3.51	5.69	
Levocabastine eye-drops	5.28	4.69	7.61	
Ketoconazole cream	6.61	5.87	9.52	
Fucidin cream	3.24	2.88	4.67	
Mupirocin ointment	3.26	2.90	4.70	
Hydrocortisone cream	0.44	0.39	0.63	
Triamcinolone cream	0.91	0.81	1.31	
Other treatments, estimate per day				
Salbutamol inhaler	0.11	0.10	0.16	
Fluticasone inhaler	0.34	0.30	0.49	
Oral dexamethasone	2.82	2.50	4.06	
Diazepam	0.87	0.77	1.25	
Esomeprazole sachets	0.98	0.87	1.41	
Domperidone suppository	1.87	1.66	2.69	
Deslortadine suspension, per month	8.43	7.49	12.14	
Pharmacist fee (per prescription)	5.50	4.88	7.92	Guideline
Over-the-counter medicines[ii]				Retail prices
Analgesics, per day				
Diclofenac	0.14	0.12	0.20	
Paracetamol	0.09	0.08	0.13	
Paracetamol suppository	0.34	0.30	0.49	
Ibuprofen	0.76	0.67	1.09	
Aspirin	0.65	0.58	0.94	
Lidocaine eardrops	0.61	0.54	0.88	
Nasal sprays, per week				
Xylometazoline	2.65	2.35	3.82	
Saline	2.00	1.78	2.88	
Nasal spray, not specified	2.00	1.78	2.88	
Cough medicines, per day				
Bromhexine	0.08	0.07	0.12	
Codeine syrup	1.20	1.07	1.73	
Acetylcysteine suspension	0.33	0.29	0.48	
Homeopathy, per day				
Throat spray	0.30	0.27	0.43	
Menthol and eucalyptus balm	0.19	0.17	0.27	
Topical drops	0.21	0.19	0.30	
Other, per day				
Vitamin supplements	0.30	0.27	0.43	
Travel expenses to hospital (per visit)	5.80	5.15	8.36	Guideline
Parental time off work (per hour)[iv]	26.37	23.42	37.99	Guideline
Childcare (per hour)	5.00	4.44	7.20	NIBUD

i = the exchange rate of December 31, 2009, was used to convert cost estimates in Euros to Pounds Sterling (€1 = £0.8881) and US Dollars (€1 = US$1.4406)[18]; ii = dosages were estimated by using the mean age and/or weight of the trial participants (4.5 years; 18 kilograms); iii = costs including 6% taxes; iv = mean productivity loss employee aged 25-35 years.

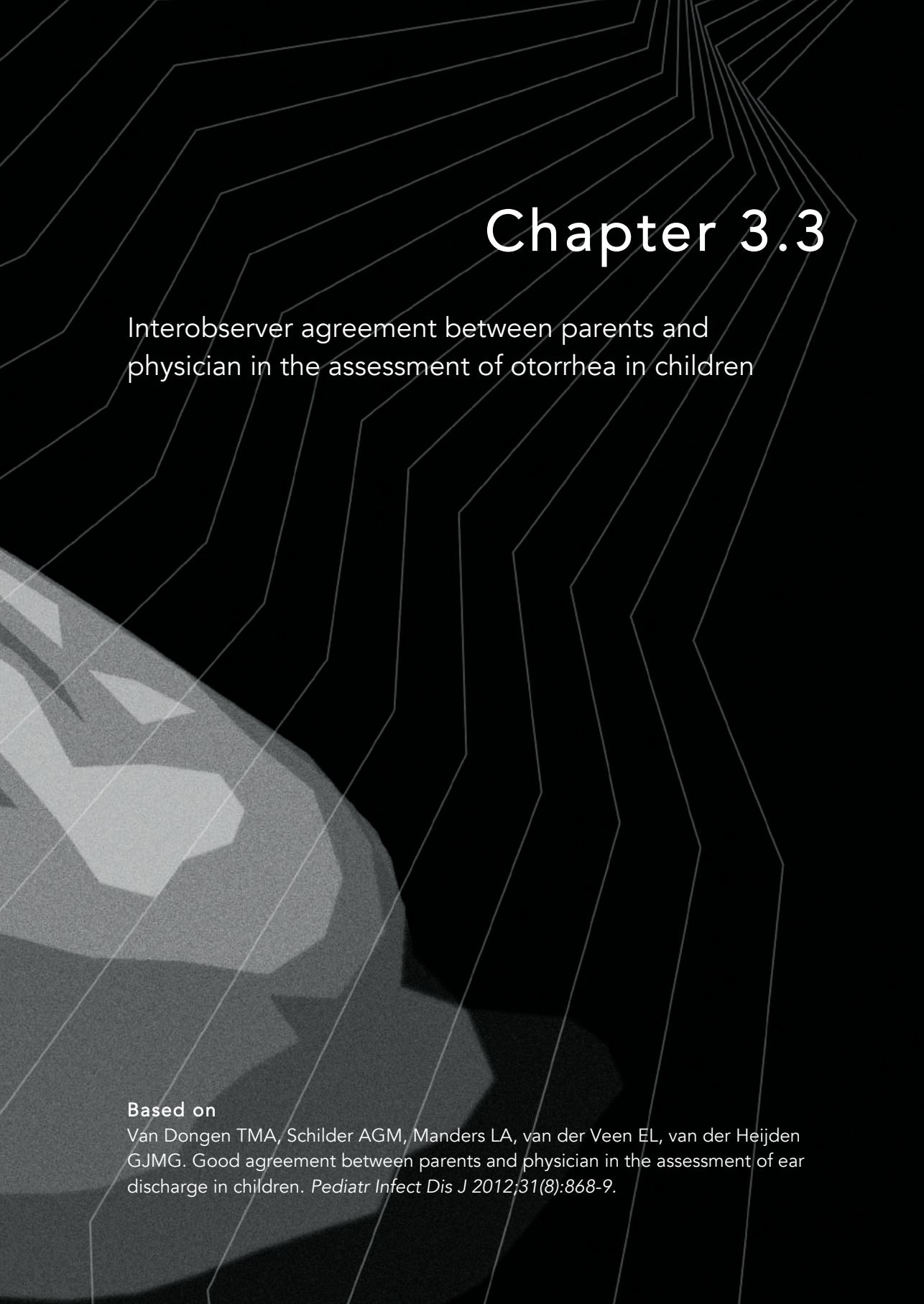
Appendix Figure. Flowchart of participants through trial of treatment of acute tympanostomy-tube otorrhea in children.





Chapter 3.3

Interobserver agreement between parents and physician in the assessment of otorrhea in children



Based on

Van Dongen TMA, Schilder AGM, Manders LA, van der Veen EL, van der Heijden GJMG. Good agreement between parents and physician in the assessment of ear discharge in children. *Pediatr Infect Dis J 2012;31(8):868-9.*

Abstract

Background

Ear discharge, or otorrhea, is a common symptom of otitis media in children. In clinical practice, physicians often rely on parental observation of resolution or persistence of ear discharge in the follow-up after treatment, but little is known about the reliability of this assessment.

Objective

To determine the interobserver agreement between parents and physicians regarding the presence of ear discharge in children, during follow-up after an initial diagnosis of acute or chronic otorrhea.

Methods

Datasets of 2 randomized trials were used including 191 children treated for acute tympanostomy-tube otorrhea (ATTO) and 100 children treated for active chronic mucosal otitis media (COM). Parents documented symptoms of ear discharge in a diary. These diaries were compared to assessments by physicians at planned follow-up visits, using the latter as the reference.

Results

At 2-weeks follow-up for children with ATTO the kappa value was 0.69 and at 6-weeks follow-up for those with COM the kappa value was 0.68, indicating a substantial level of agreement between parents' and physician's assessments. Positive predictive values at these visits were 95% for ATTO and 90% for COM and negative predictive values were 87% for ATTO and 85% for COM.

Conclusions

Parents and physicians agree in most cases about the persistence of ear discharge after treatment of ATTO or COM, suggesting that the need for further treatment can be based on parents' judgement.

Introduction

Ear discharge, or otorrhea, is a common problem during childhood. It is usually a symptom of otitis media (OM), when middle ear secretions drain through a perforation in the tympanic membrane or through a tympanostomy tube into the ear canal.[1] Treatment of otorrhea includes local and systemic antibiotics. In day-to-day practice, follow-up after treatment is often done over the phone. Ear, nose and throat (ENT) surgeons or family physicians then rely on parental observation of resolution or persistence of ear discharge. It is not known however, how well this parental assessment agrees with an actual clinical examination by a physician. Parents base their judgement merely on symptoms and signs while physicians have an otoscope or otomicroscope at their disposal.

The objective of this study is to determine the interobserver agreement between parents and physicians regarding the presence of otorrhea in children, during follow-up after an initial diagnosis of acute or chronic otorrhea.

Materials and methods

Study population

For this study, datasets of 2 randomized trials were used. The first is based on a trial of treatment for acute tympanostomy-tube otorrhea (ATTO). Children aged 1 to 9 years with tympanostomy-tube otorrhea present for no more than 7 days and symptoms having started at least 2 weeks after placement of the tube were included. They were randomized into treatment by oral antibiotics (amoxicillin/clavulanate), ototopical antibiotic-glucocorticoid drops (bacitracin/colistin/hydrocortisone) or watchful waiting strategy. The second dataset is based on a trial on the treatment of active chronic mucosal otitis media (COM).[2] Children aged 1 to 12 years with a documented history of more than 12 weeks of continuous otorrhea through either a tympanic membrane perforation or a tympanostomy tube were included. They were randomized into treatment by oral antibiotics (trimethoprim/sulfamethoxazole) or placebo.

Data sources

Ears of children with unilateral or bilateral ATTO or COM with oto(micro)scopic signs of otorrhea at baseline were included. For the ATTO study, otoscopic observation of otorrhea by the study physician at 2 weeks and 6 months follow-up was compared with parental report of ear discharge as documented in a daily diary. Using otomicroscopy rather than otoscopy, the same comparisons were made for the COM study at 6 and 12 weeks follow-up. For both studies we included assessments by parents and physicians performed on the same day or with a 1-day difference (parents' assessments always preceded the physician's).

Statistical analysis

We determined the 'chance-corrected agreement' between physicians and parents for otorrhea versus no otorrhea. The kappa coefficient expresses the degree of agreement exceeding chance.[3] A kappa value of 1 indicates full agreement, while a value of 0 indicates merely chance. We used the ranges for agreement as suggested by Landis and Koch, with values between 0.41 and 0.60 indicating moderate agreement, 0.61 and 0.80 indicating substantial agreement and 0.81 and 1.00 indicating almost perfect agreement.[4]

Kappa coefficients were calculated for each follow-up visit for the ATTO and COM trials. Using the physician's observation of otorrhea as the reference standard, we also calculated the positive predictive value (PPV) and negative predictive value (NPV) of the parents' assessments. All statistical analyses were performed with SPSS 19.

Results

A total of 291 children were included, 191 of whom were diagnosed with ATTO between July 2009 and November 2011, and 100 with COM between February 2003 and November 2005 (Table 1).

Agreement

The kappa value for the assessments at 2-weeks follow-up of children with ATTO (n = 219 ears) was 0.69 (95% CI: 0.58 ; 0.80) (table 2). This is a substantial strength of agreement according to the criteria of Landis and Koch.[4] At 6-months follow-up (n = 116 ears) the prevalence of otorrhea was very low, resulting in an inaccurate kappa value with a wide confidence interval.

For the children with COM, the kappa value was 0.68 (95% CI: 0.56 ; 0.81) at 6 weeks follow-up (n = 145 ears), again suggesting a substantial strength of agreement. At 12 weeks follow-up (n = 80 ears) the kappa value was 0.54 (95% CI: 0.30 ; 0.78), indicating a moderate strength of agreement.

Predictive values

The positive predictive value (PPV) of the parental assessment of ear discharge was 95.1% (95% CI: 85.7 ; 99.2) at the 2-week follow-up visit for children with ATTO, and 90.0% (95% CI: 78.3 ; 96.8) at the 6-week follow-up visit for children with COM. Negative predictive values at these follow-up visits were 87.1% (95% CI: 81.6 ; 91.5) for ATTO and 84.8% (95% CI: 77.1 ; 90.8) for COM (see table 2). At 6 months and 12 weeks follow-up, the prevalence of otorrhea was low, resulting in inaccurate predictive values.

Table 1. Baseline characteristics of included children in a trial of acute tympanostomy-tube otorrhea and of active chronic mucosal otitis media.

	Acute tympanostomy-tube otorrhea	Active chronic mucosal otitis media
Children, n	191	100
Mean age, years (SD) [range]	4.5 (2.0) [1.0 - 8.7]	4.8 (3.1) [1.0 - 12.1]
1-3 years, n (%)	76 (40)	47 (47)
4-9 years, n (%)	115 (60)	44 (44)
> 9 years, n (%)	0 (0)	9 (9)
Male, n (%)	105 (55)	56 (56)
Sibling(s) with OM history, %	37	36
Parent(s) with OM history, n (%)	55	45
Number of tympanostomy-tube insertions, n (%)		
0	0 (0)	8 (8)
1	144 (75)	55 (55)
2	32 (17)	27 (27)
>2	15 (8)	10 (10)
Bilateral otorrhea, n (%)	29 (15)	46 (46)

n = number; SD = standard deviation, OM = otitis media

Table 2. Interobserver agreement between parents and physician in the assessment of presence of otorrhea in children

	Acute tympanostomy-tube otorrhea		Active chronic mucosal otitis media	
Follow-up visit	2 weeks	6 months	6 weeks	12 weeks
Total ears; n	219	116	145	80
Prevalence otorrhea; %	28	4	36	20
Agreement; %	89	97	86	86
Parents + / Physician +; n	39	1	36	9
Parents + / Physician -; n	2	0	4	4
Parents - / Physician +; n	23	4	16	7
Parents - / Physician -; n	155	111	89	60
Kappa-coefficient (95% CI)	0.69 (0.58 ; 0.80)	0.32 (0 ; 0.80)	0.68 (0.56 ; 0.81)	0.54 (0.30 ; 0.78)
Positive predictive value parents, % (95% CI)	95.1 (85.7 ; 99.2)	100.0*	90.0 (78.3 ; 96.8)	69.2 (42.3 ; 89.3)
Negative predictive value parents, % (95% CI)	87.1 (81.6 ; 91.5)	96.5 (92.1 ; 98.9)	84.8 (77.1 ; 90.8)	89.6 (80.8 ; 95.4)

n = number; CI = confidence interval; * CI could not be calculated

Discussion

Our study shows good agreement between parents and physicians in the assessment of otorrhea during follow-up after treatment of children with ATTO or COM. We found high PPV's indicating that when parents stated that their child's ear still discharged, the physician agreed in almost all cases. The lower NPV's suggest that when parents believed their child's ear to be dry, the physician less often agreed.

In 1997 Browning reported on self-evaluation of otorrhea by adult patients prior to surgery for active chronic otitis media.[5] He compared the frequency of ear discharge as reported by the patient to the physician's opinion of its likelihood. The reported interobserver agreement was lower than in our study; he found a close correlation in 50% of patients, and considerable disagreement in 15%.

When interpreting our findings, some limitations need to be taken into account. First, we performed the analyses per ear rather than per child. Children with bilateral otorrhea at inclusion therefore contributed 2 ears to the follow-up data. Parents may not have assessed both ears of their child independently. We did however find similar results for analyses performed on patient- and ear-level, but due to the smaller sample sizes the confidence intervals were somewhat wider (data not shown). Second, we also included physician's assessments that took place one day after those by the parents. An additional analysis excluding these assessments yielded the same results (data not shown). Third, our datasets allowed for comparisons between parents' and physicians 'assessments of ear discharge during follow-up after treatment of ATTO or COM only. Our findings are therefore not necessarily generalizable to all children presenting with ear discharge. In addition, our data was collected in the context of randomised trials. Parents used a diary for reporting ear discharge after treatment of ATTO or COM. Keeping a diary in the context of randomised trials may imply extra attention by the parents. Compared to daily practice, this may have resulted in more accurate data.

To our knowledge, this is the first study of the agreement between parents' and physician's assessment of ear discharge in children. Given the setting and circumstances of our data collection, we believe that we report accurate data, which allow for conclusions that are applicable to ENT and family practice in the follow-up of otorrhea in children with ATTO and COM.

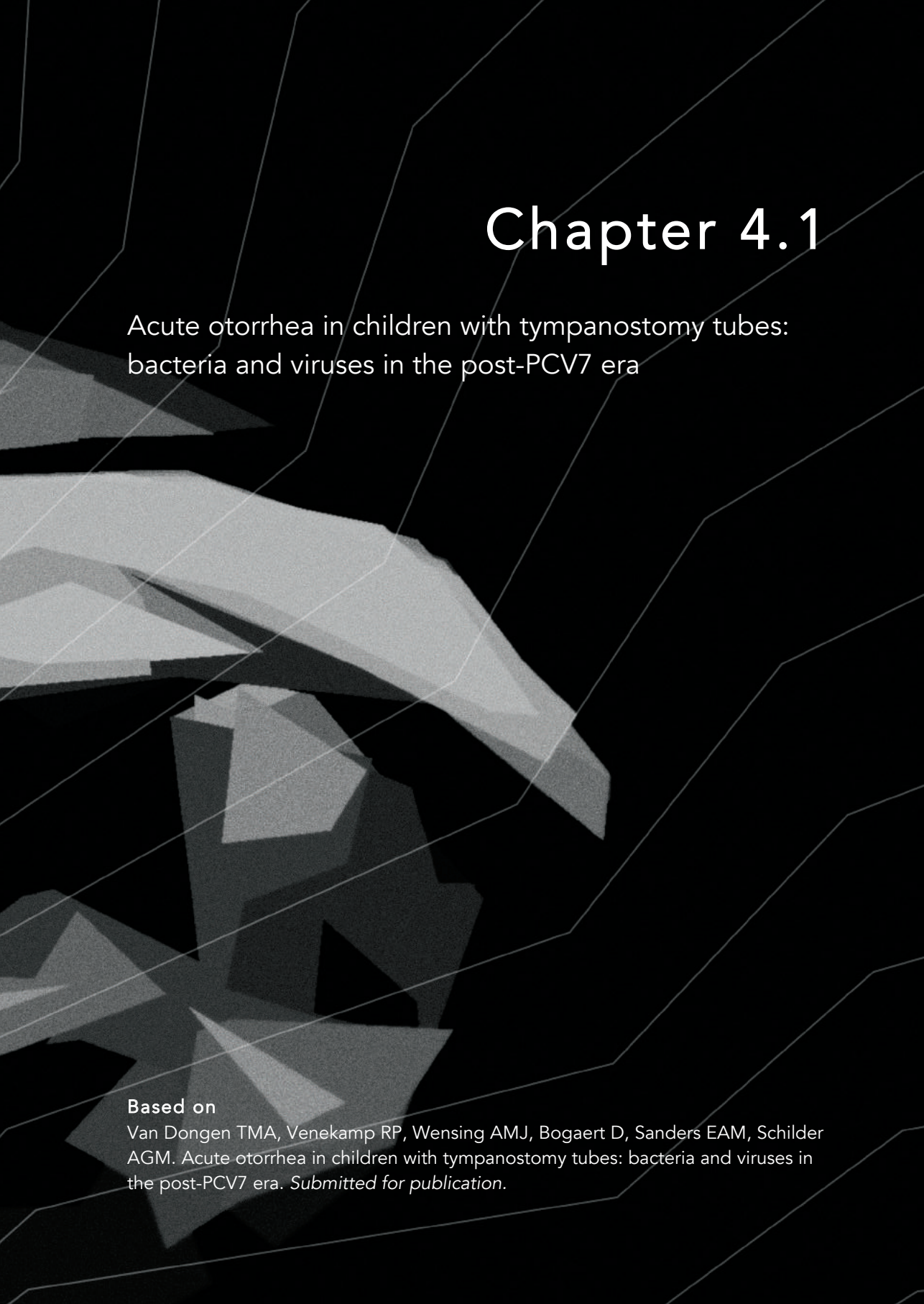
In conclusion, parents and physicians agree in most cases about the persistence of ear discharge after treatment of ATTO or COM, suggesting that the need for further treatment can be based on parents' judgement.

References

1. Rosenfeld RM, Blustone CD. Evidence-Based Otitis Media. 2nd ed. Hamilton,Ontario,Canada: BC Decker Inc.; 2003.
2. Veen van der EL, Rovers MM, Albers FWJ, et al. Effectiveness of trimethoprim/sulfamethoxazole for children with chronic active otitis media: A randomized, placebo-controlled trial. Pediatrics. 2007;119:897-904.
3. Rigby AS. Statistical methods in epidemiology. V. Towards an understanding of the kappa coefficient. Disabil Rehabil. 2000;22:339-44.
4. Landis JR, Koch GG. The measurement of Observer Agreement for Categorial Data. Biometrics. 1977;33:159-74.
5. Browning GG. Do patients and surgeons agree?: the Gordon Smyth Memorial Lecture. Clin Otolaryngol Allied Sci. 1997;22:485-96.

