Evidence into practice; upper respiratory tract infections in children

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Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.
Thesis. University Utrecht, Faculty of medicine, with a summary in Dutch

ISBN/EAN: 978-90-393-5765-1
Author Chantal W.B. Boonacker
Layout Monique den Hartog
Cover photo Katharine Hepburn, film "Song of Love", USA, 1947
Cover design Ferdinand van Nispen, Citroenvlinder-DTP.nl, Bilthoven
Printed by Ponsen& Looijen, Ede

Evidence into practice; upper respiratory tract infections in children

Van kennis naar praktijk; bovenste luchtweginfecties bij kinderen

(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
dinsdag 24 april 2012 des ochtends te 10.30 uur

door

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geboren op 23 maart 1977 te Nieuwegein

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This thesis was (partly) accomplished with financial support from ZonMw grant 80-007022-98-07901 and NHS HTA Project 10/124/01.

Financial support for the publication of this thesis was kindly provided by the Stichting 'Kleine kwalen in de huisartspraktijk', J.E. Jurriaanse Stichting, Dutch ENT-society (KNO-vereniging), Nationale Hoorstichting/VriendenLoterij, GlaxoSmithKline, Atos Medical BV, Entermed b.v., Daleco Pharma BV, and EmiD audiologische apparatuur.

Voor mijn ouders

Contents

Chapter 1

General introduction

Chapter 1

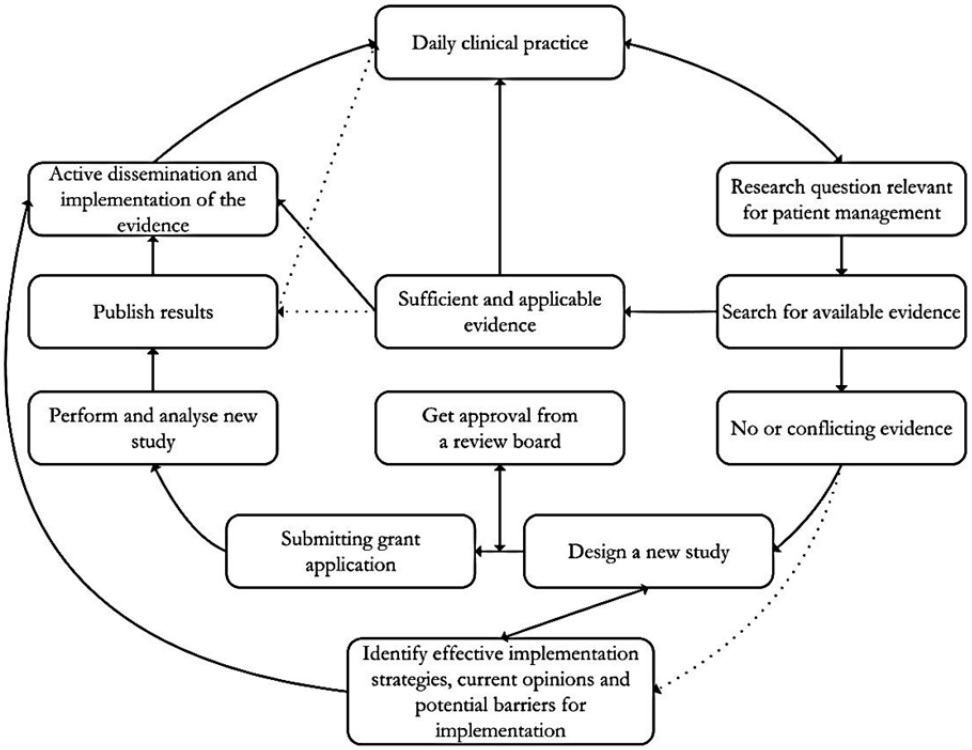
Transfer of evidence into practice is often slow and therefore remains an important challenge.[1-3] Many factors influence the uptake of evidence into practice. These include not being aware of or, disagreement with available evidence, doubts about the applicability of the evidence to one's own patients or pressure from patients to start a particular treatment.[4, 5] Management of children with upper respiratory tract infections (URTI), which is the most common diagnosis in children in primary care, serves as a good example.[6] Despite ample evidence from randomized controlled trials on the effects of specific management strategies such as surgery, antibiotic therapy or watchful waiting, current practice in children with URTI varies considerably across [7-10] and within countries.[11-13] Change in patient management in daily practice requires changes in beliefs.[14, 15] For example, a study of otorhinolaryngologists' beliefs regarding the effects of tympanostomy tubes in children with otitis media with effusion (OME) before and after a randomized controlled trial (RCT), showed that their expectations regarding the effectiveness of tympanostomy tubes remained high, despite their awareness of evidence that a watchful waiting strategy conferred similar results.[16, 17] Apparently, successful dissemination of trial results alone does not necessarily change beliefs and evidence is not automatically implemented in daily practice.

Why is the transfer of evidence into practice such a difficult task, even though patients, health care providers, and policy makers, when asked, agree that findings of research should be incorporated into clinical practice? It is increasingly recognized that there are multiple barriers that prevent evidence from being routinely applied in practice. The huge and rapidly increasing number of scientific publications on treatment effects challenges health care providers to remain up-to-date and decide which information is relevant and important.[4, 5, 18-22] Another important explanation is "lack of familiarity", which can occur when recommendations derived from trials are not interpreted by health care providers to pertain to the patients *they* manage in daily practice.[23] If doctors do not recognize their patients in the population included in the trial, this may lead to lack of agreement with the results and thus lack of motivation to change routine management of their patients. Subsequently, the results are likely to be ignored.[4, 5, 20, 24-26] In addition, there are multiple barriers to evidence-based clinical practice that operate at levels beyond the control of an individual health care provider. These include structural barriers (e.g. financial (dis)incentives), organizational barriers (e.g. lack of facilities or equipment), peer group barriers (e.g. local standards of care not in line with recommendations resulting from the trial findings), and professional-

patient interaction barriers (e.g. information provided by the physician is not interpreted appropriately by the patients).[27]

Ideally, research is performed according to the clinical research cycle presented in *Figure 1.1*. Research starts with a clinically relevant question. When no *or* conflicting evidence is available to answer this question, it can be translated into a grant proposal and, when funded, a research project. Already at that stage, it is important to explore the optimal strategies and potential barriers to implement the results of the proposed study so that these can be incorporated in the research project. For example, when there are strong opinions on the benefits of a treatment across professionals, early collaboration with the involved specialist associations may accelerate the acceptance of the research results. Finally, all collected data should be analysed and researchers should make every effort to have their research published, regardless of the outcome, to enable the implementation of their results in daily practice.

Figure 1.1: The clinical research cycle



The best chance of bridging the gap between health research and implementation in daily clinical practice is created by optimizing all steps of the research cycle. Potential barriers in this process include skipping some of these essential steps, focussing on an irrelevant research question, ignoring the available evidence, making unrealistic assumptions, not involving patients in defining relevant outcomes, presenting a grand mean which is not applicable to individual patients, and lack of notion of the most effective implementation strategies.

In this thesis we will use the example of management of children with upper respiratory tract infections (URTI) to study several of the crucial steps in the research cycle. With URTIs, like rhinitis and otitis media, being so common in children, national and international variation in its management strategies, and available evidence regarding preventive and therapeutic management strategies accumulating, it will serve as a relevant and illustrative example of the steps that could be taken from the design of a new study up to successful implementation of its results.

Objective(s):

The general objective of this thesis is:

- To study several of the crucial steps in the 'clinical research cycle' from clinical question to implementation of evidence in daily practice, taking interventions in children with URTIs as an example.

Specific research questions include:

- Which strategies are being applied to promote evidence based interventions in the management of children with URTIs, and which strategy is most effective?
- Which evidence is available regarding the cost-effectiveness of pneumococcal vaccination for acute otitis media in children, and how do the underlying assumptions regarding the effectiveness of the vaccine and the cost associated with acute otitis media influence the applicability?
- Can we provide the currently lacking but crucial evidence on the (cost-) effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections by performing a pragmatic multi-centre trial?
- Does a collaborative action of pooling individual patient data of several randomised controlled trials of adenoidectomy in otitis media provide us with information on subgroups of patients in whom adenoidectomy is most effective

or, in contrast ineffective, thus facilitating application of research findings in daily practice?

- Do primary outcomes and subgroup analyses that were pre-specified in the grant proposal differ from those finally published, and what are the consequences of such potential discrepancies?

Outline of this thesis

In *chapter 2* we present an overview of the implementation strategies that have been developed to promote evidence based management of children with URTIs in daily practice. We critically assess the available evidence on the effectiveness of these strategies to determine which strategy works best. (*Figure 1.1*: "Identify effective implementation strategies")

In *chapter 3* we take a first step in the clinical research cycle and systematically review the available evidence to answer the question 'What is the balance between costs and effects of pneumococcal conjugate vaccinations against AOM in children?' (*Figure 1.1*: "Search for available evidence")

In *chapter 4* we present new evidence generated by our randomised controlled trial on the effectiveness of adenoidectomy as compared to watchful waiting in children with recurrent URTIs. The clinical results are presented in *chapter 4.1* and the costs associated with both treatment strategies are compared in *chapter 4.2*. (*Figure 1.1*: "Design a new study" and following steps)

In *chapter 5* we study the process from design to publication of clinical research in general. For this we studied all projects awarded a grant of the Health Care Efficiency Research Program of the Netherlands Organization for Health Research and Development (ZonMw) (i.e., the Dutch "National Institutes of Health"). In *chapter 5.1* we compare the primary outcomes of these projects as reported in the grant application, the trial registry, and their related publications. In *chapter 5.2* we compare the subgroup analyses as reported in grant applications with those presented in the related publications. (*Figure 1.1*: "Submitting grant application" and "Publish results")

In *chapter 6* we present the results of an Individual Patient Data meta-analysis pooling the original data of 4 trials on the effectiveness of adenoidectomy with or without tympanostomy tubes in children with otitis media with effusion (OME). With this meta-analysis we aim to identify subgroups of children with OME most likely to

benefit from adenoidectomy and as such facilitate clinical decisions about surgery in OME. (*Figure 1.1*: "Search for available evidence")
In *chapter 7,* we take a broader perspective on the process of implementing research into practice and suggest measures that could be taken to minimize discrepancies between grant applications and publications.