Chapter 4.1

Acute otorrhea in children with tympanostomy tubes: bacteria and viruses in the post-PCV7 era



Based on

Van Dongen TMA, Venekamp RP, Wensing AMJ, Bogaert D, Sanders EAM, Schilder AGM. Acute otorrhea in children with tympanostomy tubes: bacteria and viruses in the post-PCV7 era. *Submitted for publication.*

Abstract

Background

Acute tympanostomy-tube otorrhea (ATTO) is a common sequela in children with tympanostomy tubes. ATTO is generally a symptom of an acute middle ear infection, whereby middle ear fluid drains through the tube. The widespread use of pneumococcal vaccination (PCV) has changed the bacterial prevalence in the upper respiratory tract of children, but its impact on bacterial and viral pathogens causing ATTO is yet unknown.

Methods

This study was performed in the post-PCV7 era parallel to a randomized clinical trial of the clinical and cost-effectiveness of ototopical and systemic antibiotics and initial observation in 230 children aged 1 to 10 years with untreated, uncomplicated ATTO. Otorrhea and nasopharyngeal samples were collected at baseline (before treatment), at 2 weeks (after treatment) and at 6 months. Conventional bacterial culture was performed followed by antimicrobial resistance assessment. Viruses were identified by polymerase chain reaction.

Main results

At baseline, *Haemophilus influenzae* (41%), *Staphylococcus aureus* (40%), and *Pseudomonas aeruginosa* (18%) were the most prevalent bacteria in otorrhea, followed by *Streptococcus pneumoniae* (7%) and *Moraxella cattarhalis* (4%). Most pneumococci were non-PCV7 serotypes. Viruses were detected in 45 otorrhea samples at baseline (21%). Most infections were polymicrobial and overall antimicrobial resistance was low.

Conclusions

H. influenza, *S. aureus* and *P. aeruginosa* are the most common microorganisms in children with untreated ATTO. Prevalence of *S. pneumonia* has decreased since the introduction of PCV and most pneumococci are non-vaccine serotypes.

Introduction

Insertion of tympanostomy tubes is one of the most frequently performed surgical procedures in children.[1,2] Whilst aimed at managing otitis media, up to 67% of children with tubes develop episodes of acute tympanostomy-tube otorrhea (ATTO) in the year following placement.[3] ATTO is generally a symptom of an acute middle ear infection, whereby middle ear fluid drains through the tube. Bacteria involved in ATTO include those most commonly found in AOM (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella cattarhalis*) and also *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[4-11] The introduction of pneumococcal conjugate vaccination (PCV) in the past decade, has changed the prevalence of bacteria in the upper respiratory tract of both healthy children and those with AOM; *S. pneumoniae* has decreased while *H. influenzae* and *S. aureus* are increasingly detected.[12-23] So far, it is unknown whether such changes are reflected in children with ATTO.

We therefore evaluated the presence of bacteria and viruses and bacterial susceptibility to antibiotics, before and after treatment, in otorrhea and the nasopharynx of children with ATTO who participated in a randomized clinical trial of treatment for ATTO performed in the Netherlands after introduction of PCV.

Materials and methods

Population characteristics

This study was conducted in the Netherlands between June 2009 and May 2012 parallel to an open label randomized clinical trial of treatment for ATTO.[24] Children aged 1 to 10 years with tympanostomy-tube otorrhea present for a maximum of 7 days were included and randomly allocated to hydrocortisone-bacitracin-colistin eardrops (76 children), oral amoxicillin-clavulanate suspension (77 children) or initial observation (77 children). We excluded children with fever (body temperature of 38.5°C or higher), children who developed otorrhea within 14 days after tube placement, those who had used antibiotics in the previous 14 days, and children who had experienced an episode of otorrhea in the previous 28 days, or 3 or more otorrhea episodes in the previous 6 months or 4 or more episodes in the previous year. We also excluded children with Down's syndrome, craniofacial anomalies, a known immunodeficiency, and children with an allergy for any of the study medications. The study was approved by the University Medical Center Utrecht medical ethics committee. The methodology is reported in more detail elsewhere.[24] Vaccination with CRM197-conjugated 7-valent pneumococcal vaccine (PCV-7, Prevenar®, Pfizer Pharmaceuticals) was introduced in the Dutch National Vaccination Program in June 2006 and was recommended for all infants born April 1, 2006 and onwards, at 2, 3, 4, and 11 months of age. In 2011 this vaccine was replaced by the 10-valent pneumococcal vaccine conjugated to protein D, which is a surface lipoprotein of nontypeable *H. influenzae* (PD-PCV-10, Synflorix®, GlaxoSmithKline), for all children born March 1, 2011 and onwards.

Collection of specimens

The study physician took otorrhea and nasopharyngeal samples at baseline (before treatment was initiated) and at follow-up visits at 2 weeks and 6 months, using a flexible applicator swab with flocked nylon fiber tip (ESwab, Copan Diagnostics Inc., California,

USA). Otorrhea was sampled by swabbing the discharge in the external ear canal while avoiding skin contact. Nasopharyngeal fluid was obtained according to World Health Organization standard procedures by the transnasal approach; a swab was inserted under the inferior turbinate along the floor of the nose until the nasopharynx was reached. When resistance was felt, the swab was rotated and subsequently removed.[25]

Microbiological investigation

The swabs were immediately stored in liquid amies at room temperature, transported to the microbiology laboratory of the University Medical Center Utrecht and inoculated within 24 hours of sampling onto sheep blood (5%), *Haemophilus*, and MacConkey agar plates according to standard procedures for the identification of *S. pneumoniae, H. influenzae, M. cattarhalis, S. aureus* and *P. aeruginosa*. The culture plates were incubated aerobically at 37°C (MacConkey agar) and less than 5% carbon dioxide (blood and *Haemophilus* agars) and were examined at 24 and 48 hours. Bacteria were identified using colony morphology and conventional methods of determination. After plating, the swabs were stored at -80°C until further analysis.

Serotyping of *S. pneumonia* was performed by capsular swelling method (Quellung reaction) using type-specific antisera from the Statens Seruminstitut (Copenhagen, Denmark). The antibiotic susceptibility of the isolated strains was determined using a broth dilution method in micro-titre plates, up to January 2011 according to the CLSI standards and from January 2011 onwards according to the EUCAST standards.[26,27] The compounds tested included penicillin, amoxicillin-clavulanate, colistin and ciprofloxacin.

Clinical samples were tested for the presence of respiratory pathogens using realtime polymerase chain reaction (PCR). Total nucleic acids were extracted from 50ul of a clinical sample using the MagnaPure96 extraction system (Roche, Penzberg, Germany) and dedicated Total Nucleic Acid Isolation kit (Roche). To monitor for efficient sample extraction and amplification, each sample was spiked with a fixed amount of a non-human RNA and DNA viruses, i.e. phocine herpes virus and murine encephalomyocarditis virus (EMC) respectively, prior to extraction.[28] Purified nucleic acids were eluted in 100ul of elution buffer and subsequently amplified for the detection of the internal control viruses, influenzavirus, respiratory syncytial virus (RSV), human rhinovirus, human metapneumovirus, human coronaviruses, para-influenzaviruses 1-4, adenoviruses, human bocavirus and the polyomaviruses WU and KI. All diagnostic realtime PCR's were performed using pathogen specific realtime PCR assays as previously described, using Taqman universal Mastermix (Lifetechnologies, Foster City, USA) and a ABI7500 Real Time PCR system (Lifetechnologies), for 45 cycles.[29-33] Samples expressing a cycle threshold (Ct) <45 were considered positive for the target in the amplification reaction.

Data analysis

For the presence of bacteria and viruses in both otorrhea and nasopharyngeal samples, we calculated proportions of children with a sample testing positive for the predefined microorganisms and established co-occurrence of these microorganisms. In case of bilateral otorrhea, we defined children as positive for a microorganism, if a sample from at least one ear tested positive for that microorganism. Subgroup analyses were performed for age (preschool, i.e. younger than 4 years versus school age, i.e. 4 to 10 years) and treatment allocation (antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation). We

present proportions for pneumococcal serotypes and bacterial resistance for otorrhea and nasopharyngeal samples before and after treatment.
Concordance between otorrhea and nasopharyngeal samples for presence of bacteria and viruses is presented as positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity using the otorrhea sample as the reference.

Results

Study population

230 children with ATTO were included. Their mean age was 4.5 years (SD: 2.0), 133 (58%) children were male and 38 (17%) presented with bilateral otorrhea. The median duration of otorrhea before sampling at baseline was 3 days (interquartile range: 3) and 148 (64%) children had experienced an upper respiratory tract infection in the previous week. 119 (52%) children had been vaccinated with PCV7 and the oldest vaccinated participant was 5.6 years of age. Demographic and clinical characteristics are described in more detail elsewhere.[24]

Completeness of data

Before treatment, otorrhea was sampled in all 230 children and the nasopharynx in 224 (97%) children. At 2 weeks, otorrhea was sampled in all 79 children who had persisting ear discharge and the nasopharynx in 185 of 230 (80%) children. At 6 months, the nasopharynx was sampled in 187 (81%) children. All samples were cultured for bacteria. Due to storage issues, 29 (26%) colonies of 112 *S. pneumoniae* positive samples were not available for serotype testing. Viral analyses could be performed for 217 (94%) otorrhea and 205 (92%) nasopharyngeal samples, taken before treatment.

Otorrhea

Before treatment

At baseline, *H. influenzae* (41%), *S. aureus* (40%) and *P. aeruginosa* (18%) were the most prevalent bacteria, while *S. pneumoniae* (7%) prevalence was low (Table 1). *S. pneumoniae* serotypes were assessed in 11 of the 15 samples (73%); in one (9%) of these vaccine serotype 19F was found, the remaining 10 samples contained non-vaccine serotypes (Table 2).
Presence of viruses was low, with polyomaviruses (5%), human rhinovirus (5%) and RSV (4%) being the most prevalent (See table 1).
In most otorrhea samples, infections were polymicrobial. Only *P. aeruginosa* (55%) and *S. aureus* (43%) infections were often monomicrobial (Appendix table 1).

After treatment

At 2 weeks, 4 children treated with antibiotic-glucocorticoid eardrops had persistent otorrhea. In these samples, of the common pathogens only *P. aeruginosa* (n=2, 3%) and *S. aureus* (n=1, 1%) were present (Table 3). In 34 children treated with oral amoxicillin-clavulanate suspension and 41 children managed by initial observation, *H. influenzae* (17% and 27%, respectively), *S. aureus* (12% and 24%) and *P. aeruginosa* (12% and 11%) were most prevalent in persistent otorrhea.

Table 1. Prevalence of bacteria and viruses in the otorrhea and nasopharyngeal samples in children with acute tympanostomy-tube otorrhea before treatment

	Otorrhea, n (%)			Nasopharynx, n (%)		
	Age (years)		Total	Age (years)		Total
	1 – 3	4 – 9		1 – 3	4 – 9	
Bacteria	**(n=97)**	**(n=133)**	**(n=230)**	**(n=95)**	**(n=129)**	**(n=224)**
Any bacterium	90 (93)	122 (92)	212 (92)	89 (94)	116 (90)	204 (91)
Haemophilus influenzae	58 (60)	36 (27)	94 (41)	76 (80)	73 (57)	149 (67)
Staphylococcus aureus	30 (31)	61 (46)	91 (40)	21 (22)	52 (40)	73 (33)
Pseudomonas aeruginosa	12 (12)	30 (23)	42 (18)	4 (4)	10 (8)	14 (6)
Streptococcus pneumoniae	12 (12)	3 (2)	15 (7)	20 (21)	26 (20)	46 (21)
Moraxella cattarhalis	6 (6)	2 (2)	8 (4)	21 (22)	10 (8)	31 (14)
Other bacteria	23	23	46	21	13	34
Total number of bacterial species	150	175	326	165	191	358
Viruses	**(n=91)**	**(n=126)**	**(n=217)**	**(n=89)**	**(n=116)**	**(n=205)**
Any virus	28 (31)	17 (13)	45 (21)	66 (74)	52 (45)	118 (58)
Polyomaviruses (pooled)	8 (9)	4 (3)[i]	12 (5)[i]	24 (27)	11 (9)[i]	35 (17)[i]
WU	6 (7)	4 (3)	10 (5)	15 (17)	7 (6)	22 (11)
KI	2 (2)	1 (1)	3 (1)	9 (10)	5 (4)	14 (7)
Human rhinovirus	6 (7)	5 (4)	11 (5)	22 (25)	15 (13)	37 (18)
Respiratory syncytial virus	7 (8)	1 (1)	8 (4)	9 (10)	1 (1)	10 (5)
Para-influenzaviruses (pooled)	2 (2)	5 (4)	7 (3)	7 (8)	1 (1)	8 (4)
Type 1/3	2 (2)	0 (0)	2 (1)	1 (1)	0 (0)	1 (0)
Type 2/4	0 (0)	5 (4)	5 (2)	6 (7)	1 (1)	7 (3)
Human bocavirus	3 (3)	2 (2)	5 (2)	16 (17)	7 (6)	23 (11)
Human coronaviruses	3 (3)	0 (0)	3 (1)	6 (7)	6 (5)	12 (6)
Adenovirus	1 (1)	1 (1)	2 (1)	27 (30)	21 (18)	48 (23)
Influenza virus	1 (1)	0 (0)	1 (0)	1 (1)	2 (2)	3 (2)
Human metapneumovirus	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (0)

n = number; i = one sample was positive for both WU and KI; multiple microorganisms can be present in one sample so percentages do not add up to 100.

Nasopharyngeal carriage

Before treatment

At baseline, H. influenzae (67%) was the most prevalent bacterium followed by *S. aureus* (33%) and *S. pneumoniae* (21%) (See table 1). *S. pneumoniae* serotypes could be assessed in 35 of the 46 samples (76%). Vaccine serotypes were found in six (17%) samples, the remaining 29 (83%) samples contained non-vaccine serotypes (See table 2).

Adenovirus (23%) was the most prevalent virus in the nasopharyngeal samples, followed by human rhinovirus (18%), polyomaviruses (17%) and human bocavirus (11%) (See table 1).

Most nasopharyngeal samples contained multiple microorganisms (Appendix table 2). Most monomicrobial samples contained *S. aureus* (16%) and *H. influenza* (11%).

After treatment

At 2 weeks, nasopharyngeal carriage of all bacteria was lower only in children treated with oral antibiotics as compared to baseline (Table 4). This decrease was largest for *S. aureus*, *M. catarrhalis* and *S. pneumonia*. In children managed with eardrops or initial observation, prevalence of *S. aureus* and *M. cattarhalis* increased or remained stable. At 6 months, no substantial differences in nasopharyngeal carriage were observed between treatment groups. Bacterial prevalence was lower as compared to baseline, only the prevalence of *M. cattarhalis* increased during follow-up.

S. pneumoniae serotypes could be assessed in 21 of the 23 samples (91%) at 2 weeks: vaccine serotypes were found in three (14%) samples, the remaining 18 (86%) samples contained non-vaccine serotypes (Table 2). At 6 months, serotypes could be assessed in 16 (57%) of the 28 samples. Vaccine serotypes were detected twice (13%), while the other 14 (88%) pneumococci were non-vaccine serotypes.

Table 2. Prevalence of pneumococcal serotypes in the otorrhea and nasopharyngeal samples in children with acute tympanostomy-tube otorrhea before treatment.

	Otorrhea, n (%)		Nasopharynx, n (%)		
	Baseline	At 2 weeks	Baseline	At 2 weeks	At 6 months
PCV7 serotypes					
4	0 (0)	0 (-)	0 (0)	0 (0)	0 (0)
6B	0 (0)	0 (-)	1 (2)	1 (4)	0 (0)
9V	0 (0)	0 (-)	0 (0)	0 (0)	1 (4)
14	0 (0)	0 (-)	1 (2)	0 (0)	1 (4)
18C	0 (0)	0 (-)	1 (2)	1 (4)	0 (0)
19F	1 (7)	0 (-)	2 (4)	1 (4)	0 (0)
23F	0 (0)	0 (-)	1 (2)	0 (0)	0 (0)
PCV10 serotypes					
1	1 (7)	0 (-)	0 (0)	0 (0)	0 (0)
5	0 (0)	0 (-)	0 (0)	0 (0)	0 (0)
7F	0 (0)	0 (-)	1 (2)	0 (0)	0 (0)
Non-PCV serotypes					
6A	0 (0)	0 (-)	1 (2)	0 (0)	0 (0)
16F	2 (13)	0 (-)	3 (7)	1 (4)	0 (0)
19A	3 (20)	0 (-)	3 (7)	5 (22)	7 (25)
22F	2 (13)	0 (-)	3 (7)	1 (4)	0 (0)
35F	1 (7)	0 (-)	0 (0)	0 (0)	0 (0)
6C	1 (7)	0 (-)	0 (0)	4 (17)	0 (0)
10A	0 (0)	0 (-)	3 (7)	1 (4)	1 (4)
11A	0 (0)	0 (-)	3 (7)	2 (9)	1 (4)
15A	0 (0)	0 (-)	1 (2)	0 (0)	0 (0)
17F	0 (0)	0 (-)	1 (2)	0 (0)	0 (0)
23A	0 (0)	0 (-)	2 (4)	1 (4)	2 (7)
23B	0 (0)	0 (-)	4 (9)	0 (0)	0 (0)
3	0 (0)	0 (-)	2 (4)	0 (0)	0 (0)
33A	0 (0)	0 (-)	1 (2)	1 (4)	0 (0)
8	0 (0)	0 (-)	1 (2)	0 (0)	0 (0)
35B	0 (0)	0 (-)	0 (0)	2 (9)	0 (0)
15C	0 (0)	0 (-)	0 (0)	0 (0)	1 (4)
24F	0 (0)	0 (-)	0 (0)	0 (0)	1 (4)
31	0 (0)	0 (-)	0 (0)	0 (0)	1 (4)
Not available*	4 (27)	0 (-)	11 (24)	2 (9)	12 (43)
Total	15 (100)	0 (-)	46 (100)	23 (100)	28 (100)

n = number; PCV = pneumococcal vaccine; * = due to storage issues of some samples, not all colonies were available for serotype testing.

Table 3. Prevalence of bacteria in otorrhea samples from children with acute tympanostomy-tube otorrhea, before and after treatment.

	Before treatment				After treatment			
	n (%)				n (%)			
	Antibiotic-glucocorticoid eardrops	Oral antibiotics	Initial observation	Total	Antibiotic Glucocorticoid eardrops	Oral antibiotics	Initial observation	Total
	(n=76)	(n=77)	(n=77)	(n=230)	(n=76)	(n=77)	(n=75)	(n=228)
No otorrhea	0 (0)	0 (0)	0 (0)	0 (0)	72 (95)	43 (56)	34 (45)	151 (66)
Otorrhea	76 (100)	77 (100)	77 (100)	230 (100)	4 (5)	34 (44)	41 (55)	79 (35)
Bacterial species								
H. influenzae	31 (41)	32 (42)	31 (40)	94 (41)	0 (0)	13 (17)	20 (27)	33 (14)
S. aureus	25 (33)	27 (35)	39 (51)	91 (40)	1 (1)	9 (12)	18 (24)	28 (12)
P. aeruginosa	16 (21)	16 (21)	10 (13)	42 (18)	2 (3)	9 (12)	8 (11)	19 (8)
S. pneumoniae	5 (7)	5 (7)	5 (7)	15 (7)	0 (0)	0 (0)	0 (0)	0 (0)
M. cattarhalis	3 (4)	2 (3)	3 (4)	8 (4)	0 (0)	3 (4)	4 (5)	7 (3)
No bacteria	7 (9)	5 (7)	6 (8)	18 (8)	1 (1)	3 (4)	2 (3)	6 (3)
Other bacteria	19	26	31	76	3	5	14	22

n = number; multiple bacteria can be present in one sample so percentages do not add up to 100.

Table 4. Prevalence of bacteria in nasopharyngeal samples from children with acute tympanostomy otorrhea, before and after treatment.

	Before treatment				After treatment							
					2 weeks				6 months			
	n (%)				n (%)				n (%)			
	Eardrops	Oral antibiotics	Initial observation	Total	Eardrops	Oral antibiotics	Initial observation	Total	Eardrops	Oral antibiotics	Initial observation	Total
	(n=75)	(n=75)	(n=74)	(n=224)	(n=62)	(n=66)	(n=57)	(n=185)	(n=61)	(n=65)	(n=61)	(n=187)
Bacterial species												
H. influenzae	50 (67)	50 (67)	49 (66)	149 (67)	34 (55)	42 (64)	33 (58)	109 (59)	29 (48)	29 (45)	27 (44)	85 (45)
S. aureus	21 (28)	27 (36)	25 (34)	73 (33)	21 (34)	14 (21)	19 (33)	54 (29)	14 (23)	16 (25)	14 (23)	44 (24)
P. aeruginosa	4 (5)	7 (9)	3 (4)	14 (6)	0 (0)	4 (6)	1 (2)	5 (3)	0 (0)	1 (1)	0 (0)	1 (1)
S. pneumoniae	15 (20)	16 (21)	15 (20)	46 (21)	8 (13)	4 (6)	11 (19)	23 (12)	6 (10)	11 (17)	11 (17)	28 (15)
M. cattarhalis	7 (9)	14 (19)	10 (14)	31 (14)	14 (23)	6 (9)	8 (14)	28 (15)	12 (20)	10 (15)	15 (25)	37 (20)
No bacteria	10 (13)	5 (7)	5 (7)	20 (9)	7 (11)	13 (20)	7 (12)	27 (15)	17 (28)	17 (26)	13 (21)	47 (25)
Other bacteria	18	13	14	45	6	9	13	28	13	6	14	33

n = number; multiple bacteria can be present in one sample so percentages do not add up to 100.