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Chapter 1

Chapter 2

Interventions in health care professionals to improve treatment in children with upper respiratory tract infections

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International journal of pediatric Otorhinolaryngology 74 (2010) 1113–1121

Chapter 2

Abstract

Objective: To analyse which strategies are used to promote evidence-based interventions in the management of children with upper respiratory tract infections (URTIs) in daily practice. To assess the effectiveness of these interventions, and when more are effective - which works best. And to analyse the costs associated with these interventions.

Methods: We systematically searched Pubmed, Embase and CENTRAL bibliographies for studies on the effectiveness of strategies aimed at changing health care professionals' behavior in the management of children with URTIs.

Results: The search yielded 11,788 references, of which 18 studies were eligible, and 10 met the inclusion criteria. Most strategies were aimed at changing antibiotic prescribing behavior in children with acute otitis media. All strategies used (i.e. computer interventions, educational sessions with or without education materials, collaborative development of guidelines and a training video in combination with a risk factor checklist) were effective in changing health care professionals practice regarding children with URTIs. Multifaceted and computer strategies work best. Computer interventions reduced antibiotic prescribing by 4% and 34% and increased guideline compliance by 41%. Educational sessions combined with education materials reduced inappropriate antibiotic prescription by 2% and 17% and increased knowledge of compliance enhancing strategies by 28% and 29%. Collaborative guideline development combined with educational materials reduced inappropriate antibiotic prescription by 24% and 40%. Finally, by a combination of a training video and a risk factor checklist appropriate referrals by the GP to the otolaryngologist increased by 37%. Since the costs associated with the interventions were not explicitly mentioned in the articles, no conclusion on cost-effectiveness can be drawn.

Conclusion: Multifaceted and computer strategies appear to be most effective to put evidence into practice in the area of URTIs in children.

Introduction

Upper respiratory tract infections (URTIs) presenting as common colds, rhinosinusitis, tonsillopharyngitis and otitis media (OM) are the most common diagnosis in children in general practice. [1] Current practice in these children, e.g. watchful waiting versus antibiotic or surgical treatment, varies strongly between [2-4] and even within countries [5], despite ample evidence on treatments being available.

Each year, the number of scientific publications on treatment effects in URTIs is increasing, challenging health care professionals to remain up-to-date.[6-8] Passive dissemination of trial results and meta-analyses, may therefore not reach these professionals [9], nor affect how they manage their patients.[10, 11] In general, clinical practice guidelines are issued to this matter. Alternative strategies comprise educational materials, education sessions, audits and feedbacks, reminders and computerized decision support systems. So far, it is unknown whether such strategies have been effective in changing health care professionals' behavior and reducing inappropriate use of antibiotics and/or surgery in children with URTIs. Besides, various specialties, i.e., general practitioners, pediatricians and otolaryngologists are involved in the care of children with URTIs. We have shown previously that beliefs regarding the effectiveness of surgical interventions vary across these specialties [11], and thus dissemination and implementation of trial results may require a "specialty specific approach".
Research so far has focused on reducing both inappropriate treatment and selection of antibiotics in acute illnesses in adult or mixed adult/pediatric populations and no superior strategy has been identified.[12] The results of these studies cannot be transferred directly to the pediatric population as in the care of children not only the patient but also its caregivers are involved. We therefore performed a systematic review of studies on the effectiveness of strategies aimed at changing health care professionals' behavior in the management of children with URTIs. The objectives of this review were: 1) to analyse which strategies are used to promote evidence-based interventions in the management of children with URTIs; 2) to assess the effectiveness of these interventions, and when more are effective - which works best; 3) to analyse the costs associated with these interventions.

Chapter 2

Material and Methods

Search methods for identification of studies

We systematically searched Pubmed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) using the following search terms and their synonyms; implementation, evidence, guideline, upper respiratory tract infection, otitis media, compliance, behavior and children, and their synonyms (see also *Appendix 2.1*). The last search was performed on 26 February 2009. The references of all retrieved relevant studies were searched for additional trials. No language restrictions were applied.

Eligibility criteria and study selection

Randomized controlled trials (RCT), non randomized controlled trials (NRCT) and controlled before after studies (CBA) were considered eligible for our review when they met the following criteria;1) they used implementation methods to change health care professionals' behavior regarding the treatment of children with URTIs presenting as e.g. common colds, rhinosinusitis, tonsillopharyngitis and otitis media, and 2) they investigated the effectiveness of implementation strategies. Any comparison (e.g. intervention vs. no intervention, intervention a vs. intervention b) was allowed. Studies were excluded when it was impossible to subtract results in children only or in URTI only. Two authors (CB, MJD) accomplished the search and scanned the titles and abstracts to identify relevant articles. The full texts of these relevant articles were reviewed by the same two authors. Any differences in opinion were resolved by discussion between the two authors.

Quality assessment

The methodological quality of the eligible papers was critically appraised by two authors (CB, MJD) using the Cochrane Collaboration's tool for assessing risk of bias[13], including a judgment on sequence generation, allocation concealment (whether or not assignment to the intervention or control group could be foreseen by the participants or the investigators), blinding, incomplete outcome data, selective outcome reporting and evaluation of other possible bias. By answering pre-specified questions the quality of the execution of the study was assessed and the risk of bias was judged for each item. The outcome for each item was reported as either 1) a low risk, 2) a high risk or 3) an unclear risk of bias. When no sufficient information was

giving for one of the quality items, the outcome of that item was judged as an unclear risk of bias. In cases where there was insufficient information provided to judge blinding, the authors judged the risk of bias as if the study was not blinded. Any differences in opinion were resolved by discussion between the two authors.

Data extraction and analysis

The following data were extracted from each study: aim, setting, description of health care professionals and patients involved, intervention, number of health care professionals and patients or visits related to URTI per intervention group, and outcomes. For all outcomes we extracted or calculated risk differences (RD) with their corresponding 95% CIs, i.e. (proportion of participants with outcome present in the intervention group) – (proportion of participants with outcome in the control group). If it was not possible to calculate RDs, we used the effect measure as presented in the article.

Results

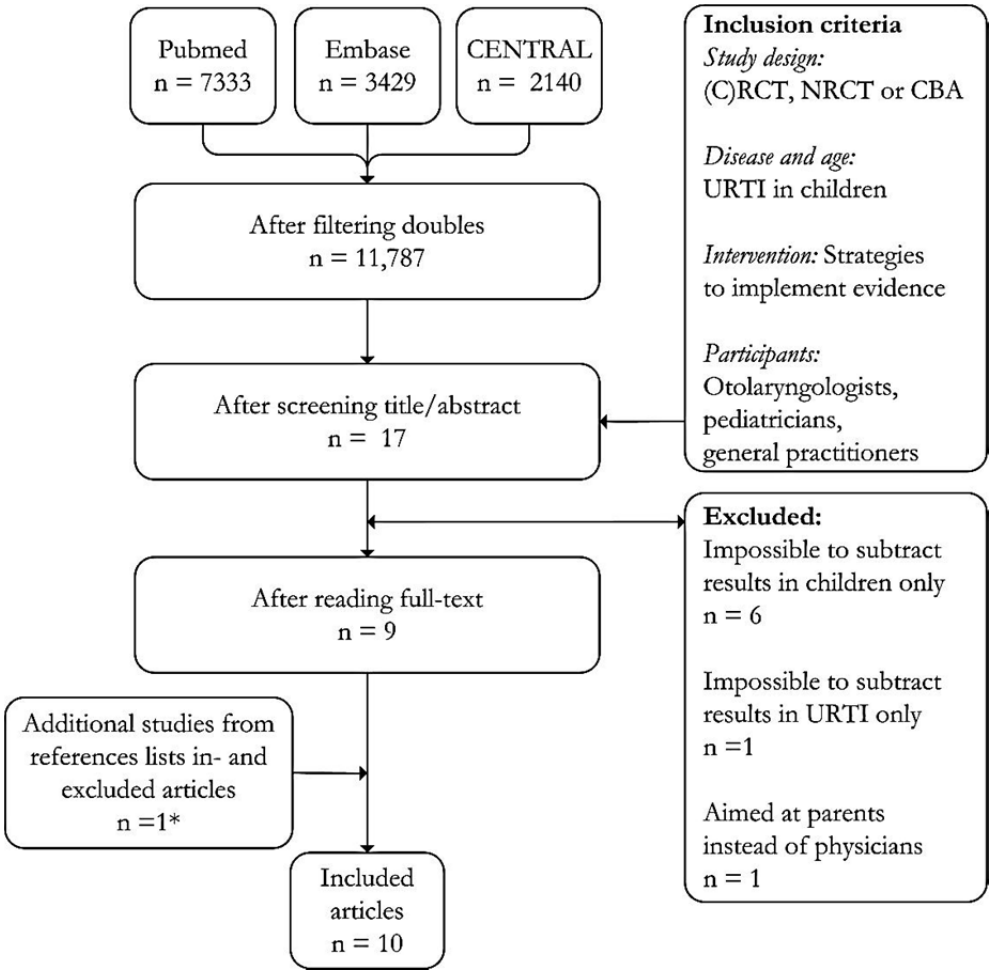
Search results

The search retrieved 11,787 references, of which 17 studies were eligible. After reading the full-text articles, 9 studies were included. From the reference lists one additional, unpublished trial [14] was obtained (*Figure 2.1*).

Quality assessment

Table 2.1 summarizes the results of the quality assessment. Seven studies[14-20] were (cluster) randomized controlled trials. Three studies[21-23] were non-randomized controlled trials or controlled before after studies and therefore scored 'high risk of bias' on sequence generation and allocation concealment. No study provided sufficient information on blinding, but only in one study[19] the potential lack of blinding may have caused bias because the outcome (behavior) was measured by a self-administered questionnaire rather than by an independent or blinded assessor. In three studies different interventions were allocated to individual health care providers within one practice.[17-19] This may have led to bias due to contamination because health care providers in the control group may have been aware of, and executed the intervention, when discussing the study with their colleagues in the intervention group.

Figure 2.1. Flow-chart of search strategy



Legend figure 2.1:
CENTRAL: Cochrane Central Register of Controlled Trials
(C)RCT: (Cluster) Randomized controlled trial
NRCT: Non-randomized controlled trial
CBA: Controlled before and after study
URTI: Upper respiratory tract infection
***** Unpublished study

Table 2.1. Summary of the methodological quality of the included studies

	Adequate sequence generation?	Allocation conceal-ment?	Blinding?	Incomplete outcome data addressed?	Free of selective outcome reporting?	Free of other bias?
Bauchner 2006[15]	?	?	+	+	+	+
Bennett 2001[16]	?	?	+	+	?	+
Bush 1979[21]	-	-	+	+	+	+
Christakis 2001[17]	+	?	+	+	+	?
Davis 2007[18]	+	+	+	+	+	?
Juzych 2005[22]	-	-	+	+	+	+
Maiman 1988[19]	?	?	?	+	+	?
Margolis 1992[20]	?	?	+	+	+	+
Smabrekke 2002[23]	-	-	+	+	+	+
Wilson 2002[14]	+	+	+	+	+	+

Legend table 2.1:
+ = Yes (low risk of bias)
? = Unclear (risk of bias unclear)
- = No (high risk of bias)

Types of implementation and dissemination strategies used

Both the type of implementation strategy, as well as the number and specialty of the health care professionals, the domain of patients and the outcomes varied across the included studies (*Tables 2.2 – 2.4*). Most studies focused on the dissemination of evidence regarding interventions in children with otitis media. Five studies[15, 17-20] were performed in pediatric practices, three[14, 16, 22] in general practice, one[21] in a community health plan and another[23] in an emergency care setting. In four studies[15, 16, 22, 23] the intervention was allocated to practices, whereas in the other six studies[14, 17-21] the intervention was allocated to individual health care professionals. The number of included health care professionals and patients varied across the studies, ranging from 6 to 175 and from 324 to 13,460, respectively. In two studies[15, 23] the number of health care professionals, and in four studies[16-18, 20] the number of patients or visits related to URTI was not specified.

The number, combination and content of the dissemination strategies varied substantially across the included studies. Three types of studies could be distinguished according to the type of strategy used: 1) computer interventions i.e. a computerized evidence based support system or a computerized clinical algorithm (three studies[17,18,20]), 2) educational sessions with or without educational materials (four studies[15, 19, 22, 23]) and 3) other interventions i.e. a risk factor checklist and a training

video (one study[16]), and a collaboratively developed protocol or clinical practice guideline (two studies[14, 21]).

Outcome measurements

In six studies[14, 17, 18, 20, 22, 23] either the number of antibiotic courses, treatment duration or choice of antibiotics was defined as the primary outcome, and in one study the quality of antibiotic prescribing was studied[21]. The adherence to guidelines or recommendations was reported in two studies.[15, 20] Two studies reported on the appropriateness of referrals[16], and pediatrician's knowledge about compliance enhancing behavior and their performance[19], respectively.

Effectiveness per strategy used

Computer interventions, i.e. computerized evidence based decision support systems or computerized clinical algorithms (*Table 2.2*) improved antibiotic prescribing behavior: antibiotic prescription rates were reduced by 34% (95% CI: 14% - 54%) in one study[20], and in another study these rates were reduced in both the intervention and the control group, but without a statistical significance between the groups; 4% vs. 16% (RD -12, p = 0.095)[17]. The rate of courses of more than 10 days were reduced by 7% (95% CI: -6% - 21%)[18] and 34% (95% CI: 29 – 39)[17]. Furthermore, computer interventions resulted in a 41% (95% CI: 29 – 53) higher guideline compliance.[20] One study showed an 15% increase in antibiotic prescriptions after introduction of an evidence based support system. This increase however was seen both in the intervention and the control group. The intervention seemed to slow down the increase in antibiotic prescription rate.[18]

Table 2.2. Design, aim intervention and outcomes of the included studies: *computer interventions*

Study	Design	Aim	Setting	Intervention	Allocation	Participants	Patients	Outcome	Results	Effect measure
Christakis (2001)[17]	RCT	decrease of duration and proportion of AB prescriptions	pediatric practice, affiliated with university training program	I: computerized evidence based decision support system C: none	individual health care professionals	pediatricians nurse practitioners I: 19 C: 19	children with AOM, age not specified number of patients not specified for intervention period	1) reduced duration (< 10 days) of prescribed AB courses 2) reduced proportion of prescribed AB courses	1) Behavior change I: 44% C: 10% 2) Behavior change I: 4% C: 16%	Difference in behavior change 1) 34% (29% - 39%) 2) -12% p = 0.095
Davis (2007)[18]	CRCT	investigate if successful DSS for AOM (study Christakis[18]) could demonstrate similar effect in wide range of common pediatric conditions (AOM, allergic rhinitis, sinusitis, constipation, pharyngitis, croup, urticaria, and bronchiolitis)	pediatric practice, affiliated with university training program	I: computerized evidence based decision support system C: none	individual health care professionals allocation per condition, at least one condition per health care professional	pediatricians nurse practitioners I: 16 - 19 C: 13 - 17	children with AOM, age not specified number of patients not specified for intervention period	consistency with evidence for: 1) AB treatment 2) amoxicillin 3) < 10 days of antibiotics	1) Behavior change I: -20% C: -23% 2) Behavior change I: 12% C: -23% 3) Behavior change I: 7% C: 13%	Adjusted difference in behavior change [a] 1) 15% (2% - 13%) [b,c] 2) -2% (-17%-13%) [b, d] 3) -7% [b] (-21% - 6%)

Table 2.2 Continued

Study	Design	Aim	Setting	Intervention	Allocation	Participants	Patients	Outcome	Results	Effect measure
Margolis (1992)[20]	RCT	assess the use of clinical algorithm for primary care pediatric problems	pediatric practice	I: use of a computerized clinical algorithm C: none	Individual health care professionals	pediatricians Total 6[1]	children with OM[2] 0 – 16 years number of patients not specified	1) compliance with recommended management plan 2) incorrect AB use	1) Post intervention I: 44% C: 3% 2) Post intervention I: 12% C: 46%	1) RD = 41% (29% - 53%) 2) RD for the reduction of in correct AB use = 34% (14% - 54%)

Legend and abbreviations table 2.2

Design (C)RCT = (cluster) randomized controlled trial

Intervention: I = intervention group C = control group DSS = decision support system

Participants: [1] = The 6 physicians were assigned to at least 3 of 6 problems, for which they used the clinical algorithm, for the remaining problems the physicians used the computer but without algorithm and served as the control group.

Patients: [2] = Researchers also measured outcomes in children with URI and pharyngitis

Patients: OM = otitis media AOM = acute otitis media

Aim / outcome: AB = antibiotics

RD: Risk difference **=** Post-intervention measurement in intervention group – post-intervention measurement in control group (in %), with 95% CI

[a] = adjusted for clustering of data by the individual providers

[b] = Percent change in behavior refers to the absolute difference (in percentage points) in prescribing behavior between the baseline period and the study period (a negative number reflects worsening of prescribing behavior relative to the evidence provided).

[c] = While the change from baseline was negative in both the intervention group and the control group, the effect of the intervention was positive. This reflects the effect the intervention had on slowing the rate of increased antibiotic prescribing for AOM.

[d] = While change from baseline appears to be positive, the regression analyses demonstrate an overall slightly negative effect. This apparent discrepancy results from presenting individual-prescription-level data in the table, while the researchers performed statistical analyses at the clustered provider level.

Educational sessions (*Table 2.3*) combined with educational materials for physicians resulted in a 8% (95% CI: 4 – 11) higher guideline adherence compared to educational sessions alone.[15] The combination of educational sessions and materials also increased the knowledge of compliance enhancing strategies of pediatricians by 28% (95% CI 4 – 51) and 29% (95% CI: 5 – 53) as compared to printed materials alone or no intervention.[19] Educational sessions combined with education materials for both physicians and parents resulted in a 2% (95% CI: 0 – 5)[22] and 17% (95% CI: 10 – 25)[23] higher decrease of antibiotic use compared to no intervention, which showed also a slight decrease in antibiotic use in both studies.