Antimicrobial resistance of otorrhea and nasopharyngeal samples

Before treatment

One (1%) *H. influenza*e strain from an otorrhea sample, and three (2%) *H. influenzae* strains from nasopharyngeal samples were resistant to amoxicillin-clavulanate. Except for *P. aeruginosa*, which is inherently resistant, all other pathogens were susceptible to amoxicillin-clavulanate or penicillin. Colistin susceptibility was tested for *P. aeruginosa*; three (7%) strains from otorrhea samples were resistant. All tested bacteria were susceptible to ciprofloxacin.

After treatment

Both at 2 weeks and at 6 months, one (1%) *H. influenza*e strain from the nasopharynx was resistant to amoxicillin-clavulanate. One (4%) 6-month nasopharyngeal *S. pneumoniae* strain was intermediate resistant to penicillin. All other pathogens were susceptible to amoxicillin-clavulanate. In addition, all *P. aeruginosa* strains were susceptible to colistin and all bacteria were susceptible to ciprofloxacin.

Concordance between nasopharyngeal and otorrhea samples

The overall concordances varied between 66% and 88% for bacteria, and between 77% and 98% for viruses (Appendix table 3). Qualitative and quantitative analyses of bacteria gave more or less similar results. NPVs were high for most microorganisms. PPVs were high for *P. aeruginosa* (100%) and *S. aureus* (74%) as compared to the other bacteria. So if these bacteria were present in the nasopharynx, the otorrhea samples also tested positive in all or a majority of the children. For viruses, PPVs were overall low, except for RSV (60%).

Discussion

Our study on the microbiology of ATTO performed after introduction of routine PCV vaccination shows that *H. influenza* and *S. aureus* are most prevalent in both otorrhea and the nasopharynx of children with untreated ATTO. Viruses are rarely present in otorrhea, while nasopharyngeal samples more frequently tested positive mainly for adenovirus, human rhinovirus and polyomaviruses.

S. pneumonia was less prevalent in our otorrhea samples (7%) than in previous studies on ATTO from Western countries conducted before routine introduction of PCV (20%[7,9-11] to 50%[8]). Our study confirms a low prevalence of pneumococcal vaccine serotypes and high colonization rate of serotype 19A in both vaccinated and unvaccinated children after the introduction of PCV in the Dutch National Vaccination Program in 2006.[21] In a previous trial of PCV7 vaccination by our team, *S. aureus* was more prevalent in otorrhea of vaccinated children as compared to unvaccinated children.[13] In our study, *S. aureus* was also highly prevalent in the otorrhea (40%) and single present in many infections. Considering these results, the negative association found between *S. aureus* and *S. pneumonia* in several studies and the higher nasopharyngeal carriage rate of *S. aureus* in healthy PCV7 vaccinated children as compared to unvaccinated children, *S. aureus* can be regarded as an important upper respiratory tract pathogen in the post-PCV7 era.[20,21,34-36]

The distribution of viruses in the otorrhea samples of our study is comparable to the single previous study of viruses in middle ear fluid of children with ATTO, although the absolute prevalences are lower. These lower prevalences may be due to the other team sampling

only during respiratory virus season while we sampled throughout the year.[8] The nasopharyngeal prevalence of most viruses in our population was comparable to that in healthy children, except adenovirus, which was more prevalent in children with ATTO.[34,37]

H. influenza (67%) was the most prevalent microorganism in the nasopharynx of untreated children, while *S. pneumoniae* was present in only 21%. Taking into consideration the higher mean age of our study population, our results are comparable to those of others looking at nasopharyngeal carriage of these bacteria during middle ear infections after PCV7 introduction.[18]

H. influenzae, S. aureus and *P. aeruginosa* were the most prevalent bacteria in otorrhea samples both before and after treatment. Antimicrobial resistance was low: only inherent antimicrobial resistance was seen in the otorrhea samples from failures of all three treatment groups.

Based on the traditional etiologic point of view that middle ear infections are caused by pathogens ascending from the nasopharynx through the Eustachian tube into the middle ear cavity, many studies have used nasopharyngeal samples as a proxy for samples of the middle ear. Our results suggest that these studies should be interpreted carefully, supporting the conclusions of our recent systematic review that showed predictive values of nasopharyngeal samples to be moderate to poor.[38]

Although numbers were low and results should be interpreted with caution, we found that *P. aeruginosa* was present in the nasopharynx (n=14) only when concurrently present in otorrhea (total n=42). This suggests that microorganisms may also descend from the middle ear to the nasopharynx through the Eustachian tube.

Some aspects of our study deserve further attention. First, children with a body temperature higher than 38.5°C were excluded from the trial. Although many children with ATTO do not develop a fever, this may have led to an underestimation of bacterial presence, especially pneumococci, and an overestimation of viral presence.[39] Second, due to storage issues of some samples, not all swabs were available for viral analyses and not all pneumococcal colonies for serotype testing. Third, we sampled otorrhea from the ear canal while some previous studies aspirated middle ear fluid through the tube.[8,9] A study comparing bacterial presence in ear canal samples as compared to middle ear fluid aspirates in 34 children suggested that ear canal sampling could lead to an underestimation of the prevalence of *H. influenza*, *S. pneumonia* and *M. catarrhalis* and to an overestimation of *P. aeruginosa*.[40] To evaluate the accuracy of our sampling method, we compared bacterial presence in otorrhea samples swabbed from the ear canal as compared to samples taken from the lumen of the tympanostomy tube in 20 children participating in the trial and found a high concordance [data not shown].

Conclusion

H. influenza, *S. aureus* and *P. aeruginosa* are the most common microorganisms in children with untreated ATTO. Prevalence of *S. pneumonia* has decreased since the introduction of PCV and most pneumococci are non-vaccine serotypes.

References

1. Cullen K, Hall M, Golosinskiy A. Ambulatory Surgery in the United States, 2006. National health statistics reports; no 11. Revised. In. Hyattsville, MD: National Center for Health Statistics; 2009.
2. Dutch Hospital Data (Landelijke medische registratie). 2010.
3. van Dongen TM, van der Heijden GJ, Freling HG, et al. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. PLoS One 2013;8:e69062.
4. Mandel EM, Casselbrant ML, Kurs-Lasky M. Acute otorrhea: bacteriology of a common complication of tympanostomy tubes. Ann Otol Rhinol Laryngol 1994;103:713-8.
5. Roland PS, Anon JB, Moe RD, et al. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tubes. Laryngoscope 2003;113:2116-22.
6. Dohar J. Microbiology of otorrhea in children with tympanostomy tubes: implications for therapy. Int J Pediatr Otorhinolaryngol 2003;67:1317-23.
7. Roland PS, Kreisler LS, Reese B, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2004;113:e40-6.
8. Ruohola A, Meurman O, Nikkari S, et al. Microbiology of acute otitis media in children with tympanostomy tubes: prevalences of bacteria and viruses. Clin Infect Dis 2006;43:1417-22.
9. Dohar J, Giles W, Roland P, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2006;118:e561-9.
10. Granath A, Rynnel-Dagoo B, Backheden M, et al. Tube associated otorrhea in children with recurrent acute otitis media; results of a prospective randomized study on bacteriology and topical treatment with or without systemic antibiotics. Int J Pediatr Otorhinolaryngol 2008;72:1225-33.
11. Heslop A, Lildholdt T, Gammelgaard N, et al. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhea in children: the results of a randomized clinical trial. Laryngoscope 2010;120:2516-20.
12. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403-9.
13. Veenhoven R, Bogaert D, Uiterwaal C, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. Lancet 2003;361:2189-95.
14. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995-2003. Pediatr Infect Dis J 2004;23:824-8.
15. Block SL, Hedrick J, Harrison CJ, et al. Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. Pediatr Infect Dis J 2004;23:829-33.
16. McEllistrem MC, Adams JM, Patel K, et al. Acute otitis media due to penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis 2005;40:1738-44.
17. Brook I, Gober AE. Bacteriology of spontaneously draining acute otitis media in children before and after the introduction of pneumococcal vaccination. Pediatr Infect Dis J 2009;28:640-2.
18. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. JAMA 2010;304:2161-9.
19. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J 2010;29:304-9.
20. van Gils EJ, Hak E, Veenhoven RH, et al. Effect of seven-valent pneumococcal conjugate vaccine on Staphylococcus aureus colonisation in a randomised controlled trial. PLoS One 2011;6:e20229.
21. Spijkerman J, Prevaes SM, van Gils EJ, et al. Long-term effects of pneumococcal conjugate vaccine on nasopharyngeal carriage of S. pneumoniae, S. aureus, H. influenzae and M. catarrhalis. PLoS One 2012;7:e39730.
22. Pichichero ME. Otitis media. Pediatr Clin North Am 2013;60:391-407.
23. Casey JR, Kaur R, Friedel VC, et al. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. Pediatr Infect Dis J 2013;32:805-9.
24. van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med 2014;370:723-33.

25. O'Brien KL, Nohynek H. Report from a WHO Working Group: standard method for detecting upper respiratory carriage of Streptococcus pneumoniae. Pediatr Infect Dis J 2003;22:e1-11.
26. Clinical and Laboratory Standards Institute (CLSI). (Accessed at http://www.clsi.org.)
27. European Committee on Antimicrobial Susceptibility Testing (EUCAST). (Accessed at http://www.eucast.org/.)
28. van Doornum GJ, Guldemeester J, Osterhaus AD, et al. Diagnosing herpesvirus infections by real-time amplification and rapid culture. J Clin Microbiol 2003;41:576-80.
29. van Elden LJ, van Loon AM, van Alphen F, et al. Frequent detection of human coronaviruses in clinical specimens from patients with respiratory tract infection by use of a novel real-time reverse-transcriptase polymerase chain reaction. J Infect Dis 2004;189:652-7.
30. van Elden LJ, van Loon AM, van der Beek A, et al. Applicability of a real-time quantitative PCR assay for diagnosis of respiratory syncytial virus infection in immunocompromised adults. J Clin Microbiol 2003;41:4378-81.
31. van Elden LJ, Nijhuis M, Schipper P, et al. Simultaneous detection of influenza viruses A and B using real-time quantitative PCR. J Clin Microbiol 2001;39:196-200.
32. van de Pol AC, van Loon AM, Wolfs TF, et al. Increased detection of respiratory syncytial virus, influenza viruses, parainfluenza viruses, and adenoviruses with real-time PCR in samples from patients with respiratory symptoms. J Clin Microbiol 2007;45:2260-2.
33. Nijhuis M, van Maarseveen N, Schuurman R, et al. Rapid and sensitive routine detection of all members of the genus enterovirus in different clinical specimens by real-time PCR. J Clin Microbiol 2002;40:3666-70.
34. van den Bergh MR, Biesbroek G, Rossen JW, et al. Associations between Pathogens in the Upper Respiratory Tract of Young Children: Interplay between Viruses and Bacteria. PLoS One 2012;7:e47711.
35. Bogaert D, van Belkum A, Sluijter M, et al. Colonisation by Streptococcus pneumoniae and Staphylococcus aureus in healthy children. Lancet 2004;363:1871-2.
36. McNally LM, Jeena PM, Gajee K, et al. Lack of association between the nasopharyngeal carriage of Streptococcus pneumoniae and Staphylococcus aureus in HIV-1-infected South African children. J Infect Dis 2006;194:385-90.
37. Bosch A, Biesbroek G, Trzcinski K, et al. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog 2013;9:e1003057.
38. van Dongen TM, van der Heijden GJ, van Zon A, et al. Evaluation of Concordance between the Microorganisms Detected in the Nasopharynx and Middle Ear of Children with Otitis Media. Pediatr Infect Dis J 2013.
39. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg 2013;149:S1-S35.
40. Brook I, Yocum P, Shah K. Aerobic and anaerobic bacteriology of otorrhea associated with tympanostomy tubes in children. Acta Otolaryngol 1998;118:206-10.

Appendix table 1. Co-occurrence of microorganisms in 217 otorrhea samples from children with acute tympanostomy otorrhea, before treatment.

	Co-occurrence, n (% of total)									
Microorganisms (total)	*H. influenza*	*S. aureus*	*P. aeruginosa*	*S. pneumoniae*	*M. cattarhalis*	Polyomaviruses	Human rhinovirus	Respiratory syncytial virus	Para-influenzaviruses	No other microorganism
H. influenza (n=89)	-	28 (31)	1 (1)	9 (10)	5 (6)	6 (7)	7 (8)	7 (8)	4 (4)	21 (24)
S. aureus (n=84)	28 (33)	-	4 (5)	3 (4)	1 (1)	4 (5)	4 (5)	3 (4)	0 (0)	36 (43)
P. aeruginosa (n=42)	1 (2)	4 (10)	-	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	3 (7)	23 (55)
S. pneumoniae (n=12)	9 (75)	3 (25)	0 (0)	-	0 (0)	1 (8)	2 (17)	2 (17)	0 (0)	2 (17)
M. cattarhalis (n=7)	5 (71)	1 (14)	0 (0)	0 (0)	-	0 (0)	0 (0)	1 (14)	1 (14)	0 (0)
Polyomaviruses (n=12)	6 (50)	4 (33)	1 (8)	1 (8)	0 (0)	-	2 (17)	0 (0)	0 (0)	1 (8)
Human rhinovirus (n=11)	7 (64)	4 (36)	1 (9)	2 (18)	0 (0)	2 (18)	-	0 (0)	1 (9)	0 (0)
Respiratory syncytial virus (n=8)	7 (88)	3 (38)	0 (0)	2 (25)	1 (13)	0 (0)	0 (0)	-	0 (0)	0 (0)
Para-influenzaviruses (n=7)	4 (57)	0 (0)	3 (43)	0 (0)	1 (14)	0 (0)	1 (14)	0 (0)	-	0 (0)

n = number; numbers/percentages do not add up to total/100 because combinations of >2 microorganisms are possible

Appendix table 2. Co-occurrence of microorganisms in 205 nasopharyngeal samples from children with acute tympanostomy otorrhea, before treatment.

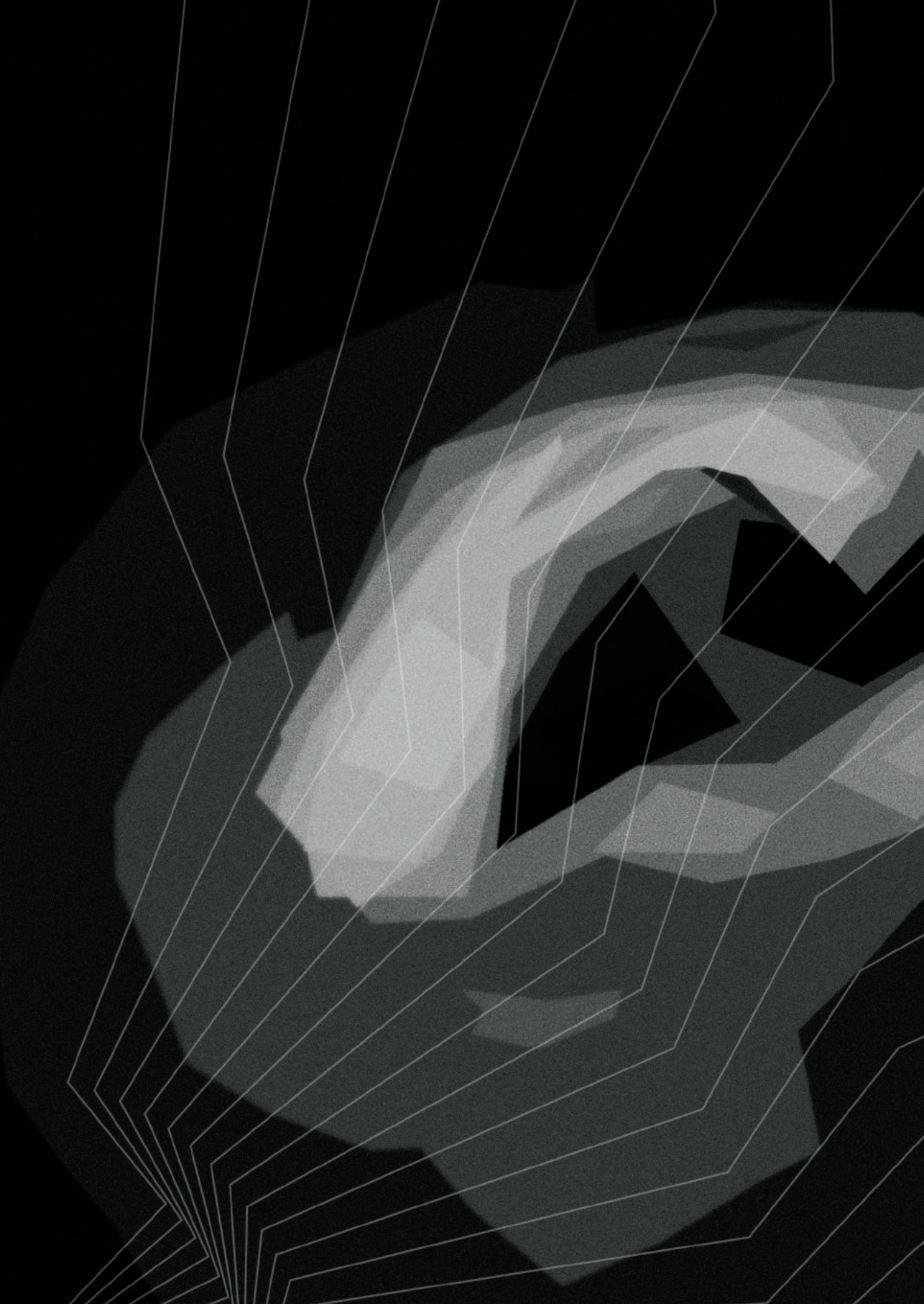
	Co-occurrence, n (% of total)										
Microorganisms (total)	*H. influenza*	*S. aureus*	*S. pneumoniae*	*M. cattarhalis*	*P. aeruginosa*	Adenovirus	Human rhinovirus	Polyomaviruses	Human bocavirus	Respiratory syncytial virus	No other microorganism
H. influenza (n=137)	-	38 (28)	31 (23)	23 (17)	5 (4)	33 (24)	30 (22)	25 (18)	19 (14)	9 (7)	15 (11)
S. aureus (n=64)	38 (59)	-	9 (14)	6 (9)	4 (6)	16 (25)	10 (16)	7 (11)	4 (6)	2 (3)	10 (16)
S. pneumoniae (n=38)	31 (82)	9 (24)	-	6 (16)	1 (3)	5 (13)	10 (26)	6 (16)	3 (8)	2 (5)	1 (3)
M. cattarhalis (n=28)	23 (82)	6 (21)	6 (21)	-	2 (7)	9 (32)	2 (7)	4 (14)	4 (14)	2 (7)	1 (4)
P. aeruginosa (n=14)	5 (36)	4 (29)	1 (7)	2 (14)	-	5 (36)	2 (14)	4 (29)	1 (7)	0 (0)	1 (7)
Adenovirus (n=48)	33 (69)	16 (33)	5 (10)	9 (19)	5 (10)	-	8 (17)	10 (21)	8 (17)	3 (6)	1 (2)
Human rhinovirus (n=37)	30 (81)	10 (27)	10 (27)	2 (5)	2 (5)	8 (22)	-	8 (22)	4 (11)	1 (3)	2 (5)
Polyomaviruses (n=35)	25 (71)	7 (20)	6 (17)	4 (11)	4 (11)	10 (29)	8 (23)	-	8 (23)	4 (11)	0 (0)
Human bocavirus (n=23)	19 (83)	4 (17)	3 (13)	4 (17)	1 (4)	8 (35)	4 (17)	8 (35)	-	2 (9)	1 (4)
Respiratory syncytial virus (n=10)	9 (90)	2 (20)	2 (20)	2 (20)	0 (0)	3 (30)	1 (10)	4 (40)	2 (20)	-	0 (0)

n = number; numbers/percentages do not add up to total/100 because combinations of >2 microorganisms are possible

Appendix table 3. Concordance between microorganisms detected in nasopharyngeal and otorrhea samples of children with acute tympanostomy-tube otorrhea, before treatment.