By a combination of a training video and a risk factor checklist appropriate referrals by the GP to the otolaryngologist increased by 37% (95% CI: 25 – 49) compared to either or none of these strategies.[16] Collaborative protocol development combined with educational materials reduced the antibiotic prescription rate by 40% (OR 0.60, 95% CI 0.43 – 0.83).[14] Collaborative protocol development alone increased the proportion of prescriptions according to the developed protocol from 60% to 83% ($p < 0.001$).[21] Discussion and providing a protocol decreased the prescription rate of courses in which three or more different drugs were prescribed by 22% (95% CI: 10 – 35) compared to no intervention.[21] (*Table 2.4*).

Overall effectiveness

All interventions (i.e. computer interventions, educational sessions with or without education materials, collaborative development of guidelines and a training video in combination with a risk factor checklist) were effective in changing health care professionals practice regarding children with URTIs. Computer interventions and multifaceted interventions (e.g. risk factor checklist combined with a training video or educational session combined with printed materials) appeared to work best.

Costs associated with the interventions

Since none of the studies reported on the actual costs of their strategies, we could not evaluate the cost-effectiveness.

Table 2.3. Design, aim, intervention and outcomes of the included studies: *educational sessions with or without educational materials*

Study	Design	Aim	Setting	Intervention	Allocation	Participants	Patients	Outcome	Results	Effect measure
Bauchner (2006)[15]	CRCT	increase adherence to CDC recommend-dations	pediatric practice	I: educational sessions on diagnosis and treatment and educational materials C: educational session on diagnosis	practices	pediatricians I: 6 practices C: 6 practices	children with AOM, 3 - 36 months I: 1138 C: 1368	adherence rate to CDC recommendation	I: 78% C: 71%	RD = 8% (4% - 11%) After adjustment[a] OR = 1.29 (0.69 – 2.41)
Juzych (2005)[22]	NRCT	evaluate the effect of an intervention on improving AB prescribing for acute URTIs	general practice	I: educational session, educational materials for participants and patients C: none	practices	pediatricians I: 9 C: 6	children with URTI, <15 years[1] I: 2664 C: 1445	AB prescribing rates	I: 28% C: 30%	RD for reduction in AB prescribing rates = 2% (0% – 5%)
Maiman (1988)[19]	RCT	improvement of pediatricians compliance-enhancing strategies	pediatric practice	Ia: tutorial and printed materials Ib: only printed materials C: none	Individual health care professionals	pediatricians Ia: 33 Ib: 30 C: 27	children with OM, 6 m – 10 y Ia: 303 Ib: 259 C: 209	1) pediatricians knowledge of compliance enhancing strategies 2) pediatricians self-reports of quantity of compliance enhancing behavior	1) Ia: 50% Ib: 22% C:21% 2) Ia: 78% Ib: 63% C: 46%	1) RD = Ia vs. Ib : 28 (4% - 51%) Ia vs. C: 29 (5% - 53%) Ib vs. C: 1 (-21%- 24%) 2) RD = Ia vs. Ib : 15 (-5% - 38%) Ia vs. C: 32 (8% - 57%) Ib vs. C: 17 (-10 - 44%)

Table 2.3 Continued

Study	Design	Aim	Setting	Intervention	Allocation	Participants	Patients	Outcome	Results	Effect measure
Smabrekke (2003)[23]	CBA	reduce both the total consumption of AB and the use of broad-spectrum AB	emergency care setting	I: educational sessions, educational materials for participants and patients C: none	practices	physicians, nurses, pharmacists number of participants not specified	children with AOM, 1 – 15 years I: 210 C: 114	1) proportion of patients treated with AB	1) I: 74% C: 91%	1) RD for reduction of proportion patients treated with AB = 17 (10 %– 25%)
								2) proportion of patients treated with small-spectrum AB	2) I: 85% C: 78%	2) RD = 6 (-3% - 16%)

Legend and abbreviations table 2.3

Design (C)RCT = (cluster) randomized controlled trial CBA = controlled before and after study
NRCT = non-randomized controlled trial

Aim / outcome CDC = Centers for Disease Control and Prevention AB = antibiotics

Intervention I (a / b) = intervention group (a / b) C = control group

Patients OM = otitis media AOM = acute otitis media (U)RTI = (upper) respiratory tract infections
[1] = Also patients > 15 years in the study (including adults), only pediatric patients are included.

Results Post intervention values

RD Risk difference **=** Post-intervention measurement in intervention group – post-intervention measurement in control group (in %), with 95% CI

OR Odds ratio, with 95% CI

[a] = adjusted for cluster randomization an d the following covariates: marital status, education level, income, insurance status, age of child, age of primary care givers, Hispanic ethnicity, breastfeeding and presence of smokers in household

Table 2.4. Design, aim, intervention and outcomes of the included studies: *other interventions*

Study	Design	Aim	Setting	Intervention	Allocation	Participants	Patients	Outcome	Results	Effect measure
Bennett (2001)[16]	CRCT	Improve-ment appropria-teness of referrals	general practice	Ia: risk factor checklist Ib: training video Ic: a and b C: none	practices	general practitioners Ia: 43 Ib: 56 Ic: 37 C: 41	children with suspected OME 0 – 15 years, average: 6.85 number of patients not specified	rate of appropriateness of referral	1) post intervention Ia: 16% Ib: 24% Ic: 52% C: 15%	RD = Ia vs Ib: -8 (-19% - 3%) Ia vs C: 1 (-9% - 11%) Ib vs C 9 (-19% - 20%) Ic vs C: 37 (25% - 49%)
Bush (1979)[21]	CBA	to improve general prescribing quality	community health plan	Ia: development of protocol Ib: discussion and providing of protocol C: none	Individual health care professionals	pediatricians and physician extenders Ia: 12 Ib: 6 C: ?	children with OM[1], 80% < 15 years Ia: 251 Ib: 51 C: 139	1) proportion of episodes with ≥3 different drugs 2) proportion of protocol drugs prescribed	1) post intervention Ia: 19% Ib: 27% C: 5% Difference pre-post intervention 2) Ia: 23 1b: -4 C: -18	1) RD 1a vs 1b: -8 (-22 – 5) 1a vs C: 14 (8 – 20) 1b vs C: 22 (10 – 35) P value for behavior change 1a: <0.001 1b and C: not mentioned

Table 2.4 Continued

Study	Design	Aim	Setting	Intervention	Allocation	Participants	Patients	Outcome	Results	Effect measure
Wilson (2002)[14]	RCT	more judicious use of antibiotics	general practice	I: collaborative development of CPG + educational materials C: none	Individual health care professionals	general practitioners I: 24 C: 30	children with ARI, <2 years at inclusion, follow-up 2 years I: 257 C: 245	AB prescribing during ARI episodes	1) post intervention I: 36% C: 38%	OR, adjusted for patient age and severity: 0.60 (0.43 – 0.83)

Legend and abbreviations table 2.4

Design (C)RCT = (cluster) randomized controlled trial CBA = controlled before and after study

Aim / outcome: AB = antibiotics

Intervention: I (a / b / c) = intervention group (a / b / c) C = control group CPG = clinical practice guideline

Patients: OM = otitis media OME = otitis media with effusion (glue ear) ARI = acute respiratory infection

[1] = Researchers measured effects in purulent and serous otitis media, only for the effects in purulent otitis media results in the control group are provided, therefore only those results are included.

RD: Risk difference **=** Post-intervention measurement in intervention group – post-intervention measurement in control group (in %), with 95% CI

OR: Odds ratio, with 95% CI

Chapter 2

Discussion

This review shows that all dissemination and implementation strategies used, i.e. computer interventions, educational sessions with or without education materials, collaborative development of guidelines and a training video in combination with a risk factor checklist, are effective in changing health care professionals' management in children with URTIs.

To our knowledge, we are the first to report on current evidence on dissemination and implementation strategies regarding treatment of URTIs in children. Implementation of the available evidence on this topic is important since it may minimize unnecessary surgery and inappropriate antibiotic prescribing. As passive dissemination of evidence regarding treatment options, is known to be ineffective, it is important to apply effective dissemination and implementation strategies adjusted for the mix of health care professionals involved in the care of children with URTIs.
Our results indicate any strategy to be at least moderately effective in changing health care professionals' management of children with URTIs. Multifaceted or computer strategies were most effective. They are in agreement with those of two generic reviews[24, 25] and a review focused on appropriate antibiotic usage in common infections[26]. They also found multifaceted strategies and computer-based support systems to be effective in implementing guidelines.

Some potential limitations are worth discussing.
First, we only identified studies that reported on effective strategies, although not all were statistically significant. This results suggest that any active intervention to implement evidence is more effective than passive dissemination of evidence-based interventions. Other systematic reviews on implementation strategies in general, however, report on ineffective strategies or strategies with an uncertain or variable effectiveness.[24, 25] Publication bias can therefore not be excluded.
Second, since none of the studies reported on the actual costs of their strategies, we could not study the cost-effectiveness of the strategies used. Such knowledge of the cost-effectiveness of the strategies is needed before decisions can be made to use a specific strategy.
Third, we judged 17% of the quality criteria as unclear since many studies provided not enough information to judge the risk of bias as 'no risk' or 'high risk.

Furthermore, contamination may have played a role in three studies, which may have caused an underestimation of the effect of the interventions.
Fourth, no studies were found on implementation strategies focused on changing otolaryngologists' behavior regarding surgery for URTIs in children. The results of our review may therefore not be generalizable to that specialty. This calls for further research in this domain.
Fifth, it can be questioned whether the presented effects of the dissemination and implementation strategies are determined by the actual strategy or the intervention at study. For, the effect of the strategies may be influenced by willingness of health care professionals to accept a certain intervention. In our review most studies, however, focused on antibiotic treatment. We therefore believe that the presented effects are indeed those of the dissemination and implementation strategies.
Sixth, in this review we focused on health care professionals only, whereas in daily practice both health care professional as well as patient characteristics influence decision making.[12, 27-29] To optimize dissemination and implementation of evidence, both parties should be targeted.
In conclusion, multifaceted and computer strategies appear to be most effective in changing health care professionals' management behavior in children with URTIs.

Conflict of interest statement

None of the authors has any conflict of interest regarding this paper, and the project was not funded by any grant.

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Appendix 2.1. Search strategies for Pubmed, Embase and Central Register of Controlled Trials

Pubmed	
#1	"intervention"[Title/Abstract] OR "implementation"[Title/Abstract] OR "dissemination"[Title/Abstract] OR "strategy"[Title/Abstract] OR "pretest" [Title/Abstract] OR "pretest"[Title/Abstract] OR evaluat*[Title/Abstract] OR (continuing[Title/Abstract] AND medical[Title/Abstract] AND education[Title/ Abstract]) OR "information"[Title/Abstract] OR (physician[Title/ Abstract] AND patient[Title/Abstract]) OR (health [Title/Abstract] AND care[Title/ Abstract]) OR "evidence" [Title/Abstract] OR recommendation* [Title/Abstract] OR "consensus"[Title/Abstract] OR research*[Title/Abstract] OR finding*[Title/ Abstract] OR outreach* [Title/Abstract] OR "poster" [Title/Abstract] OR "posters"[Title/Abstract] OR pamphlet*[Title/Abstract] OR guideline*[Title/ Abstract] OR reminder* [Title/Abstract] OR "audit and feedback"[Title/Abstract] OR "marketing" [Title/Abstract] OR printed material*[Title/Abstract] OR "computer based"[Title/Abstract] OR "clinical reminder system*"[Title/Abstract] OR "outreach" [Title/Abstract] OR "local opinion leader*"[Title/Abstract] OR "education" [Title/Abstract] OR "decision support system*"[Title/Abstract] OR "incentive" [Title/Abstract] OR "multifaceted"[Title/Abstract] OR "organisation" [Title/Abstract] OR "organization"[Title/Abstract] OR traditional* [Title/Abstract]
#2	"urti"[Title/Abstract] OR "uri"[Title/Abstract] OR "respiratory tract infection*" [Title/Abstract] OR "otitis media"[Title/Abstract] OR "ear* infection*" [Title/Abstract] OR "ear* disease*"[Title/Abstract] OR "glue ear"[Title/Abstract] OR "earache*"[Title/Abstract] OR "otalgia*" [Title/ Abstract] OR "ottorhoea" [Title/Abstract] OR "otorrhea"[Title/Abstract] OR "hearing loss"[Title/Abstract] OR "rhinosinusitis"[Title/Abstract] OR "sinusitis"[Title/Abstract] OR "common cold"[Title/Abstract] OR "sore throat*"[Title/Abstract] OR "tonsillopharyngitis" [Title/Abstract] OR "tonsilopharyngitis"[Title/Abstract] OR "pharyngitis"[Title/ Abstract] OR "tonsillitis"[Title/Abstract] OR "throat infection*"[Title/Abstract] OR "rhinorrhoea"[Title/Abstract] OR "om"[Title/Abstract] OR "com" [Title/ Abstract] OR "csom"[Title/Abstract] OR "aom"[Title/Abstract] OR "oma" [Title/Abstract] OR "ome"[Title/Abstract] OR "mee"[Title/Abstract] OR "ent" [Title/Abstract] OR "ear nose throat"[Title/Abstract] OR "otorhinolaryngology" [Title/Abstract] OR "otolaryngology"[Title/Abstract] OR "ORL"[Title/Abstract]

#3	(behaviour*[Title/Abstract] OR "compliance"[Title/Abstract] OR reduce* [Title/Abstract] OR reduci* [Title/Abstract] OR reduct*[Title/Abstract] OR increas*[Title/Abstract] OR decreas*[Title/Abstract] OR chang* [Title/Abstract] OR improv*[Title/Abstract] OR modif*[Title/Abstract] OR "care"[Title/ Abstract] OR effect*[Title/Abstract] OR impact*[Title/Abstract] OR evaluat*[Title/Abstract] OR compar*[Title/Abstract] OR "quality" [Title/Abstract] OR "clinical"[Title/Abstract] OR "role"[Title/ Abstract] OR "value"[Title/Abstract] OR "outcome"[Title/Abstract] OR manage* [Title/Abstract] OR "application"[Title/Abstract] OR "practice" [Title/Abstract] OR influence*[Title/Abstract]
#4	child*[Title/Abstract] OR pediatric*[Title/Abstract] OR paediatric* [Title/Abstract]
#5	#1 AND #2 AND #3 AND #4

Embase	
#1	intervention:ti,ab OR implementation:ti,ab OR dissemination:ti,ab OR strategy:ti,ab OR pre test:ti,ab OR pretest:ti,ab OR evaluat*:ti,ab OR (continuing AND medical AND education):ti,ab OR information:ti,ab OR (physician AND patient):ti,ab OR (health AND care) :ti,ab OR evidence:ti,ab OR recommendation*:ti,ab OR consensus:ti,ab OR research*:ti,ab OR finding*:ti,ab OR outreach*:ti,ab OR poster:ti,ab OR posters:ti,ab OR pamphlet*:ti,ab OR guideline*:ti,ab OR reminder* :ti,ab OR (audit and feedback) :ti,ab OR marketing:ti,ab OR printed material*:ti,ab OR (computer based) :ti,ab OR (clinical reminder system*):ti,ab OR outreach:ti,ab OR (local opinion leader*):ti,ab OR education:ti,ab OR (decision support system*):ti,ab OR incentive:ti,ab OR multifaceted:ti,ab OR organization:ti,ab OR traditional*:ti,ab
#2	urti:ti,ab OR uri:ti,ab OR (respiratory tract infection*):ti,ab OR (otitis media) :ti,ab OR (ear* infection*):ti,ab OR (ear* disease*):ti,ab OR (glue ear):ti,ab OR earache*:ti,ab OR otalgia*:ti,ab OR ottorhoea:ti,ab OR otorrhea:ti,ab OR (hearing loss):ti,ab OR rhinosinusitis:ti,ab OR sinusitis:ti,ab OR (common cold):ti,ab OR (sore throat*):ti,ab OR tonsillopharyngitis:ti,ab OR tonsilopharyngitis:ti,ab OR pharyngitis:ti,ab OR tonsillitis:ti,ab OR (throat infection*):ti,ab OR rhinorrhoea:ti,ab OR rhiniti*:ti,ab OR om:ti,ab OR com:ti,ab OR csom:ti,ab OR aom:ti,ab OR oma:ti,ab OR ome:ti,ab OR mee:ti,ab OR ent:ti,ab OR (ear nose throat):ti,ab OR otorhinolaryngology:ti,ab OR otolaryngology:ti,ab OR ORL:ti,ab

#3	behaviour*:ti,ab OR compliance:ti,ab OR reduc*:ti,ab OR increas*:ti,ab OR decreas*:ti,ab OR chang*:ti,ab OR improv*:ti,ab OR modif*:ti,ab OR care:ti,ab OR effect*:ti,ab OR impact*:ti,ab OR evaluat*:ti,ab OR compar*:ti,ab OR quality:ti,ab OR clinical:ti,ab OR role:ti,ab OR value:ti,ab OR outcome:ti,ab OR manage*:ti,ab OR application:ti,ab OR practice:ti,ab OR influence*:ti,ab
#4	(child*:ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab)
#5	#1 AND #2 AND #3 AND #4

Cochrane Central Register of Controlled Trials	
#1	Implementation*

Chapter 3

The cost effectiveness of pneumococcal conjugate vaccination against acute otitis media in children: a review

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PharmacoEconomics; 2011;29(3):199-211 [a]

Chapter 3

Abstract

Background: While pneumococcal conjugate vaccines have shown to be highly effective against invasive pneumococcal disease, their potential effectiveness against acute otitis media (AOM) might become a major economic driver for implementing these vaccines in national immunization programs. The relation between the costs and benefits of available vaccines, however, remains a controversial topic.

Objective: To systematically review the literature on the cost-effectiveness of pneumococcal conjugate vaccination against AOM in children.

Methods: We searched PubMed, Cochrane, and the CRD databases DARE, NHS EED and HTA from inception up to 18 February 2010. We used the following keywords with their synonyms: 'Otitis Media', 'Children', 'Cost-effectiveness', 'Costs', and 'vaccine'. Cost per AOM episode averted were calculated based on the information in the papers.

Results: Twenty-one studies evaluating the cost-effectiveness of pneumococcal conjugate vaccines were included. The quality of the included studies was moderate to good. The cost per AOM episode averted varied from €168 to €4,214, and assumed incidence rates varied from 20,952 to 118,000 per 100,000 children aged 0 to 10 years. Assumptions regarding direct and indirect costs varied between studies. The assumed vaccine efficacy of the 7-valent pneumococcal CRM197-conjugate vaccine was mainly adopted from two trials, who reported 6-8% efficacy. Some studies, however, assumed additional effects such as herd immunity or only took into account AOM episode caused by serotypes included in the vaccine, which resulted in efficacy rates varying from 12 to 57%. Cost per AOM episode averted were inversely related to the assumed incidence rates of AOM and positively related to the estimated costs per AOM episode. The costs per AOM episode averted tend to be lower in industry sponsored studies.

Conclusion: Key assumptions regarding the incidence and costs of AOM episodes have major implications for the estimated cost-effectiveness of pneumococcal conjugate vaccination against AOM. Uniform methods for estimating direct and

indirect costs of AOM should be agreed upon to reliably compare the cost-effectiveness of the available and future pneumococcal vaccines against AOM.