Pathogen	O+N+ n (%)	O+N- n (%)	O-N+ n (%)	O-N- n (%)	Concordance n (%)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
Bacteria (n=224)									
H. influenzae	82 (37)	10 (5)	67 (30)	65 (29)	147 (66)	55 (47 to 63)	87 (77 to 93)	89 (81 to 95)	49 (40 to 58)
S. aureus	54 (24)	35 (16)	19 (9)	116 (52)	170 (76)	74 (62 to 84)	77 (69 to 83)	61 (50 to 71)	86 (79 to 91)
P. aeruginosa	14 (6)	27 (12)	0 (0)	183 (82)	197 (88)	100 (68 to 100)	87 (82 to 91)	34 (20 to 51)	100 (97 to 100)
S. pneumoniae	6 (3)	9 (4)	40 (18)	169 (76)	175 (78)	13 (5 to 26)	95 (91 to 98)	40 (16 to 68)	81 (75 to 86)
M. catarrhalis	2 (1)	5 (2)	29 (13)	188 (84)	190 (85)	6 (1 to 21)	97 (94 to 99)	29 (4 to 71)	87 (81 to 91)
Viruses (n=201)									
Polyomaviruses	3 (1)	9 (4)	31 (15)	158 (79)	161 (80)	9 (2 to 24)	95 (90 to 98)	25 (5 to 57)	84 (78 to 89)
Human rhinovirus	6 (3)	4 (2)	31 (15)	160 (80)	166 (83)	16 (6 to 32)	98 (94 to 99)	60 (26 to 88)	84 (78 to 89)
Respiratory syncytial virus	6 (3)	1(0)	4 (2)	190 (95)	196 (98)	60 (26 to 88)	99 (97 to 100)	86 (42 to 100)	98 (95 to 99)
Para-influenzaviruses	1 (0)	5 (2)	7 (3)	188 (94)	189 (94)	12 (0 to 53)	97 (94 to 99)	17 (0 to 64)	96 (93 to 99)
Human bocavirus	3 (1)	2 (1)	20 (10)	176 (88)	179 (89)	13 (3 to 34)	99 (96 to 100)	60 (15 to 95)	90 (85 to 94)
Human coronavirus	1 (0)	2 (1)	10 (5)	188 (94)	189 (94)	9 (0 to 41)	99 (96 to 100)	33 (1 to 91)	95 (91 to 98)
Adenovirus	1 (0)	0 (0)	47 (23)	153 (76)	154 (77)	2 (0 to 11)	100 (96 to 100)	100 (1 to 100)	76 (70 to 82)

O = otorrhea culture; N = nasopharyngeal culture; + = positive test result; - = negative test result; n = number; CI = confidence interval. Due to rounding, these percentages do not always add up to 100.



Chapter 4.2

Concordance between microorganisms detected in the nasopharynx and middle ear of children with otitis media: a systematic review

Based on

Van Dongen TMA, van der Heijden GJMG, van Zon A, Bogaert D, Sanders EAM, Schilder AGM. Evaluation of concordance between the microorganisms detected in the nasopharynx and middle ear of children with otitis media. *Pediatr Infect Dis J 2013;32(5):549-52*.

Abstract

Background

Studies of microorganisms involved in otitis media in children often use a nasopharyngeal (NP) sample as a proxy for the middle ear fluid (MEF) to test for bacteria and viruses.

Objective

To determine whether studies using NP samples provide an accurate estimate of the prevalence of microorganisms involved in middle ear infections.

Methods

We performed a systematic review of the literature reporting on the concordance between test results of NP and MEF samples, for the most prevalent microorganisms in children with otitis media. We summed the data of the studies for each microorganism for acute otitis media and for otitis media with effusion separately and presented their overall concordance. We also calculated the positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity using the MEF sample as the reference.

Results

We included 18 studies comprising 5377 paired MEF and NP samples from 3478 children with acute otitis media and 769 paired samples from 509 children with otitis media with effusion. Overall concordances varied from 68% to 97% per microorganism. For the most prevalent microbes, positive predictive values were around 50%. Most negative predictive values were moderate to high, with a range from 68% up to 97%.

Conclusion

Test results from nasopharyngeal samples do not always provide an accurate proxy for those of the middle ear fluid. It is therefore important to interpret and use results of such studies carefully.

Introduction

Studies of microorganisms involved in otitis media (OM) in children often use a nasopharyngeal (NP) sample as a proxy for the middle ear fluid (MEF) to test for bacteria and viruses.[1-4] Obtaining a MEF sample when the tympanic membrane is intact involves tympanocentesis or myringotomy. While this procedure may be indicated for selected patients in clinical practice, in a research setting one usually faces practical and medical ethical conflicts.[5] The question is whether studies using NP samples provide an accurate estimate of the prevalences of the various microorganisms involved in OM. This is of particular importance in studies of the impact of antibiotic treatment or vaccination against microorganisms causing OM, where it is essential that valid estimates of these potential pathogens are used.

The most recent overview of studies comparing NP and MEF samples dates from 1979; Shwartz et al. supported the use of NP samples as a proxy for MEF.[6] We present an update on this topic with a systematic review of literature reporting on the concordance between test results of MEF and NP samples for the most prevalent microorganisms in children with acute otitis media (AOM) and otitis media with effusion (OME).

Methods

Literature search

We used synonyms of OM, MEF and NP to search publications in PubMed, EMBASE and the Cochrane library up to January 2012 (Table 1). Related publications were searched in Pubmed, and Scopus was used for cross-reference checking.

Selection of publications

We screened titles and abstracts of all retrieved publications to identify potentially relevant publications in English, Dutch, German or French. At subsequent full-text screening, studies were selected if the publication included the results of bacterial or viral detection from samples taken simultaneously from both the NP and MEF in children with AOM or OME. Studies had to report original data of conventional cultures or molecular methods for detection of at least one of the 4 bacteria most commonly involved in OM: *Streptococcus pneumoniae*, *Haemophilus influenzae, Moraxella catarrhalis* and *Staphylococcus aureus*; and/or results of cultures, molecular methods, enzyme-immunoassay (ELISA) or immunofluorescence (IF) for detection of one of the 5 most common OM viruses: human rhinovirus, respiratory syncytial virus (RSV), influenzaviruses, adenovirus, enterovirus.[7-9] Studies were excluded if the full-text was not available, or if more than 10% of included patients were over 18 years of age and their results could not be separated from those of the children. Case reports and case series were excluded, as well as studies that only reported positive results or when 2 by 2 tables could not be reproduced.

Data extraction

Information was extracted from each article by 2 independent reviewers (TvD and AvZ) using standardized data extraction forms for assessing study characteristics (country, design, setting, in- and exclusion criteria), patient characteristics (age, conditions studied), sampling periods and methods, and test results of MEF and NP samples.

Data analysis

We extracted the data of the paired NP and MEF sample test results or recalculated these from the reported data. In addition, we summed the data for each microorganism in AOM and OME separately and present their prevalence for the NP and MEF, the concordant and discordant paired samples and their overall concordance. Overall concordance represents the proportion of patients with the same test result for NP and MEF samples. We also used the summed data to calculate the positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity using the MEF sample as the reference. The PPV then represents the proportion of NP samples that tested positive for a certain microorganism, for which the paired MEF sample was also positive. The NPV represents the proportion of NP samples that tested negative for a microorganism, for which the paired MEF sample was also negative. The sensitivity represents the proportion of MEF samples that tested positive for a certain microorganism, for which the paired NP sample was also positive. The specificity represents the proportion of MEF samples that tested negative for a microorganism, for which the paired NP sample was also negative.

Table 1. Search syntax used in this review.

Pubmed, EMBASE and Cochrane Library	
Domain	otitis media OR middle otitis OR ear inflammation OR ear infection OR middle ear disease OR glue ear OR middle ear effusion
Determinant 1	Fluid* OR mucoid* OR mucous* OR purulent* OR pus OR serous* OR effusion* OR exudat* OR MEE OR MEF OR dischar* OR otorrh* OR suppurative*
Determinant 2	nasophar* OR NP OR rhinophar* OR RP

Pubmed: search limited to [tiab]; Cochrane Library: search limited to :ab,ti; EMBASE: search limited to :ab,ti and [embase]/lim NOT [medline]/lim.

Results

The literature search resulted in 620 publications. After screening titles and abstracts 73 publications appeared to be relevant. Of these 73 studies, 18 met the inclusion criteria, 12 focusing on AOM and six on OME.[10-27] A cross-reference search did not reveal additional publications.

Study characteristics

The characteristics of the included studies are presented in Appendix table 1.

Patients

Overall, the selected studies include 4791 paired NP and MEF samples from 3278 patients with AOM and 849 paired samples from 661 children with OME. The study sizes ranged from 52 to 1416 episodes of AOM and 15 to 325 ears with OME. The majority of the children in the AOM studies were younger than 2 years old, while the majority of the children with OME were between 2 and 15 years of age. Half of the studies were performed in tertiary care setting, but the larger studies were set in primary or secondary care.

Microbiology

Two studies did not report the method of MEF sampling; most other studies aspirated MEF after paracentesis and in 2 studies otorrhea was swabbed from the ear canal. Nasopharyngeal samples were taken with swabs in 8 studies, by aspiration in 7, and the method was not clearly reported in 3 studies. All studies reporting on bacteria used conventional cultures, 2 studies used additional molecular techniques (PCR). For detection of viruses, 2 studies used IF, 2 used PCR, 2 used viral cultures, 1 used different rapid antigen tests (IF, immunochromatography) and 1 used ELISA (See Appendix table 1). We were unable to retrieve studies testing for viruses in OME.

Positive test proportions

After summing data of all studies, the proportion of positive tests for NP samples was larger than that of MEF for all microorganisms, except for *S. aureus* (table 2). The results of the individual studies included in this review are presented in Appendix tables 2 and 3.

S. pneumoniae was most often cultured in the AOM studies, with 30% positive MEF cultures and 55% positive NP cultures. *H. influenzae* was found in 25% of MEF cultures and 33% of NP cultures. *M. catarrhalis* was cultured from 7% MEF samples and 37% NP samples. Human rhinovirus was the most prevalent virus with 14% positive MEF samples and 20% positive NP samples. RSV and enterovirus were detected in 6% and 9 % of the MEF samples and 11% and 12% of the NP samples, respectively. For the OME studies, the most prevalent microorganism in both MEF and NP samples was *H. influenzae*, with 16% positive MEF samples and 26% positive NP samples.

Concordance between NP and MEF test results

The highest concordance in AOM was found for the least prevalent microorganisms: the viruses (see table 2). The most prevalent virus was the human rhinovirus, which had an overall concordance of 86%. For the bacteria, concordance was highest for *H. influenzae*: 80%. Concordances for *S. pneumoniae* and *M. catarrhalis* in AOM were lower, reflecting the large proportions of discordant pairs with NP positive and MEF negative samples.

In OME, concordance for *H.* influenzae was high at 81%, comprising a proportion of positive paired samples of 11%. Concordance for *S. pneumoniae* and *M. catarrhalis* was even higher, but was mainly determined by the large numbers of negative paired samples.

For the most prevalent microorganisms, PPVs were around 50%. Most NPVs were moderate to high, with a range from 68% up to 97%. The NPV was particularly high for the least prevalent microorganisms. The sensitivity was high for the most prevalent microorganisms, especially when compared to the PPV, indicating that if a bacterium or virus is present in the MEF it is very often also detected in the NP. The specificities were comparable to the NPVs and, just like the NPVs, particularly high for the least prevalent microorganisms.

Table 2. Summed data of NP and MEF sample test results in AOM and OME for various microorganisms.

	Number of studies	Total number of paired MEF - NP samples	Prevalence		Paired MEF/NP samples, %#				Positive predictive value %	Negative predictive value %	Sensitivity, %	Specificity, %	Overall Concordance %
			MEF (M+) %(range*)	NP (N+) %(range*)	M+N+	M+N-	M-N+	M-N-					
AOM-studies													
S. pneumoniae	6	1489	30 (10-53)	55 (0-69)	27	3	27	43	50	70	90	61	70
H. influenzae	5	1381	25 (2-37)	33 (0-62)	19	6	14	61	58	80	76	82	80
M. catarrhalis	4	541	7 (0-9)	37 (0-54)	6	1	31	62	17	68	87	67	68
S. aureus	2	112	33 (5-65)	10 (0-21)	7	26	3	64	73	71	22	96	71
RSV	6	3582	6 (3-19)	11 (6-28)	5	1	6	88	46	93	87	94	93
Influenzaviruses†	5	3490	1 (0-4)	3 (2-6)	1	0	2	96	33	97	85	98	97
Adenovirus	4	3437	1 (0-1)	4 (2-6)	1	0	3	96	17	97	88	97	97
Human rhinovirus	4	3359	14 (0-26)	20 (1-30)	10	4	10	76	48	86	70	88	86
Enterovirus	2	2508	9 (0-16)	12 (1-20)	6	3	6	85	52	91	67	94	91
OME-studies													
H. influenzae	6	849	16 (9-58)	26 (8-90)	11	4	14	70	44	81	72	83	81
S. pneumoniae	5	769	5 (2-19)	19 (12-40)	3	2	16	79	16	82	58	83	82
M. catarrhalis	5	769	2 (0-9)	12 (0-52)	2	1	10	87	13	89	63	90	89
S. aureus	3	599	3 (0-3)	13 (5-20)	1	3	12	84	6	85	25	87	85

MEF = middle ear fluid; NP = nasopharynx; M+/- = positive or negative MEF-sample; N+/- = positive or negative NP-sample; * = in included studies; # = distribution of the test results of paired samples, due to rounding these percentages do not always add up to 100; RSV = respiratory syncytial virus; † = results for type A were used if only presented in subtypes

Discussion

OM is a polymicrobial disease.[7-9] Microorganisms involved in OM often asymptomatically reside in the nasopharynx where they interact with each other and the host's mucosal immune system.[28] The traditional etiological view suggests that when existing balance in this microbiome is disturbed, for example by the acquisition of a new virus or bacterium, this may lead to expansion of microorganisms.[29] Viruses and bacteria may then ascend through the Eustachian tube into the middle ear and cause an infection.[7,9,30] From that perspective, NP samples are taken as a proxy in clinical research, when MEF cannot be sampled. Currently, however, the etiological pathway of OM is thought to be more complex; interactions between microorganisms are increasingly demonstrated, revealing a more diverse microbial pathogenesis.[30]

Our findings show moderate concordance between test results for microorganisms of NP and MEF samples taken from children with AOM or OME. When a bacterium or virus is present in the MEF, it is detected in the NP sample in most cases. However, when a NP sample is positive, the same microorganism is not always found in the MEF, reflecting the presence of some microorganisms possible residing in the nasopharynx as pure commensals. Especially *M. catarrhalis* is more frequently detected in the NP than in the MEF of children with OM, suggesting this bacterium to be a commensal rather than a primary pathogen.

Our results therefore indicate that test results from NP samples do not always provide an accurate proxy for MEF test results. Still, for some microorganisms, like *H. influenzae* in AOM and OME and *S. pneumoniae*, human rhinovirus and enterovirus in AOM, positive test results from NP samples may provide useful information when MEF samples cannot be obtained. For PPVs are higher than MEF prevalences of these microorganisms, suggesting that a positive NP sample does considerably increase the chance of a correct estimation of the pathogen present in the MEF. Moreover, the high NPVs and specificities for some microorganisms, e.g. *H. influenzae*, RSV, enterovirus and human rhinovirus, indicate that test results from NP samples can be used to exclude their presence in the MEF, keeping in mind that high NPVs and specificities are largely influenced by the prevalence of bacteria and viruses in the NP and MEF.

S. aureus is the only microorganism detected more frequently in MEF than the NP of children with AOM. Since most studies have not tested for *S. aureus*, we could only include two studies with 112 paired samples testing for this microorganism in AOM; one recent study from Africa and one study published in 1962.[16,24] These were also the two studies that included children presenting with otorrhea. This may partly explain the high prevalence of *S. aureus* as it is known that this microbe is more often involved in OM in children with tympanostomy tubes or perforated eardrums.[31-33] In addition, it may sometimes reflect a commensal from the ear canal rather than the microorganism causing OM.

NP samples are not routinely used for the bacteriologic diagnosis of OM in clinical practice. In that setting, their use would require additional focus on microbial interactions and pathogenicity. This review focuses on clinical research of the effects of vaccines or antibiotics in OM and the question is if presence of a certain microorganism in the NP is a good proxy for its presence in the MEF.

Our study may have some limitations. Ambiguous or incomplete reporting limited the number of studies we were able to include and the amount of data we could extract. The

variation in study design, sampling methods and analyses, in particular patient or ear level, inclusion of single or multiple episodes per patient, could affect the generalizability of our findings. Next, it has been suggested that quantitative analysis of cultures increases the agreement between NP and MEF samples.[6,23] We did not include the quantitative approach in our review since clinical research of the effects of vaccines or antibiotics in OM often only focuses on the presence of microorganisms in the NP cultures regardless of their density.[1,3,4] Also, most studies included in this review did not report a quantitative analysis. Syrjanen and colleagues did perform a quantitative analysis but only found a small increase of the PPV and a decrease of the NPV.[23] Because of limited data availability we could not explore the concordance of antimicrobial resistance patterns of microorganisms found in both NP and MEF. Some studies have suggested a good agreement for serotypes and susceptibility patterns of microorganisms found in paired NP and MEF samples, suggesting that NP sampling may be of value for the monitoring of antimicrobial resistance in children with OM.[10,12,23] Lastly, only 4 studies used PCR: these detected more microorganisms in AOM and OME than conventional methods except for the study by Eser et al.[11] None used newer molecular techniques that could even provide higher accuracy in testing for microbial presence.[34,35] For a better understanding of the etiology of OM and the relation between the microflora in the nasopharynx and the middle ear, more research into microbial interactions and pathogen-host interactions is needed using more advanced diagnostic techniques.

In conclusion, we found a moderate concordance between test results for bacteria and viruses of NP and MEF samples in children with OM, indicating that it is important to carefully interpret and use results of studies using NP samples as a proxy for MEF.

References

1. Cohen R, Levy C, Bingen E, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. Pediatr Infect Dis J 2012;31:297-301.
2. Hilty M, Qi W, Brugger SD, et al. Nasopharyngeal microbiota in infants with acute otitis media. J Infect Dis 2012;205:1048-55.
3. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. N Engl J Med 2011;364:105-15.
4. Tahtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011;364:116-26.
5. Rosenfeld RM, Bluestone CD. Clinical efficacy of surgical therapy. In: Rosenfeld RM, Bluestone CD, eds. Evidence-Based Otitis Media. 2 ed. Hamilton, Ontario, Canada: BC Decker Inc.; 2003:227-40.
6. Schwartz R, Rodriguez WJ, Mann R, et al. The nasopharyngeal culture in acute otitis media. A reappraisal of its usefulness. JAMA 1979;241:2170-3.
7. Rovers MM, Schilder AG, Zielhuis GA, et al. Otitis media. Lancet 2004;363:465-73.
8. Vergison A. Microbiology of otitis media: a moving target. Vaccine 2008;26 Suppl 7:G5-10.
9. Bakaletz LO. Immunopathogenesis of polymicrobial otitis media. J Leukoc Biol 2010;87:213-22.
10. Eldan M, Leibovitz E, Piglansky L, et al. Predictive value of pneumococcal nasopharyngeal cultures for the assessment of nonresponsive acute otitis media in children. Pediatr Infect Dis J 2000;19:298-303.
11. Eser OK, Ipci K, Alp S, et al. Efficacy of nasopharyngeal culture in identification of pathogen in middle ear fluid in chronic otitis media with effusion. Indian J Med Microbiol 2009;27:237-41.
12. Gehanno P, Lenoir G, Barry B, et al. Evaluation of nasopharyngeal cultures for bacteriologic assessment of acute otitis media in children. Pediatr Infect Dis J 1996;15:329-32.
13. Kamme C, Lundgren K, Mardh PA. The aetiology of acute otitis media in children. Occurrence of bacteria, L forms of bacteria and mycoplasma in the middle ear exudate. Relationship between bacterial findings in the middle ear exudate, nasopharynx and throat. Scand J Infect Dis 1971;3:217-23.
14. Kamme C, Nilsson NI. Secretory otitis media: microbiology of the middle ear and the nasopharynx. Scand J Infect Dis 1984;16:291-6.
15. Klein BS, Dollete FR, Yolken RH. The role of respiratory syncytial virus and other viral pathogens in acute otitis media. J Pediatr 1982;101:16-20.
16. McNeill RA. Comparison of the bacteria found in the ear and nasopharynx in acute otitis media. J Laryngol Otol 1962;76:617-22.
17. Nilson BW, Poland RL, Thompson RS, et al. Acute otitis media: treatment results in relation to bacterial etiology. Pediatrics 1969;43:351-8.
18. Nokso-Koivisto J, Raty R, Blomqvist S, et al. Presence of specific viruses in the middle ear fluids and respiratory secretions of young children with acute otitis media. J Med Virol 2004;72:241-8.
19. Pitkaranta A, Virolainen A, Jero J, et al. Detection of rhinovirus, respiratory syncytial virus, and coronavirus infections in acute otitis media by reverse transcriptase polymerase chain reaction. Pediatrics 1998;102:291-5.
20. Rosenblut A, Santolaya ME, Gonzalez P, et al. Bacterial and viral etiology of acute otitis media in Chilean children. Pediatr Infect Dis J 2001;20:501-7.
21. Stenfors LE, Raisanen S. Bacterial attachment in vivo to epithelial cells of the nasopharynx during otitis media with effusion. J Laryngol Otol 1992;106:111-5.
22. Sriwardhana KB, Howard AJ, Dunkin KT. Bacteriology of otitis media with effusion. J Laryngol Otol 1989;103:253-6.
23. Syrjanen RK, Herva EE, Makela PH, et al. The value of nasopharyngeal culture in predicting the etiology of acute otitis media in children less than two years of age. Pediatr Infect Dis J 2006;25:1032-6.
24. Tanon-Anoh MJ, Kacou-Ndouba A, Yoda M, et al. Particularities of bacterial ecology of acute otitis media in an African subtropical country (Cote d'Ivoire). Int J Pediatr Otorhinolaryngol 2006;70:817-22.
25. Tomonaga K, Kurono Y, Chaen T, et al. Adenoids and otitis media with effusion: nasopharyngeal flora. Am J Otolaryngol 1989;10:204-7.
26. Ueyama T, Kurono Y, Shirabe K, et al. High incidence of Haemophilus influenzae in nasopharyngeal secretions and middle ear effusions as detected by PCR. J Clin Microbiol 1995;33:1835-8.
27. Yano H, Okitsu N, Hori T, et al. Detection of respiratory viruses in nasopharyngeal secretions and middle ear fluid from children with acute otitis media. Acta Otolaryngol 2009;129:19-24.

28. Bosch A, Biesbroek G, Trzcinski K, et al. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog 2013;9:e1003057.
29. Bogaert D, van Belkum A, Sluijter M, et al. Colonisation by Streptococcus pneumoniae and Staphylococcus aureus in healthy children. Lancet 2004;363:1871-2.
30. Peters BM, Jabra-Rizk MA, O'May GA, et al. Polymicrobial interactions: impact on pathogenesis and human disease. Clin Microbiol Rev 2012;25:193-213.
31. Mandel EM, Casselbrant ML, Kurs-Lasky M. Acute otorrhea: bacteriology of a common complication of tympanostomy tubes. Ann Otol Rhinol Laryngol 1994;103:713-8.
32. Oberman JP, Derkay CS. Posttympanostomy tube otorrhea. Am J Otolaryngol 2004;25:110-7.
33. Brook I, Gober AE. Bacteriology of spontaneously draining acute otitis media in children before and after the introduction of pneumococcal vaccination. Pediatr Infect Dis J 2009;28:640-2.
34. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev 2008;21:716-47.
35. Barken KB, Haagensen JA, Tolker-Nielsen T. Advances in nucleic acid-based diagnostics of bacterial infections. Clin Chim Acta 2007;384:1-11.

Appendix table 1 [Part 1/3]. Characteristics of the studies included in this review.

Study	Sampling period	Number of children (paired MEF-NP samples from these children)	Care setting	Study population	Age (mean/median)	Sampling methods	Microbes tested and used in this review*	Laboratory methods
AOM studies								
McNeill (1962, UK)[16]	Not reported	Not reported (52)	Secondary	I: AOM with discharge from a perforated tympanic membrane; E: -	4 months – 19 years (not reported)	NP: transoral swab MEF: otorrhea swab	SP, MC, SA	Conventional culture
Nilson (1969, USA)[17]	1966-1968	306 (306)	Tertiary	I: clinical diagnosis of AOM; E: pneumonia, vomiting, allergy for study medication, underlying debilitating disease, tympanic membrane perforation, antibiotic use in past 2 weeks, symptoms for more than 10 days.	<3 years (not reported)	NP: swab (not further defined) MEF: aspiration	HI	Conventional culture
Kamme (1971, Sweden)[13]	Not reported	75 (75)	Tertiary	I: clinical signs of AOM with bulging of tympanic membrane; E: tympanic membrane perforation, otitis or antibiotic use in past month.	1-9 years (not reported)	NP: transnasal swab MEF: aspiration	SP, HI, MC	Conventional culture
Klein (1982, USA)[15]	1981	53 (53)	Tertiary	I: clinical signs of AOM; E: otitis or antibiotic use in past 2 weeks.	2 months – 12 years (not reported)	NP: aspiration MEF: aspiration	RSV, IV	ELISA
Gehanno (1996, France)[12]	1992-1993	354 (354)	Secondary	I: clinical signs of AOM with bulging of tympanic membrane, temperature > 38°C; E: tympanic membrane perforation, severe infection.	<6 years (22 months)	NP: aspiration MEF: aspiration	SP, HI, MC	Conventional culture
Pitkäranta (1998, Finland)[19]	1990-1992	92(92)	Tertiary	I: otoscopic findings indicative of MEF with symptoms of acute infection; E: antibiotic use in past week, tympanostomy tubes, tympanic membrane perforation.	3 months – 6.5 years (30 months)	NP: aspiration MEF: aspiration	RV, RSV	RT-PCR

Appendix table 1 [Part 2/3]. Characteristics of the studies included in this review.

Study	Sampling period	Number of children (paired MEF-NP samples from these children)	Care setting	Study population	Age (mean/median)	Sampling methods	Microbes tested and used in this review*	Laboratory methods
Eldan (2000, Israel)[10]	1994-1999	362 (362)	Tertiary	I: symptoms and signs of AOM for <7 days; E: tympanic membrane perforation, tympanostomy tubes, antibiotic use in past 2 weeks.	3-48 months (10 months)	NP: not reported MEF: aspiration	SP	Conventional culture
Rosenblüt (2001, Chile)[20]	1998-1999	170 (170)	Secondary	I: AOM with symptoms <7 days and irritability/pain in at least 1 ear; E: antibiotic use in past 2 days, tympanostomy tubes, tympanic membrane perforation.	4 months–9 years (36 months)	NP: aspiration MEF: aspiration	RSV, IV, AV	Viral culture IF (of NPF samples)
Nokso-Koivisto (2004, Finland)[18]	1994–1997 1995–1999	203 (759) 459 (1416)	Primary	I: AOM (a visually abnormal tympanic membrane) concomitantly with signs of acute infection; E: -	2-24 months (not reported)	NP: aspiration MEF: aspiration	HRV, RSV, EV, IV, AV	RT-PCR (HRV, EV) IF (RSV, IV, AV)
Syrjänen** (2006, Finland)[23]	1994-1997	200 (586)**	Primary	I: AOM (a visually abnormal tympanic membrane) concomitantly with signs of acute infection; E: otitis or antibiotic use in past 2 weeks.	2-24 months (not reported)	NP: aspiration MEF: aspiration	SP, HI	Conventional culture
Tanon-Anoh (2006, Ivory Coast) [24]	2002-2003	60 (60)	Secondary	I: clinical diagnosis of AOM; E: antibiotic use in past 4 weeks.	3 months-13 years (29 months)	NP: swab (not further defined) MEF: otorrhea and MEF (paracentesis) swabs	SP, HI, MC, SA	Conventional culture
Yano (2009, Japan)[27]	2002-2004	1092 (1092)	Secondary	I: AOM (a visually abnormal tympanic membrane) with concurrent symptoms of acute respiratory infection; E: -	≤10 years (1.4 years)	NP: not reported MEF: not reported	HRV, RSV, EV, IV, AV	Viral culture + rapid viral antigen tests (only for RSV, IV, AV)

Appendix table 1 [Part 3/3]. Characteristics of the studies included in this review.

Study	Sampling period	Number of children (paired MEF-NP samples from these children)	Care setting	Study population	Age (mean/median)	Sampling methods	Microbes tested and used in this review*	Laboratory methods
OME studies								
Kamme (1984, Sweden)[14]	Not reported	117 (117)	Tertiary	I: OME for 4-12 weeks (n=101) or > 12 weeks (n=16); E: antibiotic use in past month, tympanostomy tubes, recent myringotomy.	13 months-8 years (47 months)	NP: transnasal swab MEF: aspiration	SP, HI, MC	Conventional culture
Tomonaga (1989, Japan)[25]	1984-1987	259 (325)∞	Tertiary	I: OME (not further defined) with indication for myringotomy or tympanostomy-tube insertion; E: -	2-15 years (not reported)	NP: transnasal swab MEF: aspiration	SP, HI, MC, SA	Conventional culture
Sriwardhana (1989, UK)[22]	1986-1987	152 (259)***	Secondary	I: OME of >3 months duration; E: -	2-20 years (6 years)	NP: swab (not further defined) MEF: aspiration	SP, HI, MC, SA	Conventional culture
Stenfors (1992, Finland)[21]	Not reported	15 (15)	Secondary	I: treatment-resistant OME for which 1-2 prior myringotomies were performed; E: AOM, acute sinusitis, acute tonsillitis, antibiotic use in past 2 weeks.	1-7 years (3.4 years)	NP: transoral swab MEF: aspiration	SP, HI, MC, SA	Conventional culture
Ueyama (1995, Japan)[26]	1991-1992	65 (80)	Tertiary	I: OME (not further defined); E: -	Not reported (not reported)	NP: aspiration MEF: aspiration	HI	Conventional culture PCR
Eser (2009, Turkey)[11]	2006	53 (53)	Tertiary	I: chronic OME (not further defined); E: acute febrile illness, AOM, respiratory tract infection or antibiotic use in past 2 weeks.	1-12 years (5.7 years)	NP: lavage (not further defined) MEF: not reported	SP, HI, MC	Conventional culture Multiplex-PCR

MEF = middle ear fluid; * = some studies also tested for other microbes, but the data for a 2 by 2 table could not be extracted; AOM = acute otitis media; I = inclusion criteria; E = exclusion criteria; NP = nasopharynx; SP = *Streptococcus pneumoniae*; HI = *Haemophilus influenzae*; MC = *Moraxella catarrhalis*; RSV = Respiratory syncytial virus; IV = Influenzaviruses; ELISA = enzyme-linked immunosorbent assay; SA = *Staphylococcus aureus*; HRV = Human rhinovirus; EV = Enterovirus; AV = Adenovirus; (RT-)PCR = (reverse transcriptase) polymerase chain reaction; IF = immunofluoresence; ** = same children as first cohort Nokso-Koivisto, but tested for bacteria instead of viruses[17]; OME = otitis media with effusion; *** = 107 nasopharyngeal cultures used twice in analysis for bilateral disease; ∞ = 66 nasopharyngeal cultures used twice in analysis for bilateral disease.

Appendix table 2. Concordances between middle ear fluid and nasopharyngeal sample test results for bacteria of all acute otitis media and otitis media with effusion studies included in this review.

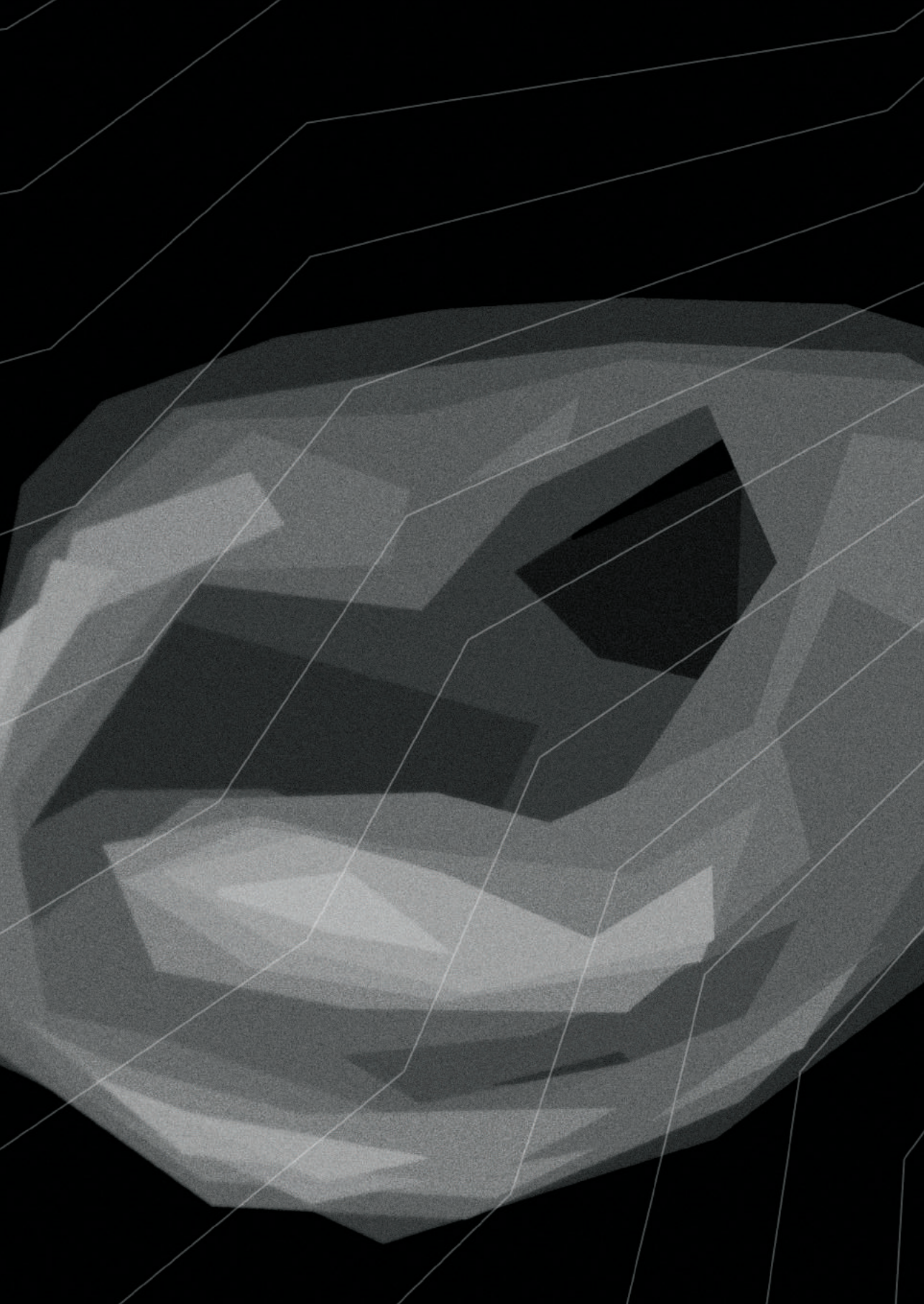
Study		*S. pneumoniae* (%)				*H. influenzae* (%)				*M. catarrhalis* (%)				*S. aureus* (%)			
AOM studies	**n**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**
McNeill (1962)[16]	52	0	10	0	90	NA	NA	NA	NA	0	0	54	46	15	50	6	29
Nilson (1969)[17]	306	NA	NA	NA	NA	12	12	7	68	NA	NA	NA	NA	NA	NA	NA	NA
Kamme (1971)[13]	75	52	1	17	29	15	0	12	73	9	0	33	57	NA	NA	NA	NA
Gehanno (1996)[12]	354	23	1	30	46	32	5	30	33	7	1	32	60	NA	NA	NA	NA
Eldan (2000)[10]	362	31	7	35	27	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Syrjänen (2006)[23]	586	27	0	27	46	17	5	9	69	NA	NA	NA	NA	NA	NA	NA	NA
Tanon-Anoh (2006)[24]	60	20	8	13	58	0	2	0	98	0	2	0	98	0	5	0	95
OME studies		**M+N**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**
Kamme (1984)[14]	117	2	0	35	63	9	6	23	62	7	3	45	45	NA	NA	NA	NA
Tomonaga (1989)[25]	325	4	2	14	80	6	4	3	87	1	0	2	97	1	2	19	77
Sriwardhana (1989)[22]	259	2	1	11	86	7	6	20	67	0	0	4	95	1	3	4	93
Stenfors (1992)[21]	15	13	0	27	60	13	0	20	67	7	0	40	53	0	0	7	93
Ueyama (1995)[26]	80	NA	NA	NA	NA	58	0	33	10	NA	NA	NA	NA	NA	NA	NA	NA
Eser (2009)[11]	53	6	13	9	72	6	6	2	87	0	8	0	92	NA	NA	NA	NA

AOM = acute otitis media; n = total number of episodes/ears; M = middle ear fluid culture; N = nasopharyngeal culture; + = positive test result; - = negative test result; NA = not available; OME = otitis media with effusion; due to rounding the percentages do not always add up to 100.

Appendix table 3. Concordances between middle ear fluid and nasopharyngeal sample test results for viruses of all acute otitis media and otitis media with effusion studies included in this review.

Study		Human rhinovirus (%)				Respiratory syncytial virus (%)				Influenzaviruses† (%)				Enterovirus (%)				Adenovirus (%)			
AOM studies	**N**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**
Klein[15]	53	NA	NA	NA	NA	17	2	11	70	4	0	2	94	NA	NA	NA	NA	NA	NA	NA	NA
Pitkäranta[19]	92	20	4	11	65	13	5	10	72	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rosenblüt[20]	170	NA	NA	NA	NA	3	0	4	94	0	0	3	97	NA	NA	NA	NA	1	0	2	98
Nokso-Koivisto[18]	1416	13	3	15	68	6	0	3	90	1	0	1	97	11	5	10	75	0	0	2	98
	759	15	11	15	59	5	1	3	91	1	0	1	97	NA	NA	NA	NA	1	0	2	97
Yano[27]	1092	0	0	1	99	3	1	11	85	1	0	4	94	0	0	1	99	1	0	5	94
OME studies		**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**	**M+N+**	**M+N-**	**M-N+**	**M-N-**
NA																					

AOM = acute otitis media; n = total number of OM episodes/ears; M = middle ear fluid culture; N = nasopharyngeal culture; + = positive test result; - = negative test result; † = results for type A were used if only presented in subtypes; OME = otitis media with effusion; NA = not available; due to rounding the percentages do not always add up to 100



Chapter 5

General discussion

Mrs. Van Kempen, mother of 5-year old Lucas who had tympanostomy tubes placed some months ago for his recurrent middle ear infections, has contacted her family physician by phone. For three days Lucas' left ear has been discharging and he seems to be having difficulty hearing. He is a bit irritable but otherwise fine.
The family physician is unsure how best to manage this problem. Usually he would suggest to wait for a week and see if the discharge resolves. On the other hand he feels that oral antibiotics may shorten the condition, while at a recent Continuing Medical Education course an ENT surgeon suggested that antibiotic(-glucocorticoid) eardrops work best in these children.

From practice to evidence

At present, practice regarding the management of children with acute tympanostomy-tube otorrhea (ATTO) varies widely both nationally and internationally.[1] Standard patient information, for example in the Netherlands and the United States, advises parents to contact a physician when their child's symptoms of tube otorrhea persist for more than a week.[2,3] At that stage, the guideline recently published by the American Academy of Otolaryngology - Head and Neck Surgery Foundation recommends physicians to prescribe antibiotic(-glucocorticoid) eardrops, while the guideline issued by the Dutch College of Family Physicians (*Nederlands Huisartsen Genootschap*) recommends oral antibiotics (amoxicillin-clavulanate).[3,4] NICE, the UK National Institute for Health and Care Excellence that provides health care guidance, advises physicians to manage ATTO as an episode of acute otitis media, i.e. initial observation for uncomplicated disease and oral antibiotics for complicated or persisting disease.[5]
When designing our trial, we asked a large number of Dutch family physicians and ear, nose, and throat (ENT) surgeons to fill out a questionnaire regarding ATTO treatment in daily clinical practice (unpublished data). It showed that they treat ear discharge differently; most family physicians start with initial observation and prescribe oral antibiotics or antibiotic(-glucocorticoid) eardrops only when discharge persists, while ENT surgeons immediately prescribe eardrops.
This inconsistent guidance and consequent variation in clinical practice, may originate from different interpretation of the limited evidence on the effects of various management strategies in children with ATTO. The few trials comparing topical and oral antibiotics included small numbers of children or had methodological limitations affecting the applicability of their results to clinical practice.[6-9] So far, no study assessed the actual need to treat children with ATTO.[6]
We designed a pragmatic trial comparing a strategy of initial observation with immediate topical or oral antibiotics. The Netherlands Organization for Health Research and Development (*ZonMw*) recognized the importance of high-quality evidence on this topic and funded our trial. With the support of a network of dedicated Ear Nose and Throat surgeons and family physicians across the Netherlands, we were the first to successfully study the clinical and cost-effectiveness of the three most common treatment strategies in children with ATTO.
Alongside this trial, and in cooperation with GlaxoSmithKline Biologicals, we collected otorrhea and nasopharyngeal samples of participating children and assessed prevalence and antimicrobial susceptibility of microorganisms involved in ATTO after the introduction of routine pneumococcal conjugate vaccination (PCV) in the Netherlands in April 2006.

From evidence to practice

Our trial showed that treatment with antibiotic-glucocorticoid eardrops was clinically superior to oral antibiotics and initial observation both in the short- and long-term *(Chapter 3.1)*. Topical treatment also has economic benefits, making it the most cost-effective treatment in children with ATTO *(Chapter 3.2)*. Although commonly practiced, initial observation had poorer clinical outcomes and was associated with higher costs compared to topical treatment; at 2 weeks, symptoms of otorrhea persisted in 55% of the children managed by initial observation. In the subsequent 6 months, children managed by initial observation also had more days with otorrhea as compared to those initially treated with eardrops.

Our pragmatic trial reflects real world practice and its results are therefore highly applicable to children with recent-onset tube otorrhea. We recommend updating current patient information and clinical practice guidelines with this new and important evidence. Our results show it is best to inform parents to contact their physician when ATTO occurs, rather than waiting for a week or more to see if the otorrhea abates without treatment. We recommend physicians to treat children with tympanostomy tubes who develop otorrhea with antibiotic-glucocorticoid eardrops shortly after onset of symptoms.