Introduction

Acute otitis media (AOM) is one of the most common childhood infections, the leading cause of doctors' consultations, and the most frequent reason children consume antibiotics or undergo surgery in developed countries.[1, 2] In 1996, annual costs of OM in the USA were estimated to be 3 to 5 billion dollars, but the true impact is probably underestimated because indirect costs might be substantially higher than estimated.[3] With current concerns about the rising costs of healthcare, the search for effective measures to prevent AOM is of major importance.

As *Streptococcus pneumoniae* is the most common bacterial pathogen in AOM, research has focused on the effectiveness of pneumococcal conjugate vaccines (PCV). Although these PCVs were originally developed for invasive pneumococcal disease, their potential effectiveness against AOM appears to become a major economic driver for implementing these vaccines in national immunization programs. More information about the costs and benefits of available vaccines regarding AOM is therefore warranted.

The potential beneficial capacity of PCV in reducing the incidence of both invasive pneumococcal disease (IPD) and AOM was tested in efficacy trials. While the efficacy of conjugate vaccines regarding IPD is high (93.9%, 95% CI 79.6 – 98.5) [4], the efficacy regarding AOM is lower, ranging from 6.4% (95% CI: 3.9 – 8.7) for 7-valent pneumococcal CRM_{197}-conjugate vaccine [4] to 33.6% (95% CI: 20.8 – 44.3) for a combined conjugate vaccine against both *Streptococcus pneumoniae* (11 serotypes) and non-typeable *Haemopihylus influenzae* (NT*Hi*).[5] For the 13- and 10-valent PCVs that were recently licensed for prevention of AOM, no efficacy data from randomized studies are available yet. Nowadays, 24 European countries offer the 7-valent PCV7 in their childhood immunization programs.[6] A potential switch towards either the newly licensed 13-valent PCV or the combined 10-valent pneumococcal conjugate–NT*Hi* vaccine is a matter of intense discussion. With varying prices of PCVs, and the current schedules including 3-4 injections, relation between costs and benefits of mass immunization with both PCV7 and its successors for AOM is an important health economic topic. This can be estimated with a cost-effectiveness study in which the costs that are involved with the vaccine are compared with the effect of the vaccine in

daily practice. However, estimating the cost effectiveness of vaccines in AOM is complex for several reasons.[7] First, definitions of AOM episodes vary across studies and countries. Second, the effect of the vaccine may wane over time when replacing pneumococcal serotypes or other otopahogens may limit vaccine efficacy.[8-11] Besides these difficulties in measuring health benefits, the controversy also lies in differences in measuring cost (e.g. societal vs health care perspective). The objective of this review therefore was to systematically review the literature on cost effectiveness of the currently used PCV against AOM.

Materials and methods

Search strategy

We searched PubMed, Cochrane and the Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects [DARE], NHS Economic Evaluation Database [NHS EED] and Health Technology Assessment database [HTA]) from inception until 18 February 2010. We used the following keywords with their synonyms: 'Otitis Media', 'Children', 'Cost effectiveness', 'Cost', and 'vaccine' (see Appendix 3.1 for complete search strategy). We checked the bibliography of all relevant studies and reviews in order to identify supplemental studies. We imposed no language restriction on the searches. Two reviewers (PB, CB) screened the titles and abstracts of the articles found by the previous described search strategy, and judged eligibility of the papers. Disagreement was resolved by discussion.

Study selection

We included all studies that met the following inclusion criteria; i) cost-effectiveness analyses were performed; ii) the intervention included a multivalent PCV; iii) the study population included children aged 0 to 5 years; iv) the number of AOM episodes averted was either reported or could be calculated; v) costs per AOM episode were either reported or could be calculated; and vi) the outcome parameter was presented or could be calculated as 'costs per AOM episode averted' or 'cost per AOM-QALY gained or AOM-DALY averted'.

Data extraction

Information was collected for each study on; country , modelling approach, population, vaccine type, vaccine efficacy, vaccine protection in years, vaccine

schedule, vaccine coverage, AOM incidence per 100,000 children, perspective, costs, and effects (both in episodes averted as well as in QALYs/DALYs).
All costs were inflated to 2009 values using country-specific inflation rates from the Organisation for Economic Co-operation and Development (OECD) [12], and converted to Euro's using the conversion rates of 31 December 2009.[13] Based on the extracted effects and costs, we calculated the cost per AOM episode averted (CE_{EA}) using equation 1:

CE_{EA} = *((vaccine dose price * vaccine schedule * 100,000 children) – (episodes averted per 100,000 children * cost of 1 AOM episode)) / episodes averted per 100,000 children)* (Eq. 1)

If possible we also extracted or calculated cost per AOM specific QALY or DALY (CE_{QALY} or CE_{DALY}) using equation 2:

CE_{QALY} or CE_{DALY} = *((vaccine dose price * vaccine schedule * 100,000 children) – (episodes averted per 100,000 children * cost of 1 AOM episode)) / (episodes averted per 100,000 children * QALY (or DALY) loss per episode)* (Eq. 2)

Study quality
Two authors (PB, CB) independently assessed the quality of all included studies using Drummond's check-list for assessing economic evaluations.[14] Ten specific domains were addressed: research question, competing alternatives, effectiveness, relevant costs and consequences, costs and consequence measures, unit measures, values, discounting, incremental analysis, sensitivity analysis and overall considerations. We used pre-specified questions to judge the quality for each domain. The outcome for each domain was either 'good', 'moderate', 'poor' or 'unclear'. Disagreement was resolved by discussion (PB, CB).

Sensitivity analyses
We performed sensitivity analyses to study the influence of some important *a priori*-defined factors: incidence rates, number of AOM episodes averted per 100,000 children, total cost per AOM episode, vaccine price, industry involvement, time horizon, and publication year.

Chapter 3

Results

Search results

Our search identified 246 studies. After titles and abstracts were screened 20 studies met the inclusion criteria. One additional article was identified by checking the bibliographies of the selected studies. Primary exclusion criteria were that the article did not include a cost-effectiveness analysis, or costs per AOM episode were not reported (see also *Figure 3.1*).

Figure 3.1. Flow-chart of search strategy

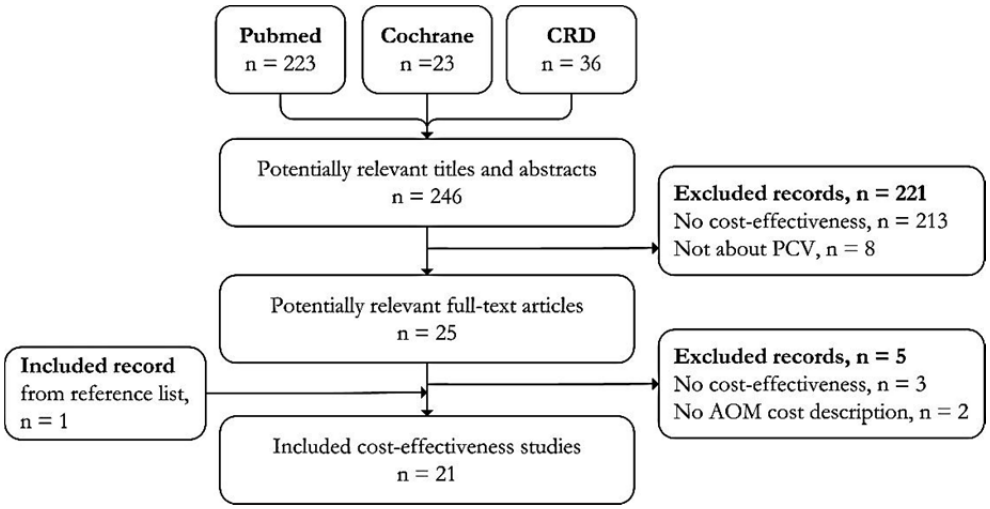


Table 3.1 shows the results of the quality assessment according to Drummond's check-list for assessing economic evaluations. All included studies provided sufficient information to calculate incremental costs, had a well defined research question and used discounting. In all studies 'no vaccination' was the alternative. In four studies (19%) the effectiveness of the vaccine was not adequately reported and in eight studies (38%) not all important and relevant costs and consequences of AOM were identified. In nine (43%) and ten (47%) studies the unit of measurement and the valued costs and consequences of AOM were not clearly reported, respectively. Five (24%) studies did not discuss all potential relevant issues of concern.

Table 3.1. Summary of the methodological quality of the included studies

Author (Year)	Well defined question	Competing alternative	Effectiveness	Costs and consequences	Unit measurement	Unit values	Discounting	Incremental analysis	Uncertainty analysis	Complete issues of concern [a]
Asensi (2004) [22]	+	+	+	+	+	±	+	+	+	+
Bergman (2008) [23]	+	+	+	+	+	+	+	+	+	+
Bos (2003) [33]	+	+	-	+	+	±	+	+	+	+
Bos (2006) [24]	+	+	+	±	-	±	+	+	+	+
Butler (2004) [34]	+	+	+	-	-	-	+	+	±	±
Claes (2003) [25]	+	+	+	+	+	+	+	+	+	+
Ess (2003) [15]	+	+	+	+	±	±	+	+	±	+
Giglio (2010) [26]	+	+	+	+	+	+	+	+	+	+
Lebel (2003) [27]	+	+	+	+	+	+	+	+	±	±
Lieu (2000) [28]	+	+	+	+	+	+	+	+	+	+
Lloyd (2008) [16]	+	+	+	+	±	±	+	+	±	±
McIntosh (2003) [17]	+	+	+	+	-	+	+	+	±	±
Navas (2005) [18]	+	+	+	-	-	-	+	+	±	+
O'Brien (2009) [7]	+	+	±	+	+	+	+	+	+	+
Ray (2009) [29]	+	+	±	-	-	+	+	+	+	+
Salo (2005) [30]	+	+	+	+	+	±	+	+	+	+
Silfverdal (2009) [19]	+	+	±	-	-	+	+	+	±	+
Sohn (2010) [20]	+	+	+	-	+	+	+	+	+	+
Vespa (2009) [21]	+	+	+	+	+	±	+	+	+	+
Wals, de (2003) [31]	+	+	+	-	-	-	+	+	±	±
Wisloff (2006) [32]	+	+	+	-	+	+	+	+	+	+

[a] Did the presentation and discussion of study results include all issues of concern to users, i.e. were the results compared to other studies, was the generalisability discussed, were other important factors taken into consideration, and did the study discuss issues of implementation?