We are the first to report on the microorganisms involved in ATTO in the post-PCV era. Compared to previous studies on ATTO microbiology, we found a lower prevalence of *Streptococcus pneumonia* and higher prevalences of *Haemophilus influenza* and *Staphylococcus aureus* in otorrhea as well as nasopharyngeal samples (*Chapter 4.1*).[8-16] This is in agreement with other studies of bacterial prevalence in the upper respiratory tract of both healthy children and those with AOM performed after implementation of PCV.[17-28] The choice of antibiotic-glucocorticoid eardrops is best based on their effectiveness against the bacteria most prevalent in otorrhea of children with ATTO: i.e. *H. influenzae*, *S. aureus* and *Pseudomonas aeruginosa*. Antibiotic-glucocorticoid eardrops most frequently used in the Netherlands for the management of middle ear infections include hydrocortisone-bacitracin-colistin eardrops (*Bacicoline-B®*), dexamethasone-framycetin-gramicidin eardrops (*Sofradex®*) and ofloxacin eye-drops (*Trafloxal®*). The bacteria most prevalent in our study are generally sensitive to Bacicoline-B, *P. aeruginosa* is resistant to Sofradex and around half of *S. pneumoniae* strains in our study were intermediately resistant to Trafloxal (*Chapter 4.1*).[29,30] Other eardrops that cover the most prevalent bacteria are generic dexamethasone-chloramphenicol-polymyxin B eardrops (less costly than Bacicoline-B), oxytetracycline-hydrocortisone-polymyxin B eardrops (*Terra-cortril + Polymyxine B®*), and trimethoprim-polymyxin B eyedrops (*Polytrim*). The latter does not contain a glucocorticoid, which may be disadvantageous, as it has been shown that a combination of antibiotic-glucocorticoid eardrops is more effective than topical antibiotics alone.[11,13]

Implications for future research

In making a treatment decision for ATTO, physicians often rely on parental observation of ear discharge. Although we have shown that parental assessment agrees well with an actual clinical examination by a physician after treatment of ear discharge, it is not known how well they agree in diagnosing ATTO when it initially develops. Existing patient information recommends parents to wait-and-see and contact their physician when ear discharge persists for a week, thereby reducing the risk of a false-positive diagnosis. Based upon the results of our trial however, we recommend updating guidance on ATTO into initiating

treatment shortly after onset of symptoms, so *within* a week. This may increase the risk of a false-positive diagnosis when physicians fully rely on parental observation for diagnosing ATTO. We feel that further research should be initiated to determine the interobserver agreement between parents and physicians in diagnosing ATTO, so that physicians know if they can indeed rely on parental observation when initiating ATTO treatment.

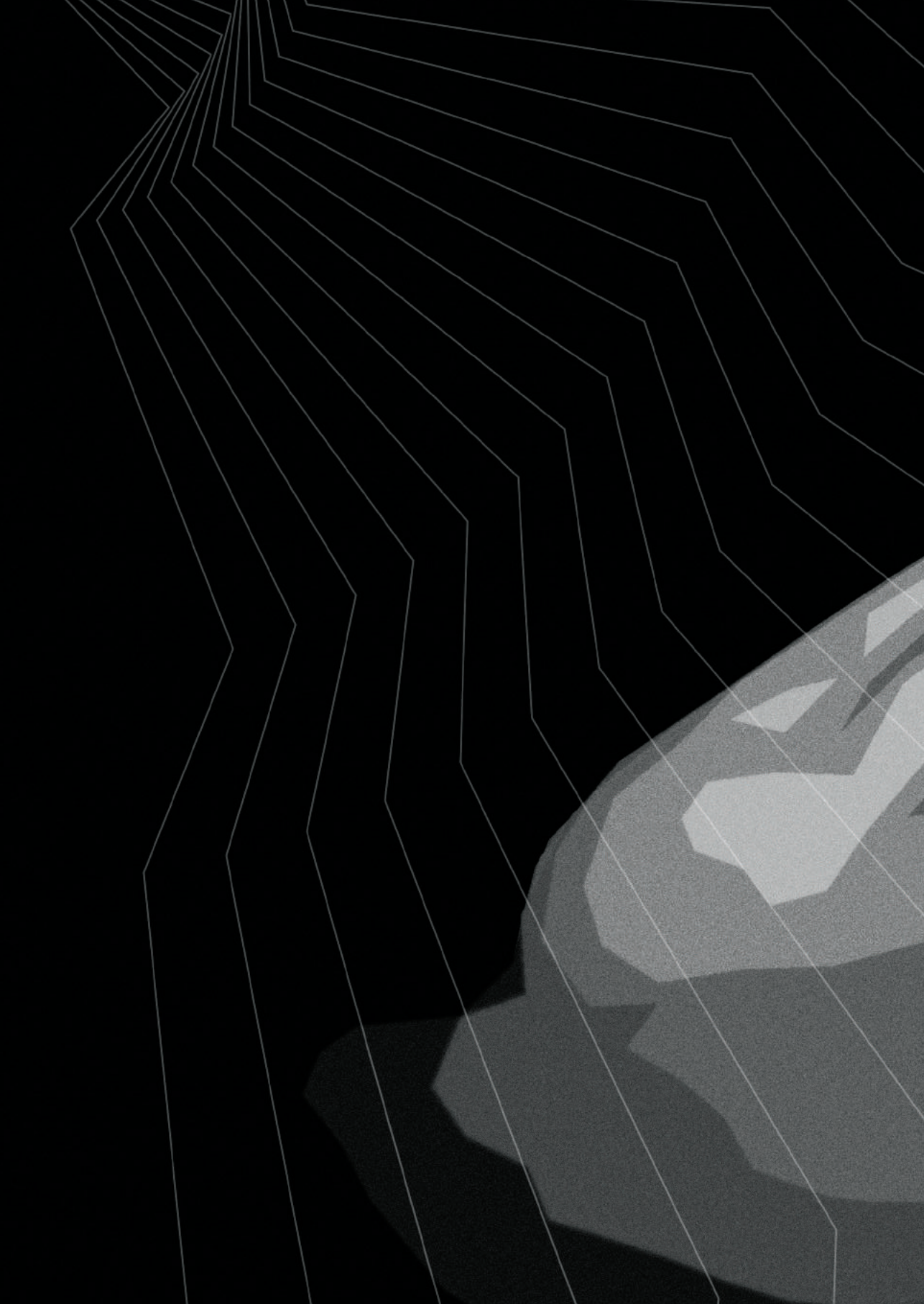
For many years, the use of topical antibiotics in children with ATTO has been questioned for their presumed inability to reach the middle ear. In vivo studies in children with a 'clean' ear canal and patent tympanostomy tube as well as in vitro studies reported low rates of spontaneous penetration of eardrops into the middle ear.[31-33] These studies raised even more doubt about eardrops reaching the middle ear in children with active tube otorrhea. Yet our study of children with middle ear fluid visibly draining through the tympanostomy tube into the ear canal showed that eardrops were highly effective, indicating that its active components do reach the site of infection. As such, one could therefore question whether antibiotic(-glucocorticoid) eardrops may also be effective in children without tubes who develop acute otitis media (AOM) and present with spontaneous otorrhea. So far, this has not been evaluated in a randomized clinical trial, presumably based upon the same rationale, i.e. that the eardrops would not reach the infected middle ear. Since topical treatment is usually well tolerated, causes no systemic side effects and is less likely to cause antimicrobial resistance as compared to oral antibiotics, a trial of the effectiveness of topical antibiotics versus oral antibiotics in children with AOM presenting with spontaneous otorrhea seems warranted.[7,8,34]

Insertion of tympanostomy tubes is one of the most frequently performed surgical procedures in children; its most common indications are persistent otitis media with effusion and recurrent AOM. Chapter 2 of this thesis shows that more than 67% of children receiving tubes for recurrent AOM develop one or more episodes of tube otorrhea in the year following tube placement, indicating further recurrences of AOM. Although such episodes may run a milder course than in children without tympanostomy tubes and are best treated with topical rather than systemic antibiotics (*Chapter 3.1*), a critical appraisal of tube insertion for children with recurrent AOM is appropriate as the evidence-base for this procedure in these children is poor.[35,36] This has also been acknowledged by the Dutch multidisciplinary practice guideline on otitis media in secondary care, which concludes that scientific evidence regarding the long-term effects of tympanostomy tubes in children with recurrent AOM is lacking.[37] An RCT evaluating the clinical and cost-effectiveness of tube insertion for recurrent AOM including long-term outcomes that are relevant to children and their parents is therefore pertinent.

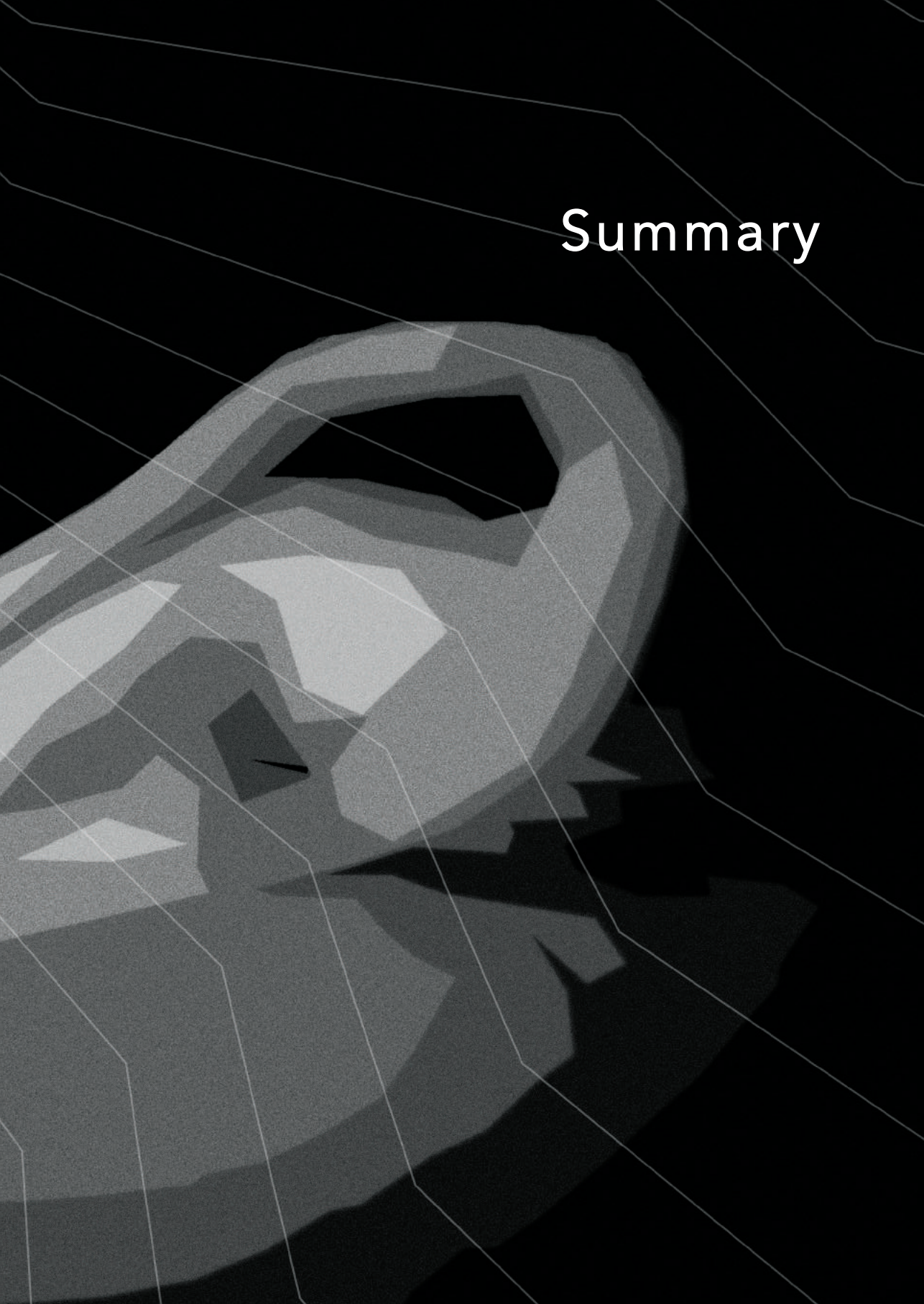
References

1. Badalyan V, Schwartz RH, Scwhartz SL, et al. Draining ears and tympanostomy tubes: a survey of pediatric otolaryngologists and pediatric emergency medicine physicians. Pediatr Emerg Care 2013;29:203-8.
2. Trommelvliesbuisjes [In Dutch]. Nederlandse Vereniging voor Keel- Neus- Oorheelkunde en Heelkunde van het Hoofd-Halsgebied. (Accessed June, 2013, at http://www.kno.nl/publiek/voorlichting/trommelvliesbuisjes.)
3. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg 2013;149:S1-S35.
4. Standaard M18: Otitis media met effusie [In Dutch]. Nederlands Huisartsen Genootschap (Accessed June, 2013, at https://http://www.nhg.org/standaarden/samenvatting/otitis-media-met-effusie.)
5. Management recurrent acute otitis media. NICE: national institute for health and care excellence. (Accessed June, 2013, at http://cks.nice.org.uk/otitis-media-acute - !scenariorecommendation:4.)
6. Vaile L, Williamson T, Waddell A, et al. Interventions for ear discharge associated with grommets (ventilation tubes). Cochrane Database Syst Rev 2006:CD001933.
7. Goldblatt EL, Dohar J, Nozza RJ, et al. Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes. Int J Pediatr Otorhinolaryngol 1998;46:91-101.
8. Dohar J, Giles W, Roland P, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2006;118:e561-9.
9. Heslop A, Lildholdt T, Gammelgaard N, et al. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhea in children: the results of a randomized clinical trial. Laryngoscope 2010;120:2516-20.
10. Mandel EM, Casselbrant ML, Kurs-Lasky M. Acute otorrhea: bacteriology of a common complication of tympanostomy tubes. Ann Otol Rhinol Laryngol 1994;103:713-8.
11. Roland PS, Anon JB, Moe RD, et al. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tubes. Laryngoscope 2003;113:2116-22.
12. Dohar J. Microbiology of otorrhea in children with tympanostomy tubes: implications for therapy. Int J Pediatr Otorhinolaryngol 2003;67:1317-23.
13. Roland PS, Kreisler LS, Reese B, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tubes. Pediatrics 2004;113:e40-6.
14. Ruohola A, Meurman O, Nikkari S, et al. Microbiology of acute otitis media in children with tympanostomy tubes: prevalences of bacteria and viruses. Clin Infect Dis 2006;43:1417-22.
15. Ruohola A, Meurman O, Nikkari S, et al. The dynamics of bacteria in the middle ear during the course of acute otitis media with tympanostomy tube otorrhea. Pediatr Infect Dis J 2007;26:892-6.
16. Granath A, Rynnel-Dagoo B, Backheden M, et al. Tube associated otorrhea in children with recurrent acute otitis media; results of a prospective randomized study on bacteriology and topical treatment with or without systemic antibiotics. Int J Pediatr Otorhinolaryngol 2008;72:1225-33.
17. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403-9.
18. Veenhoven R, Bogaert D, Uiterwaal C, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. Lancet 2003;361:2189-95.
19. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995-2003. Pediatr Infect Dis J 2004;23:824-8.
20. Block SL, Hedrick J, Harrison CJ, et al. Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. Pediatr Infect Dis J 2004;23:829-33.
21. McEllistrem MC, Adams JM, Patel K, et al. Acute otitis media due to penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis 2005;40:1738-44.
22. Brook I, Gober AE. Bacteriology of spontaneously draining acute otitis media in children before and after the introduction of pneumococcal vaccination. Pediatr Infect Dis J 2009;28:640-2.

23. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. JAMA 2010;304:2161-9.
24. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J 2010;29:304-9.
25. van Gils EJ, Hak E, Veenhoven RH, et al. Effect of seven-valent pneumococcal conjugate vaccine on Staphylococcus aureus colonisation in a randomised controlled trial. PLoS One 2011;6:e20229.
26. Spijkerman J, Prevaes SM, van Gils EJ, et al. Long-term effects of pneumococcal conjugate vaccine on nasopharyngeal carriage of S. pneumoniae, S. aureus, H. influenzae and M. catarrhalis. PLoS One 2012;7:e39730.
27. Pichichero ME. Otitis media. Pediatr Clin North Am 2013;60:391-407.
28. Casey JR, Kaur R, Friedel VC, et al. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. Pediatr Infect Dis J 2013;32:805-9.
29. Mylanus EA, Natsch S, Mulder JJ, et al. [Choice of ear drops in chronic otorrhea]. Ned Tijdschr Geneeskd 2000;144:1261-6.
30. Farmacotherapeutisch Kompas. College voor zorgverzekeringen. 2013. (Accessed at http://www.fk.cvz.nl.)
31. Saunders MW, Robinson PJ. How easily do topical antibiotics pass through tympanostomy tubes?--an in vitro study. Int J Pediatr Otorhinolaryngol 1999;50:45-50.
32. Hebert RL, 2nd, Vick ML, King GE, et al. Tympanostomy tubes and otic suspensions: do they reach the middle ear space? Otolaryngol Head Neck Surg 2000;122:330-3.
33. Boyd NH, Gottschall JA. Assessing the efficacy of tragal pumping: a randomized controlled trial. Otolaryngol Head Neck Surg 2011;144:891-3.
34. Weber PC, Roland PS, Hannley M, et al. The development of antibiotic resistant organisms with the use of ototopical medications. Otolaryngol Head Neck Surg 2004;130:S89-94.
35. Browning GG, Rovers MM, Williamson I, et al. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev 2010:CD001801.
36. McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. Cochrane Database Syst Rev 2008:CD004741.
37. Richtlijn Otitis Media bij kinderen in de tweede lijn. CBO 2012.



Summary



Tympanostomy-tube placement is one of the most common surgical procedures performed in children worldwide. Otorrhea, or ear discharge, is a frequent sequela in children with tubes; it is usually a symptom of a middle ear infection whereby fluid that has built up in the middle ear drains through the tube into the child's ear canal. Acute tympanostomy-tube otorrhea (ATTO) is mostly unpleasant and can smell bad; the underlying middle ear infection can cause general illness, pain and fever. Most episodes of tympanostomy-tube otorrhea (TTO) last days to weeks; some children develop chronic otorrhea, which may cause considerable morbidity and hearing loss. Therefore, it is important that children with ATTO receive the best treatment. The main aim of this thesis was to assess the clinical and cost-effectiveness of the three most frequently used treatment strategies in children with ATTO: antibiotic-glucocorticoid eardrops, oral antibiotics and initial observation.

Chapter 2 reports on a large cohort study designed to establish the current incidence of TTO and its predictors. Using a parental web-based questionnaire, we retrospectively collected data on TTO episodes and its potential predictors from a cohort of 1,184 children younger than 10 years of age with tympanostomy tubes. The mean duration of time between tube placement and parents filling out the questionnaire was approximately 8 months, adding up to a total of 768 years of data. Accounting for time since tube placement, 67% of the children developed one or more TTO episodes in the year following tube placement. Young age, recurrent acute otitis media being the indication for tube placement, a recent history of recurrent upper respiratory tract infections and the presence of older siblings were independently associated with the future occurrence of TTO, and can therefore be seen as predictors for TTO.

In **chapter 3** we focus on the treatment for acute otorrhea in children with tympanostomy tubes.
First, we present the clinical outcomes of our open label pragmatic trial. We randomly allocated 230 children with ATTO aged 1 to 10 years to hydrocortisone-bacitracin-colistin eardrops (76 children), oral amoxicillin-clavulanate suspension (77 children) or initial observation (77 children). Antibiotic-glucocorticoid eardrops were superior to oral antibiotics and initial observation for both the primary and secondary clinical outcomes. At 2 weeks, 5% of children treated with antibiotic-glucocorticoid eardrops had persisting otorrhea at otoscopy (primary outcome) versus 44% of those treated with oral antibiotics (risk difference (RD): -39%, 95% confidence interval (CI): -51% to -26%) and 55% of those managed by initial observation (RD: -49%, 95%CI: - 62% to -37%). The median initial otorrhea episode lasted 4 days in children treated with antibiotic-glucocorticoid eardrops versus 5 days in children treated with oral antibiotics ($p<0.001$) and 12 days in children managed by initial observation ($p<0.001$). In the long-term, the median total number of days with otorrhea during 6 months follow-up was 5 days in children receiving eardrops versus 13.5 days in those receiving oral antibiotics ($p<0.001$) and 18 days in those managed by initial observation ($p<0.001$). At baseline, the generic and disease-specific health-related quality-of-life (HRQoL) scores indicated good quality of life and were similar across the groups. At 2 weeks follow-up, the change in generic HRQoL scores did not significantly differ between groups. The changes in disease specific HRQoL scores at 2 weeks were small but consistently favored eardrops. Treatment-related adverse events were mild and no complications were reported at 2 weeks. We concluded that antibiotic-glucocorticoid

eardrops are more effective than oral antibiotics and initial observation in children with tympanostomy tubes suffering from uncomplicated acute otorrhea.
Second, we carried out cost-effectiveness analyses alongside our pragmatic randomized controlled trial using a societal perspective. At 2 weeks, mean total cost per patient was €29.45 (SE: 3.42) for antibiotic-glucocorticoid eardrops, €49.01 (SE: 13.38) for oral antibiotics and €56.94 (SE: 12.92) for initial observation. At 6 months mean total cost per patient was €255.59 (SE: 354.07), €292.05 (SE: 470.14) and €444.56 (SE: 644.91), respectively. This means that antibiotic-glucocorticoid eardrops are not only clinically most effective; they also have economic benefits over oral antibiotics and initial observation in children who develop ATTO.
Third, we used our trial data and those from a trial on treatment of active chronic mucosal otitis media, to study the interobserver agreement between parents and physicians in assessing whether children's otorrhea has persisted after treatment. We found a good agreement between parents' and physician's assessment, with high positive predictive values, but lower negative predictive values. We concluded that parents and physicians agree in most cases about persistence of ear discharge after treatment, suggesting that the need for further treatment can be based on parental judgment.

Chapter 4 reports on the results of two microbiological studies.
First, we present the prevalences of bacteria and viruses found in otorrhea and nasopharyngeal samples of the children with ATTO who participated in our trial. Both before and after treatment, *Haemophilus influenzae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most prevalent bacteria in the otorrhea of children with ATTO, while *H. influenzae* and *S. aureus* were most prevalent in the nasopharyngeal samples. In our study performed in the post-pneumococcal conjugate vaccine (PCV) era, we found a lower prevalence of *Streptococcus pneumoniae* than studies performed before introduction of PCV. Most pneumococci detected in our study were non-PCV7 serotypes. The high prevalence of *S. aureus* in our study, like in other studies performed in PCV-vaccinated children, suggests that *S. aureus* is an important upper respiratory tract pathogen in the post-PCV era. Antimicrobial resistance was low; we found only inherent antimicrobial resistance in the otorrhea samples from failures of all three study groups. We found few viruses in the otorrhea samples, while adenovirus, human rhinovirus and polyomaviruses were more frequently detected in the nasopharyngeal samples.
Second, we performed a systematic review of studies reporting on the concordance between test results of nasopharyngeal and middle ear fluid samples in children with otitis media. Studies of microorganisms involved in otitis media in children often use nasopharyngeal samples as a proxy for middle ear fluid to test for bacteria and viruses, since obtaining a sample of middle ear fluid involves tympanocentesis (myringotomy) when the tympanic membrane is still intact. As such, practical and medical ethical issues are avoided, but it is unclear whether this proxy provides an accurate estimate of the prevalences of the various microorganisms involved in otitis media. Overall, the included studies comprised of 4791 paired samples from 3278 children with acute otitis media (AOM) and 849 paired samples from 661 children with otitis media with effusion. Concordances varied from 68 to 97% per microorganism and we found low positive predictive values and moderate to high negative predictive values. These results indicate that test results from nasopharyngeal

samples do not always provide an accurate proxy for those of the middle ear fluid and that it is therefore important to interpret and use results of such studies carefully.

In **chapter 5** we discuss how our results can be implemented into daily clinical practice. At present, practice regarding the management of children with ATTO is inconsistent. Parents are generally advised to contact a physician when their child's symptoms of tube otorrhea persist for more than a week. Physician guideline recommendations vary widely from initial observation to treatment with either oral or topical antibiotics. Our trial showed that antibiotic-glucocorticoid eardrops are not only clinically superior but also have economic benefits over oral antibiotics and initial observation. The pragmatic design of our trial reflects real world practice and its results are therefore highly applicable to children with recent-onset tube otorrhea. Based on our findings as presented in this thesis we recommend updating current patient information and clinical practice guidelines with this new and important evidence. Our results show it is best to inform parents to contact their physician when ATTO occurs, rather than to wait for a week or more to see if otorrhea resolves without treatment. We recommend that physicians treat children with tympanostomy tubes who develop otorrhea with antibiotic-glucocorticoid eardrops shortly after onset of symptoms.
We also address questions we believe future research should focus on. In making a treatment decision, physicians often rely on parental observation of ear discharge. Although we have shown that this agrees well with clinical examination by a physician in case ear discharge persists after treatment, it is not known how well parents and physicians agree in diagnosing ATTO when it initially develops. Current patient information advises parents to wait-and-see and contact their physician when ear discharge persists for a week, thereby reducing the risk of a false-positive diagnosis. Our recommendations to change both current patient information (i.e. parents contacting a physician when ATTO occurs) and clinical practice guidelines (i.e. physicians initiating treatment shortly after onset of symptoms) may however increase the risk of a false-positive diagnosis. Studying the interobserver agreement between parents and physicians in diagnosing ATTO is important for physicians to know whether they can indeed rely on parental observation when initiating treatment.
So far, no RCT has evaluated whether antibiotic(-glucocorticoid) eardrops are beneficial in children with AOM without tubes who present with spontaneous otorrhea. Since topical treatment is better tolerated (no systemic side effects) and is less likely to cause antimicrobial resistance as compared to oral antibiotics, we believe that a trial of the effectiveness of topical antibiotics versus oral antibiotics in children with AOM presenting with spontaneous otorrhea is warranted.

Samenvatting

Het plaatsen van trommelvliesbuisjes is wereldwijd één van de meest uitgevoerde chirurgische ingrepen bij kinderen. Otorroe, ofwel een loopoor, is een veelvoorkomend probleem bij kinderen met buisjes: het is doorgaans een uiting van een middenoorontsteking waarbij ontstekingsvocht via het buisje de gehoorgang in loopt. Wanneer kinderen met trommelvliesbuisjes een acuut loopoor krijgen ('*acute tympanostomy-tube otorrhea*'), is dit vooral vervelend voor hen omdat het vies kan ruiken; ze kunnen ziek zijn van de onderliggende middenoorontsteking en daarbij pijn en koorts hebben. Meestal duurt een dergelijke episode een paar dagen tot weken. Sommige kinderen ontwikkelen echter een chronisch loopoor, wat aanzienlijk meer klachten en gehoorproblemen kan geven. Het is daarom belangrijk dat kinderen met buisjes die een acuut loopoor hebben snel een effectieve behandeling krijgen. Het overkoepelende doel van dit proefschrift is de klinische en kosteneffectiviteit vast te stellen van de drie meest gangbare behandelingen van een acuut loopoor bij kinderen met trommelvliesbuisjes: antibiotica-glucocorticoïd oordruppels, orale antibiotica of een afwachtend beleid.

In **hoofdstuk 2** bespreken we een grote cohortstudie die we hebben opgezet om de incidentie van een loopoor bij kinderen met trommelvliesbuisjes te bepalen evenals voorspellers voor het ontstaan ervan. Ouders van 1,184 kinderen jonger dan 10 jaar oud met trommelvliesbuisjes, hebben een internetvragenlijst ingevuld over doorgemaakte looporen en mogelijke voorspellers hiervoor. De gemiddelde tijdsduur tussen de plaatsing van trommelvliesbuisjes en het invullen van de vragenlijst was bijna 8 maanden en in totaal hebben we gegevens over 768 kinderjaren verzameld. 67% van de kinderen blijkt tenminste éénmaal een loopoor te krijgen in het jaar na plaatsing van de buisjes. De kans op een loopoor is het grootst als de buisjes op jonge leeftijd worden geplaatst, herhaalde acute middenoorontstekingen de reden zijn voor de buisjes, het kind recent herhaalde bovenste luchtweginfecties heeft doorgemaakt en oudere broertjes/zusjes heeft. Deze vier variabelen waren namelijk onafhankelijke voorspellers voor het optreden van een loopoor bij trommelvliesbuisjes.

Hoofdstuk 3 gaat over de behandeling van een acuut loopoor bij kinderen met trommelvliesbuisjes.
In hoofdstuk 3.1 presenteren we de klinische resultaten van onze gerandomiseerde pragmatische interventiestudie. In totaal deden 230 kinderen tussen 1 en 10 jaar oud met een acuut loopoor bij trommelvliesbuisjes mee aan het onderzoek. Zij werden door loting toegewezen aan één van de drie behandelgroepen: hydrocortison-bacitracine-colistine oordruppels (76 kinderen), amoxicilline-clavulaanzuurdrank (77 kinderen) of een afwachtend beleid (77 kinderen). Antibiotica-glucocorticoïd oordruppels waren effectiever dan een antibioticumdrank en een afwachtend beleid voor zowel de primaire als secundaire uitkomstmaten. We zagen bij otoscopie 2 weken na start van de behandeling, dat 5% van de kinderen die waren behandeld met antibiotica-glucocorticoïd oordruppels nog otorroe had (primaire uitkomstmaat), versus 44% van de kinderen behandeld met een antibioticumdrank (risicoverschil (RV): -39%, 95% betrouwbaarheidsinterval (BI): -51% tot -26%) en 55% van de kinderen bij wie werd afgewacht (RV: -49%, 95%BI: - 62% tot -37%). De mediane duur van dit loopoor was 4 dagen bij de kinderen die waren behandeld met antibiotica-glucocorticoïd oordruppels versus 5 dagen bij de kinderen die waren behandeld met een antibioticumdrank ($p<0.001$) en 12 dagen bij de kinderen bij wie werd afgewacht

(p<0.001). Op de langere termijn, over een periode van 6 maanden, hadden de kinderen die met antibioticum-glucocorticoïd oordruppels waren behandeld in totaal 5 dagen een loopoor (mediaan), versus 13,5 dagen (p<0.001) bij de kinderen die aan het begin van de studie met een oraal antibioticum waren behandeld, en 18 dagen (p<0.001) bij de kinderen bij wie was afgewacht. Zowel de aan gezondheid gerelateerde generieke als de ziektespecifieke kwaliteit-van-leven van de kinderen was goed bij de start van de behandeling. Na 2 weken waren de verschillen tussen de behandelgroepen in kwaliteit-van-leven-scores klein, maar de verbeteringen waren het grootst in de kinderen die waren behandeld met oordruppels. De kinderen hadden alleen milde bijwerkingen van de gebruikte medicatie en geen van de ouders rapporteerde complicaties van middenoorontstekingen gedurende de eerste 2 weken. Op basis van deze resultaten concluderen we dat antibiotica-glucocorticoïd oordruppels de beste behandeling zijn van een acuut loopoor bij kinderen met trommelvliesbuisjes.
In hoofdstuk 3.2 presenteren we de resultaten van de kosteneffectiviteit-analyses van de interventiestudie en we gebruikten hiervoor een maatschappelijk oogpunt. Na 2 weken waren de gemiddelde kosten €29.45 (standaardfout (SF): 3.42) per patiënt voor behandeling met antibiotica-glucocorticoïd oordruppels, €49.01 (SF: 13.38) voor een oraal antibioticum en €56.94 (SF: 12.92) voor een afwachtend beleid. Na 6 maanden waren de gemiddelde totale kosten respectievelijk €255.59 (SF: 354.07), €292.05 (SF: 470.14) en €444.56 (SF: 644.91). Behandeling met antibiotica-glucocorticoïd oordruppels is dus niet alleen effectiever, maar ook goedkoper dan een oraal antibioticum en een afwachtend beleid bij kinderen met een acuut loopoor bij trommelvliesbuisjes.
In hoofdstuk 3.3 beschrijven we de overeenstemming tussen ouders en artsen in de beoordeling van de aan- of afwezigheid van een loopoor tijdens een routinecontrole na behandeling van het loopoor. We hebben hiervoor gebruikgemaakt van de gegevens van onze interventiestudie evenals die van een eerdere studie naar de behandeling van kinderen met een chronisch loopoor. We vonden een goede overeenstemming tussen de beoordeling van de ouders en otoscopisch onderzoek door de artsen, met een hoge positief voorspellende waarde, maar een lage negatief voorspellende waarde voor de beoordeling van de ouders. We concludeerden hieruit dat ouders en artsen het in de meeste gevallen eens zijn over het aanhouden van een loopoor na behandeling en dat we in zo'n geval dus kunnen vertrouwen op het oordeel van de ouders.

In **hoofdstuk 4** bespreken we de resultaten van twee microbiële studies.
In het eerste deel presenteren we de prevalenties van bacteriën en virussen in de otorroe en nasopharynx van kinderen met een acuut loopoor bij trommelvliesbuisjes die hebben meegedaan aan de in hoofdstuk 3 beschreven interventiestudie. Zowel voorafgaand aan, als na behandeling, waren *Haemophilus influenzae*, *Staphylococcus aureus* en *Pseudomonas aeruginosa* de meest voorkomende bacteriën in de oorkweken, terwijl *H. influenzae* en *S. aureus* de meest prevalente bacteriën waren in de nasopharynxkweken. In onze studie, uitgevoerd in het tijdperk na introductie van het pneumokokkenconjugaat vaccin-7 (PCV-7) in het Rijksvaccinatieprogramma, vonden we een lagere prevalentie van *Streptococcus pneumoniae* dan in de studies uitgevoerd voor introductie van PCV-7. De meeste pneumokokken die we wél aantroffen waren serotypes die niet in PCV-7 zitten. De hoge prevalentie van *S. aureus* in onze studie, overeenkomstig met de resultaten van andere studies naar verwekkers van een loopoor bij PCV-gevaccineerde kinderen, suggereert dat *S.*

aureus een belangrijke verwekker van bovenste-luchtweginfecties is in het post-PCV-tijdperk. De antibioticaresistentie van de gevonden bacteriën was laag; we vonden alleen natuurlijke resistentie van bacteriën en geen verworven resistentie in de oorkweken die waren afgenomen bij kinderen bij wie het loopoor persisteerde na behandeling. We troffen maar weinig virussen aan in de otorroe, terwijl we in de nasopharynx meer frequent virussen vonden, met name het adenovirus, humaan rhinovirus en polyomavirussen.
De tweede microbiële studie is een systematische literatuurstudie naar de samenhang tussen uitslagen van middenoorkweken en nasopharynxkweken bij kinderen met een middenoorontsteking. Veel studies naar middenoorontstekingen gebruiken de nasopharynxkweek als een alternatief voor een kweek van het middenoorvocht omdat dit bij kinderen met een intact trommelvlies niet gemakkelijk te verkrijgen is; hiervoor moet men een sneetje in het trommelvlies maken (tympanocentese). Dit stuit op allerlei praktische en medisch-ethische bezwaren die kunnen worden omzeild door gebruik te maken van een nasopharynxkweek. Het was echter nog onduidelijk of de nasopharynxkweek wel een goede maat is van de prevalenties van micro-organismen in het middenoor. De studies die dit onderzochten, bevatten tezamen 4791 gepaarde nasopharynx- en middenoorkweken van 3278 kinderen met otitis media acuta (OMA) en 849 gepaarde kweken van 661 kinderen met otitis media met effusie (OME) . De overeenkomsten varieerden van 68 tot 97% per micro-organisme; we vonden lage positief voorspellende waardes en hoge negatief voorspellende waardes voor de uitslag van de nasopharynxkweek. Dit wijst erop dat nasopharynxkweken niet altijd een goede maatstaf zijn voor middenoorkweken en dat het belangrijk is om de resultaten van studies die nasopharynxkweken wel als zodanig gebruiken zorgvuldig te interpreteren.

In **hoofdstuk 5** bespreken we hoe onze resultaten kunnen worden toegepast in de dagelijkse praktijk. De behandeling van kinderen met een acuut loopoor bij trommelvliesbuisjes is op dit moment inconsistent. Ouders worden doorgaans geïnformeerd om pas naar een arts te gaan als het loopoor langer dan een week bestaat. Richtlijnen voor artsen geven verschillende adviezen over wat te doen, variërend van (nog langer) afwachten tot behandeling met orale of lokale antibiotica. Ons onderzoek laat zien dat antibiotica-glucocorticoïd oordruppels niet alleen effectiever zijn dan een oraal antibioticum of een afwachtend beleid, maar dat oordruppels vanuit een maatschappelijk perspectief ook het goedkoopst zijn. De pragmatische opzet van onze studie zorgt ervoor dat het een goede afspiegeling vormt van de klinische praktijk en dat de resultaten toepasbaar zijn op de meeste kinderen met een recent ontstaan loopoor bij trommelvliesbuisjes.
We adviseren om de huidige patiëntinformatie en richtlijnen van de beroepsverenigingen aan te passen op basis van onze bevindingen in dit proefschrift. Het is beter om ouders te adviseren contact op te nemen met hun arts kort nadat het loopoor ontstaat, in plaats van een week (of langer) af te wachten of het loopoor uit zichzelf overgaat. We adviseren artsen om deze kinderen te behandelen met antibiotica-glucocorticoïd oordruppels kort nadat de eerste symptomen optreden.
In dit hoofdstuk gaan we ook in op onderwerpen voor nieuw wetenschappelijk onderzoek op dit gebied. In de praktijk gaan de meeste artsen uit van de beoordeling van het loopoor door de ouders. We hebben in dit proefschrift laten zien dat deze beoordeling goed overeenkomt met otoscopisch onderzoek door een arts als het loopoor na behandeling blijft bestaan, maar we weten niet hoe dit overeenkomt als het loopoor pas net is ontstaan.

De huidige informatiefolders die ouders krijgen na plaatsing van de trommelvliesbuisjes adviseren om eerst een periode af te wachten en pas een arts te benaderen als het loopoor langer dan een week aanhoudt. Op deze manier is de kans op een fout-positieve beoordeling klein. Aangezien wij adviseren om patiëntinformatie en klinische richtlijnen aan te passen naar eerder contact opnemen en eerder behandelen, zou de kans op een fout-positieve beoordeling hoger kunnen zijn. Voor artsen is het belangrijk om te weten of ze kunnen vertrouwen op het oordeel van de ouders bij het starten van een behandeling of dat ze het kind eerst zelf moeten onderzoeken. Nieuw onderzoek naar de positief voorspellende waarde van de beoordeling van het oor door ouders vergeleken met otoscopisch onderzoek door een arts ten tijde van het diagnosticeren van een acuut loopoor is hiervoor van belang.

De effectiviteit van oordruppels voor een acuut loopoor bij kinderen met trommelvliesbuisjes is jarenlang in twijfel getrokken omdat werd gedacht dat de druppels tegen de stroom in door het buisje zouden moeten gaan om bij de middenoorontsteking te komen. Oordruppels zijn echter veruit het effectiefst, dus de druppels blijken toch op de juiste plek terecht te komen. Je kunt je afvragen of oordruppels dus ook effectief zijn bij kinderen met OMA zonder buisjes die zich presenteren met een acuut loopoor als gevolg van een spontane trommelvliesperforatie. Tot op heden is er nog geen gerandomiseerde interventiestudie uitgevoerd naar de effectiviteit van antibiotica(-glucocorticoïd) oordruppels bij deze kinderen en ze worden doorgaans met afwachten of orale antibiotica behandeld. Aangezien lokale behandeling minder bijwerkingen geeft dan orale antibiotica en een lagere kans heeft op het ontwikkelen van antibioticaresistentie, denken wij dat het gerechtvaardigd is om een vergelijkende studie te starten naar de effectiviteit van lokale en orale antimicrobiële behandeling voor kinderen met OMA zonder buisjes die zich presenteren met een acuut loopoor als gevolg van een spontane trommelvliesperforatie.

Dankwoord

Elke promovendus heeft het weleens gehoord: 'het best gelezen hoofdstuk van een proefschrift is het dankwoord' en dat is nou net het enige onderdeel wat ik helemaal alleen heb geschreven. Een proefschrift is het resultaat van een teamprestatie. Ik wil iedereen die een bijdrage heeft geleverd, hoe klein ook, hartelijk bedanken en een aantal mensen in het bijzonder.

Allereerst wil ik natuurlijk de 230 kinderen en hun ouders bedanken die hebben meegedaan aan de LOT-studie. Ik denk met veel plezier terug aan de vele huisbezoeken. De meesten woonden in de omgeving van Almere, Utrecht, Oss/Veghel, Nijmegen, Haarlem, Geldrop en Zwolle, en het waren dus vaak lange en vermoeiende dagen in de auto. De vaak vrolijke en hartelijke ontvangst van 'dokter Thijs' gaf me echter meer dan genoeg energie om dit vol te houden!

Alle KNO-artsen en huisartsen die kinderen hebben aangemeld ben ik zeer erkentelijk. In het bijzonder wil ik de KNO-artsen van het Flevoziekenhuis, Bernhoven, Canisius-Wilhelmina Ziekenhuis, St. Anna Ziekenhuis, Kennemer Gasthuis en het Wilhelmina Kinderziekenhuis bedanken die de meeste kinderen hebben aangemeld.

ZonMw heeft de LOT-studie mogelijk gemaakt middels het toewijzen van een subsidie.