Legend table 3.1:
+ = Yes (low risk of bias)
± = Moderate (moderate risk of bias)
- = Can't tell/no (high risk of bias)

All studies were based on (cohort-based) decision analysis models; some used a decision tree [15-21] and others the slightly more complex Markov models.[7, 22-32] *Table 3.2* lists the selected studies and their general characteristics. Twelve studies were performed in eight European countries[15-19, 22-25, 30, 32, 33]), five in north America[7, 27-29, 31], two in South America [21, 26], and one each in Australia [34], and Asia [20].
All but one study reported on the cost effectiveness of PCV7. This one study concerned a combined 9-valent pneumococcal and meningococcal B vaccine.[24] One study compared three vaccines (i.e. PCV7, the combined pneumococcal NT*Hi* vaccine, and a hypothetical combined pneumococcus-NT*Hi-Moraxella catarrhalis* vaccine.[7] Five studies focused primarily on pneumococcal otitis media [20, 24, 27, 32, 33]; the other studies on all-cause otitis media. The vaccine schedule consisted of 4 doses administered before 18 months of age, except for the Swedish and Brazilian studies that used 3 doses.[19, 21, 23] Eighteen studies used a societal perspective, whereas three studies used the health care payer's perspective.[17, 20, 29] Four studies included herd immunity in their model.[16, 17, 29, 32] Thirteen of the 21 studies had pharmaceutical company involvement (either by means of co-authors, grants or direct involvement by the pharmaceutical company).[15, 17, 19, 21-23, 25-29, 31, 32]

Vaccine efficacy
The assumed vaccine efficacy of the 7-valent pneumococcal CRM_{197}-conjugate vaccine against AOM was mainly adopted from two trials in the US and Finland.[4, 9] In these trials the vaccine efficacy against all-cause AOM varied between 5.8 and 8.3% (see also *Table 3.2*). Nevertheless 3 economic evaluations assumed considerably different vaccine efficacy for PCV7 than that reported in the US and Finnish studies.[20, 25, 29] By including herd effects Ray et al. [29] assumed a vaccine efficacy of 12.9%. Sohn et al. [20] only looked at AOM episode caused by serotypes included in the vaccine, which resulted in an efficacy of 57%. The 34% efficacy assumed by Claes et al.[25] was related to all pneumococcal infections confirmed on culture (including serotypes not covered by vaccine). The assumed vaccine efficacies of the combined 9-valent pneumococcal and meningococcal B vaccine, the combined pneumococcal NT*Hi* vaccine, and the hypothetical combined pneumococcus-NT*Hi-Moraxella catarrhalis* vaccine were 5.8, 28.0, and 31.5%, respectively.

Table 3.2. Characteristics of included studies

Author (Year)	Country	Cohort	AOM case definition	Vaccine	Vaccine efficacy used in model	Waning pattern	Vaccine protection (years)	Vaccine schedule (doses)	Vaccine coverage	AOM incidence per 100,000	AOM episodes averted per 100,000
Asensi (2004) [22]	Spain	360,000	All cause	PCV7	5.8%	N/A	10	4	N/A	60,864[a] [39]	34,762
Bergman (2008)[23]	Sweden	95,000	All cause	PCV7	6.0%	Not included [d]	5	3	N/A	44,000[b] [40]	8,223
Bos (2003) [33]	The Netherlands	202,000	Pneumococcal	PCV7	5.8%	Replacement in sensitivity analyses	10	4	N/A	22,100 [a] [41]	21,136
Bos (2006) [24]	The Netherlands	202,600	Pneumococcal	M+PCV	6.0%	Not included [d]	10	4	N/A	37,300 [a] [27, 41]	22,878
Butler (2004) [34]	Australia	250,000	All cause	PCV7	6.4%	Not included [d]	5	4	83%	106,200 [b] [42]	25,726
Claes (2003) [25]	Germany	700,000	All cause	PCV7	34.0%	Not included [d]	10	4	N/A	104,856 [b] [9]	58,452
Ess (2003) [15]	Switzerland	80,000	All cause	PCV7	7.0%	N/A	5	4	70%	22,500 [b] [43]	21,845
Giglio (2010) [26]	Argentina	696,451	All cause	PCV7	6.0%	Not included [d]	5	4	92%	110,000 [b] [42]	12,172
Lebel (2003) [27]	Canada	340,000	Pneumococcal	PCV7	5.8%	N/A	10	4	N/A	49,000 [a] [44]	23,652
Lieu (2000) [28]	United States	3,800.000	All cause	PCV7	7.0%	Age	5	4	90%	118,000 [a] [4, 42, 45]	23,026
Lloyd (2008) [16]	Germany	707,200	All cause	PCV7	6.0%	Not included [d]	10	4	83%	104,856 [b] [46]	27,998
McIntosh (2003)[17]	United Kingdom	734,000	All cause	PCV7	7.0%	Not included [d]	10	4	95%	N/A[c] [47]	6,428
Navas (2005) [18]	Spain	60,000	All cause	PCV7	6.4%	N/A	2	4	95%	106,200 [b] [48]	14,375
O'Brien (2009) [7]	United States	4,200,000	All cause	PCV7	6.4%	Age	5	4	N/A	N/A	20,905
O'Brien (2009) [7]	United States	4,200,000	All cause	PCV+NTH	28.0%	Age	5	4	N/A	N/A	88,714
O'Brien (2009) [7]	United States	4,200,000	All cause	PCV+NTH +M	31.5%	Age	5	4	N/A	N/A	99,286

Table 3.2 continued

Author (Year)	Country	Cohort	AOM case definition	Vaccine	Vaccine efficacy used in model	Waning pattern	Vaccine protection (years)	Vaccine schedule (doses)	Vaccine coverage	AOM incidence per 100,000	AOM episodes averted per 100,000
Ray (2009) [29]	United States	21,200,000	All cause	PCV7	12.9%	Age	5	4	85%	124,350 [b 49]	40,660
Salo (2005) [30]	Finland	57,574	All cause	PCV7	6.0%	Not included [d]	5	4	N/A	122,100 [b 9]	26,022
Silfverdal (2009)[19]	Sweden	105,913	All cause	PCV7	6.0%	Not included [d]	N/A	3	N/A	63,000 [b 50]	17,803
Sohn (2010) [20]	Korea	451,514	Pneumococcal	PCV7	57.0%	Not included [d]	N/A	4	N/A	20,952 [a 51]	11,253
Vespa (2009) [21]	Brazil	3,469,937	All cause	PCV7	7.0%	N/A	5	3	96%	N/A	6,048
Wals, de (2003)[31]	Canada	340,000	All cause	PCV7	8.2%	N/A	10	4	80%	92,510 [b 52]	24,370
Wisloff (2006) [32]	Norway	55,000	Pneumococcal	PCV7	6.0%	Not included [d]	5	4	N/A	23,200 [b 53]	5,569

Legend table 3.2

[a] AOM incidence per 100,000 children aged 0-10 years.
[b] AOM incidence per 100,000 children aged 1-2 years.
[c] Exact incidence not presented in article, however reference was presented
[d] Authors decided not to include a waning effect
N/A= Not applicable, not mentioned in article.

Costs

The costs per AOM episode averted (CE_{EA}) varied widely from €168 [22] to €4,214 [32] (*Table 3.3*). The vaccine price of the PCV7 vaccines varied between €19 and €83. The prices for the combined 9-valent pneumococcal and meningococcal B vaccine, the combined pneumococcal NT*Hi* vaccine, and the hypothetical combined pneumococcus-NT*Hi-Moraxella catarrhalis* vaccine were €51, €83, and €102, respectively. Both direct and indirect costs were described in 15 studies. Only direct costs were described in two studies, whereas in four studies only total costs of an AOM episode were described.

Cost per AOM-specific QALY varied from € 9.646 per QALY [7] to €182.384 per QALY [30], and the cost per AOM-specific DALY from €13.630 per DALY [34] to €50.137 per DALY [21] (*Table 3.4*).

Sensitivity analyses

Figure 3.2 shows the relationship between the assumed incidence rate of AOM and the costs per AOM episode averted. The incidence rates varied from 20,952 [20] to 118,000 [29] per 100,000 children aged 0-10 years. The costs per AOM episode averted appear to be lower in studies that assumed a higher AOM incidence as compared to those that assumed a lower incidence. *Figure 3.3* shows the relationship between number of AOM episodes averted per 100,000 children and the cost AOM episodes averted. The number of episodes averted per 100,000 children varied from 4,369 to 58,452 for PCV7, and up to 88,714 and 99,286 for the pneumoccus-NT*Hi* combination vaccine, and the hypothetical pneumococcus-NT*Hi-Moraxella catarrhalis* combination vaccine, respectively.[7] The costs per AOM episode averted appear to be lower in studies that assumed a higher number of episodes averted than in those that assumed a lower number of episodes averted.