Professor Schilder, beste Anne, ik weet nog dat ik bij jou en Maroeska op sollicitatiegesprek kwam in het WKZ. De LOT-studie was al opgestart maar snel weer stilgelegd vanwege een achterblijvende inclusie. Jullie vertrouwden mij het project toe en gaven mij de kans om deze unieke studie te mogen uitvoeren; daarvoor ben ik jullie nog altijd dankbaar. Vooral van je klinische, praktische en pragmatische blik op onderzoek heb ik veel geleerd. Samen met je ervaring, gedrevenheid en perfectionisme zorgde deze blik ervoor dat je zelfs de artikelen die wij als co-auteurs zagen als 'prefinaal', nog altijd aanzienlijk verbeterde!

Professor Van der Heijden, beste Geert, je bent Maroeska opgevolgd als projectleider toen zij naar Nijmegen vertrok. In ons eerste contact had je al meteen een aantal kritische vragen over de onderzoeksopzet van de LOT-studie. Dit was zeer zeker een voorbode: de combinatie van je epidemiologische kennis en idealisme enerzijds, en je onverschrokken directheid anderzijds, hield ons steeds weer scherp. Ik kijk met veel plezier terug op de vele besprekingen, verhelderende en soms ook zeer theoretische discussies die we samen met Roderick hadden.

Doctor Venekamp, beste Roderick, je bent pas in een later stadium aan onze projectgroep toegevoegd en dit was wat mij betreft een gouden greep. Je bent zowel klinisch als methodologisch goed onderlegd en zorgde daarmee voor een goede balans in onze publicaties. Daarnaast zorgde je met je ontspannen persoonlijkheid ook voor een goede balans binnen de projectgroep. Je was altijd laagdrempelig bereikbaar voor overleg en ging graag de strijd aan met Geert over wie als eerste feedback voor me had. Dat is verre van vervelend voor een promovendus.

Professor Rovers, beste Maroeska, als mede-initiator van de LOT-studie en mijn begeleider in het begin van mijn promotietraject heb je mij wegwijs gemaakt binnen de onderzoekswereld. Ik denk met veel plezier terug aan onze reis naar het 'International Symposium on Recent Advances in Otitis Media' in New Orleans.

Professor Sanders, beste Lieke, ik heb me altijd zeer welkom gevoeld tijdens de bijeenkomsten op/van je afdeling, bedankt voor de prettige samenwerking!

Alle andere co-auteurs ben ik natuurlijk zeer erkentelijk voor hun hulp en adviezen, Debby Bogaert, Alice van Zon, Hanneke Freling, Ardine de Wit, Lieke Manders, Erwin van der Veen en Anne Wensing.

De leden van de beoordelingscommissie, prof.dr. N.J. de Wit, prof.dr. A.M. van Furth, prof.dr. R.J. Stokroos, prof.dr. K.G.M. Moons, prof.dr. M.J.M. Bonten, wil ik hartelijk bedanken voor het beoordelen van mijn manuscript.

Pauline Winkler, in 2011 kwam je onze projectgroep versterken toen de LOT-studie al een tijdje liep. Je hebt je binnen korte tijd echter onmisbaar gemaakt! Je nam veel initiatief in het navolgen van de 'Good Clinical Practice'-richtlijnen, zorgde ervoor dat alles tiptop in orde was voor de datamonitoring-bezoeken en daar was ik maar wat blij mee! We waren een leuk team en ik denk met veel plezier terug aan de bijna dagelijkse oversteken van het Stratenum naar het 'van Geuns'.

Nelly van Eden, je hebt de LOT-studie mede opgebouwd en was als ervaren projectcoördinator erg belangrijk toen ik aan deze uitdaging begon. Vanwege omstandigheden ben je voor het einde van de studie gestopt en ben je opgevolgd door Pauline. Ik wil je bedanken voor al je ondersteuning, niet alleen in het begin van de studie maar ook in deze overgangsperiode!

Lidian Izeboud, toen het aantal inclusies een vlucht nam, heb je een deel van de afsluitende follow-upbezoeken van me overgenomen. Door je humor en flexibele instelling heb ik onze samenwerking als erg plezierig ervaren!

Dicky Mooiweer, bedankt voor je ondersteuning bij de LOT-studie in de drukkere periodes!

Afdeling datamanagement, het was fijn dat onze ruwe data op de TeleForms snel konden worden ingelezen en verwerkt op de momenten dat dit nodig was, en in het bijzonder Marloes van Beurden, bedankt voor je hulp als datamanager en het actief meedenken.

Ik wil alle studenten bedanken die als onderdeel van hun wetenschappelijke stage ook een bijdrage hebben geleverd aan de LOT-studie: Lideke Dun, Alice van Zon, Nina Kaper, Hanneke Freling, Leonie Bultje, Mayke Hentschel, Britt ter Horst, Lieke Manders en Johan Telleman.

Alle kamergenoten en collega's wil ik bedanken voor de koffiepauzes, lunches en borrels. Bedankt dat jullie me achter mijn computer wegsleurden als ik eens niet 'on the road' was, want de boog kan inderdaad niet altijd strak gespannen staan! In het bijzonder Marie, Marieke, Nienke, Laurien, Henrike en Wouter. Coby van Rijn, bedankt voor je immer vriendelijke hulp!

Marie en Marieke, ik vond het oprecht fijn om lange tijd een schrijfkamer met jullie te hebben mogen delen! Hoe jullie mijn slechte grappen hebben kunnen doorstaan zal ik nooit snappen, maar jullie waren geweldige slachtoffers. Marie, je bent enorm intelligent, lief, sociaal, hardwerkend en te bescheiden! Je (poster)presentaties waren fenomenaal en ik heb veel van je geleerd, je zult ongetwijfeld een mooie carrière tegemoet gaan! Marieke, je bent een open boek, zorgt voor gezelligheid om je heen en je wordt ongetwijfeld een hele goede huisarts. Je weet waar je het over hebt en kunt mensen goed op hun gemak stellen; ik zou je graag als mijn huisarts hebben!

Dank aan alle vrienden en vriendinnen die gedurende mijn promotietraject voor afleiding hebben gezorgd! Van mijn vrienden van Ormètikos/Otrias, de andere Maastrichtse (studie)vrienden (in het bijzonder de clan die in Eindhoven woont en die ene jaarclub die mij half heeft geadopteerd) tot en met de Tilburgse Dudes! In de afgelopen jaren heb ik veel plezier beleefd aan (en afleiding gehad van) de vele concerten in met name Tivoli, de festivals, de weekendjes en vakanties, de bezoeken aan Willem II en alle andere borrels en feestjes. Het deed me ook echt heel goed dat ik zoveel steun kreeg van jullie na het overlijden van mijn vader en tijdens zijn crematie. Het is teveel om iedereen hier te benoemen, maar een paar vrienden wil ik toch in het bijzonder bedanken (in alfabetische volgorde): Floor, Jules, Niels, Noud, Rob, Ruud, Sander, Thijs en Yvonne.

Jonas, dude, hartstikke bedankt voor het ontwerpen van de cover en illustraties!

Lieve Floor en Ruud. Bedankt dat jullie als mijn paranimfen willen fungeren! We hebben elkaar tijdens de studie geneeskunde in Maastricht leren kennen en een hechte vriendschap ontwikkeld. Het is iedere keer weer gezellig samen met de hele club in Eindhoven: hopelijk gaan we nog lang door met onze borrels, etentjes en feestjes!

Lieve Manon, een groot deel van mijn promotieonderzoek zijn we samen geweest. Bedankt voor je geduld en ondersteuning, ik weet dat het niet altijd gemakkelijk was.

Lieve families Van Dongen en Van Kempen, bedankt voor jullie ondersteuning, met name in de laatste maanden toen ik dit het hardste nodig had.

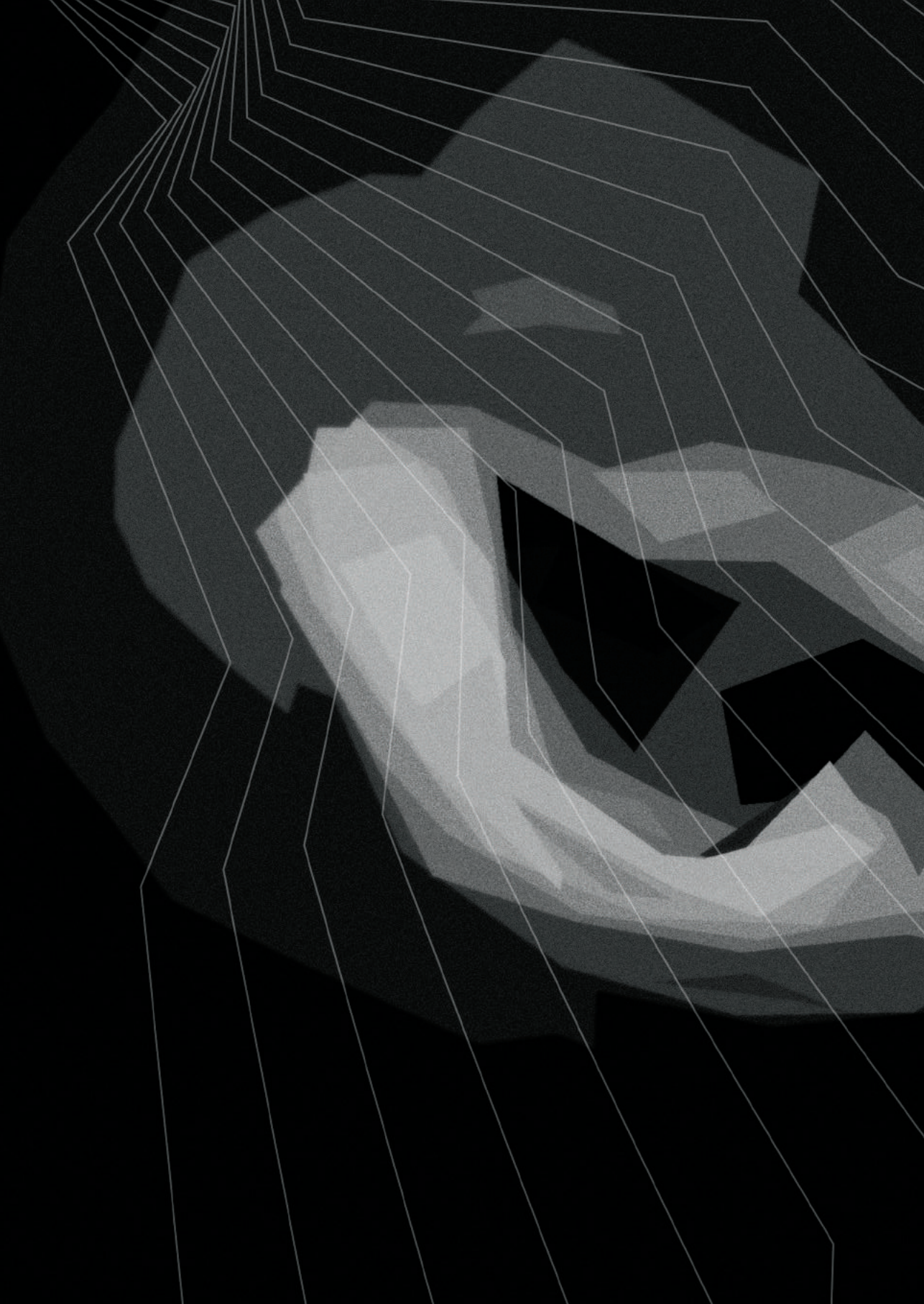
Lieve ouders, zusje en broertje, mijn promotieonderzoek was bijna een gezinsproject. Mama nam van her en der cadeautjes voor de deelnemende kinderen mee, papa maakte (met eigenlijk maar weinig ondersteuning van mijzelf) een LOT-studiewebsite en Saskia was als student-assistent een tijdje aangesteld als 'nabeller' van de LOT-aanmeldingen.

Saskia, lieve zuster, het was dan ook leuk om mijn zusje eindelijk eens een periode de baas te kunnen zijn! Het laatste jaar is erg zwaar geweest voor ons gezin en jij bent hierin een belangrijke steunpilaar geweest. Ik kijk met veel bewondering naar je prestaties als apotheker en ik hoop dat je beseft dat je zeer speciaal bent.

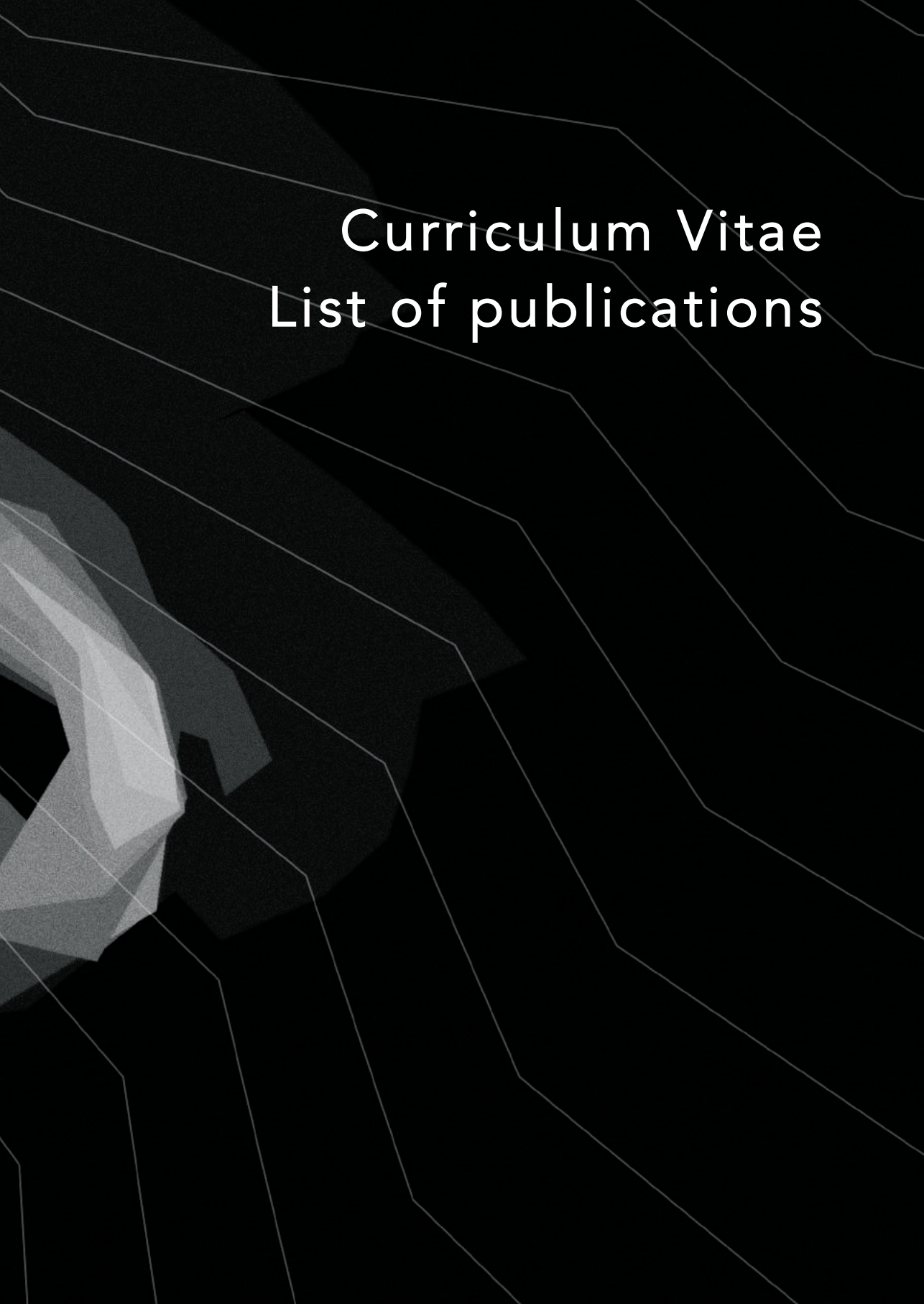
Ivo, lieve broeder, je hebt al teveel life events meegemaakt die niet allemaal even gemakkelijk waren. Toch lijk je er alleen maar sterker uit te komen en dat vind ik heel bijzonder. Je bent erg krachtig en hebt een duidelijk doel voor ogen, het doet me goed om dat te zien. Ik hoop dat al je dromen gaan uitkomen.

Lieve mama, op 14 augustus 2013 is onze wereld ingestort en die van jou nog het meeste. Ik heb veel bewondering voor de manier waarop je hiermee probeert om te gaan. Je bent een van de weinigen met wie ik alles kan/wil delen en je bent de meest zorgzame persoon die ik ken. Naar jou toegaan voelt nog steeds als thuiskomen en je creëert als geen ander gezelligheid om je heen. Je bent altijd geïnteresseerd, altijd attent, ik vraag je nog altijd om raad en adviezen en dit zal ik ook altijd blijven doen.

Lieve papa, mijn laatste woorden zijn natuurlijk voor jou. 'De laatste loodjes wegen het zwaarst' is voor mij nog nooit zo van toepassing geweest als op de laatste maanden. Tijdens de afronding van mijn proefschrift viel je met je racefiets en viel je uit ons leven weg. Je hebt me, samen met mama, gemaakt tot de persoon die ik ben, dus zonder jou had ik dit nooit kunnen doen. Ik ben trots als mensen zeggen dat ik zo op je lijk. Ik heb van jou geleerd om mezelf te waarderen en om mezelf te kunnen zijn. Ik mis je, bewonder je nog altijd en ik hoop dat het mij ooit lukt om ook een rol als de jouwe in het leven te kunnen vervullen.



Curriculum Vitae
List of publications



Thijs van Dongen was born in Tilburg on May 7th, 1985. After graduating from secondary school at the Theresialyceum, he studied medicine at Maastricht University from 2003 until 2009. In the final year of medical school he participated in a research project on imaging features of Hyperostosis Cranialis Interna and co-authored two scientific publications on this condition. After graduation in 2009, he worked as a scientific editor at the Dutch Medical Journal (Nederlands Tijdschrift voor Geneeskunde). In June 2010 Thijs started his PhD studies at the University Medical Center Utrecht, department Julius Center for Health Sciences and Primary Care, initially under supervision of prof.dr. Anne Schilder and prof.dr. Maroeska Rovers, and finally under supervision of prof.dr. Anne Schilder, prof.dr. Geert van der Heijden and dr. Roderick Venekamp. The results of these studies are described in this thesis. During his PhD study, he obtained a Master of Science degree after completion of the Postgraduate Master of Clinical Epidemiology at the Utrecht University.

This thesis:

- **Van Dongen TMA**, van der Heijden GJMG, Freling HG, Venekamp RP, Schilder AGM. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. *PLoS One 2013;8:e69062.*
- **Van Dongen TMA**, van der Heijden GJMG, Venekamp RP, Rovers MM, Schilder AGM. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med 2014;370:723-33.*
- **Van Dongen TMA**, Schilder AGM, Venekamp RP, de Wit GA, van der Heijden GJMG. Treatment for acute otorrhea in children with tympanostomy tubes: economic evaluation alongside a pragmatic randomized controlled trial. *Submitted for publication.*
- **Van Dongen TMA**, Schilder AGM, Manders LA, van der Veen EL, van der Heijden GJMG. Good agreement between parents and physician in the assessment of ear discharge in children. *Pediatr Infect Dis J 2012;31:868-9.*
- **Van Dongen TMA**, Venekamp RP, Wensing AMJ, Bogaert D, Sanders EAM, Schilder AGM. Acute otorrhea in children with tympanostomy tubes: bacteria and viruses in the post-PCV7 era. *Submitted for publication.*
- **Van Dongen TMA**, van der Heijden GJMG, van Zon A, Bogaert D, Sanders EAM, Schilder AGM. Evaluation of concordance between the microorganisms detected in the nasopharynx and middle ear of children with otitis media. *Pediatr Infect Dis J 2013;32:549-52.*

Other publications:

- Biesbroek G, Keijser BJF, **van Dongen TMA**, Schilder AGM, Roeselers G, Sanders EAM, Bogaert D. Differences in topographical microbial profiles of the respiratory tract in healthy children and adults. *Submitted for publication.*
- Langereis JD, **van Dongen TMA**, Stol K, Venekamp RP, Schilder AGM, Hermans PW. Resistance to complement-mediated killing and IgM binding to non-typeable Haemophilus influenzae is not altered when ascending from the nasopharynx to the middle ears in children with otitis media. *Med Microbiol and Immunol 2013;202:407-15.*
- van Zon A, van der Heijden GJMG, **van Dongen TMA**, Burton MJ, Schilder AGM. Antibiotics for otitis media with effusion in children. *Cochrane Database Syst Rev. 2012;9:CD009163.*
- Waterval JJ, **van Dongen TMA**, Stokroos RJ, De Bondt BJ, Chenault MN, Manni JJ. Imaging features and progression of hyperostosis cranialis interna. *AJNR Am J Neuroradiol 2012;33:453-61.*
- Vöö S, **van Dongen TMA**, Waterval JJ, Willems P, Mottaghy F, Brans B. CT combineren met scintigrafie: SPECT-CT en PET-CT. *Ned Tijdschr Geneeskd 2011;155:A2792.*
- Waterval JJ, **van Dongen TMA**, Stokroos RJ, Teule JG, Kemerink GJ, Brans B, Nieman FH, Manni JJ. Bone metabolic activity in hyperostosis cranialis interna measured with 18F-fluoride PET. *Eur J Nucl Med Mol Imaging 2011;38:884-93.*