Figure 3.4 shows the relationship between estimated total costs per AOM episode and the cost per AOM episode averted. The estimated total cost of an AOM episode varied from €28 to €545. The costs per AOM episode averted tend to be lower in studies that assume higher cost per episode as compared to those that assume lower costs per episode. *Figure 3.5* shows the relationship between the vaccine price and the costs per AOM episode averted: they appear not to be associated.

Figure 3.6 shows the relation between the costs per AOM episode averted and potential industry involvement in the studies. The median costs per AOM episode averted tend to be lower in industry sponsored studies as compared to those that were not sponsored. Furthermore, the costs per AOM episode averted were not related to time horizon used or the year of publication (data not shown).

Table 3.3. Costs of AOM and vaccine and cost-effectiveness of pneumococcal vaccination (CE_{EA})

Author (Year)	Vaccine price (€)	Direct cost per AOM episode (€)	Indirect cost per AOM episode (€)	Total cost per AOM episode (€)	Cost per AOM episode averted (€)
Asensi (2004)[22]	55	N/A	N/A	470	168
Bergman (2008)[23]	58	313	232	545	1,582
Bos (2003)[33]	52	13	86	99	891
Bos (2006)[24] M+PCV	51	13	82	95	792
Butler (2004)[34]	83	66	N/A	66	1,227
Claes (2003)[25]	80	81	157	238	313
Ess (2003)[15]	75	152	36	188	1,192
Giglio (2010)[26]	19	N/A	N/A	29	599
Lebel (2003)[27]	54	236	165	401	507
Lieu (2000)[28]	59	125	149	274	746
Lloyd (2008)[16]	75	N/A	N/A	148	927
McIntosh (2003)[17]	55	100	132	232	3,216
Navas (2005)[18]	70	N/A	N/A	N/A	766*
O'Brien (2009)[7] PCV7	57	51	87	138	954
O'Brien (2009)[7] PCV+NTH	83	51	87	138	237
O'Brien (2009)[7] PCV+NTH+M	102	51	87	138	272
Ray (2009)[29]	52	50	94	145	367
Salo (2005)[30]	57	108	240	348	525
Silfverdal (2009)[19]	51	285	243	528	327
Sohn (2010)[20]	46	49	N/A	49	1,598
Vespa (2009)[21]	24	9	19	28	1,140
Wals, de (2003)[31]	52	47	208	255	603
Wisloff (2006)[32]	61	87	70	157	4,214

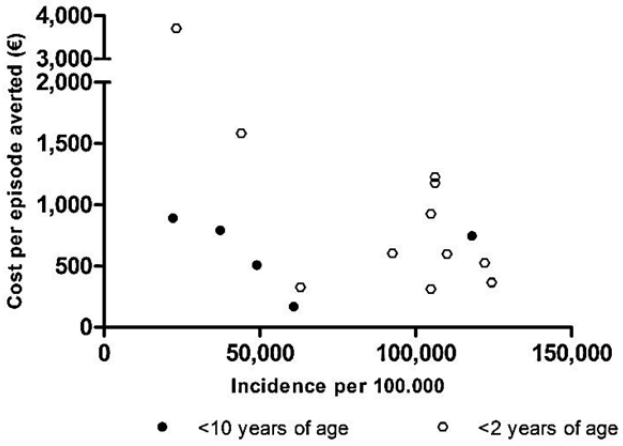
* As reported in the article (only indexed to 2009 values)
N/A = Not applicable, not mentioned in article.

Table 3.4. Secondary outcomes, € / QALY and € / DALY

Author (Year)	QALY loss due to one AOM episode	€ / AOM - QALY gained	DALY loss due to one AOM episode	€ / AOM-DALY averted
Asensi (2004) [22]	N/A	N/A	N/A	N/A
Bergman (2008) [23]	No AOM specific QALY	N/A	N/A	N/A
Bos (2003) [33]	No AOM specific QALY	N/A	N/A	N/A
Bos (2006) M+PCV [24]	No AOM specific QALY	N/A	N/A	N/A
Butler (2004) [34]	N/A	N/A	0.09	13,630
Claes (2003) [25]	N/A	N/A	N/A	N/A
Ess (2003) [15]	No AOM specific QALY	N/A	N/A	N/A
Giglio (2010) [26]	N/A	N/A	N/A	N/A
Lebel (2003) [27]	N/A	N/A	N/A	N/A
Lieu (2000) [28]	N/A	N/A	N/A	N/A
Lloyd (2008) [16]	N/A	N/A	N/A	N/A
McIntosh (2003) [17]	N/A	N/A	N/A	N/A
Navas (2005) [18]	N/A	N/A	No AOM specific DALY	N/A
O'Brien (2009) PCV7 [7]	0.011	25,970 [a]	N/A	N/A
O'Brien (2009) PCV+NTH [7]	0.011	9,646 [a]	N/A	N/A
O'Brien (2009) PCV+NTH+M [7]	0.011	11,872 [a]	N/A	N/A
Ray (2009) [29]	NA	N/A	N/A	N/A
Salo (2005) [30]	0.005	182,384	N/A	N/A
Silfverdal (2009) [19]	N/A	N/A	N/A	N/A
Sohn (2010) [20]	N/A	N/A	N/A	N/A
Vespa (2009) [21]	N/A	N/A	0.02	50,137
Wals, de (2003) [31]	No AOM specific QALY	N/A	N/A	N/A
Wisloff (2006) [32]	No AOM specific QALY	N/A	N/A	N/A

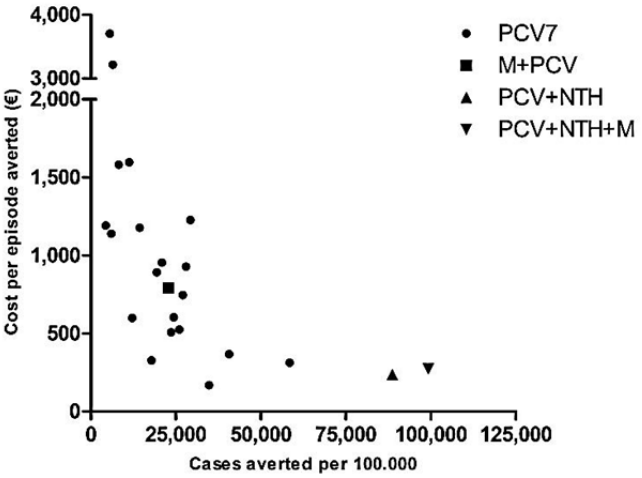
N/A Not applicable, not mentioned in article, or could not be calculated.
[a] As reported in the article

Figure 3.2. The relation between costs per AOM episode averted and assumed AOM incidence per 100,000 children



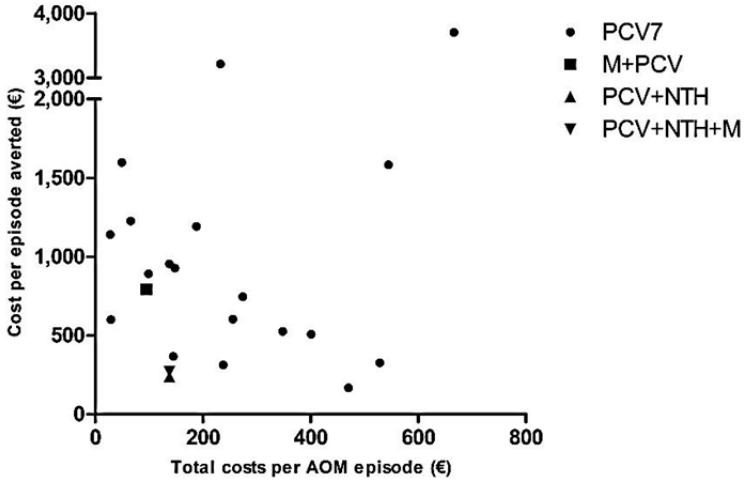
Studies using an incidence higher than 100,000 assumed several episodes per child

Figure 3.3. The relation between costs per AOM episode averted and estimated number of AOM episodes averted per 100,000 children



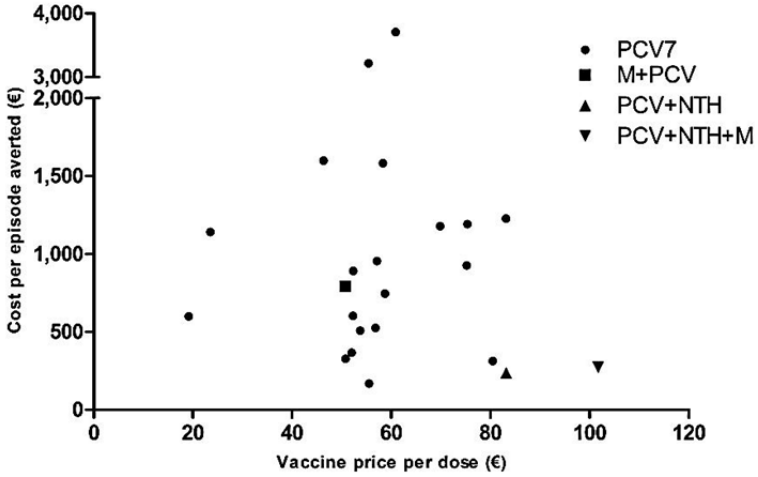
M = *Moraxella Catarrhalis*; NTH = non-typable *Haemophlius influenzae*; PCV = pneumococcal conjugate vaccines

Figure 3.4. The relation between cost per AOM episode averted and estimated total costs per AOM episode in Euros



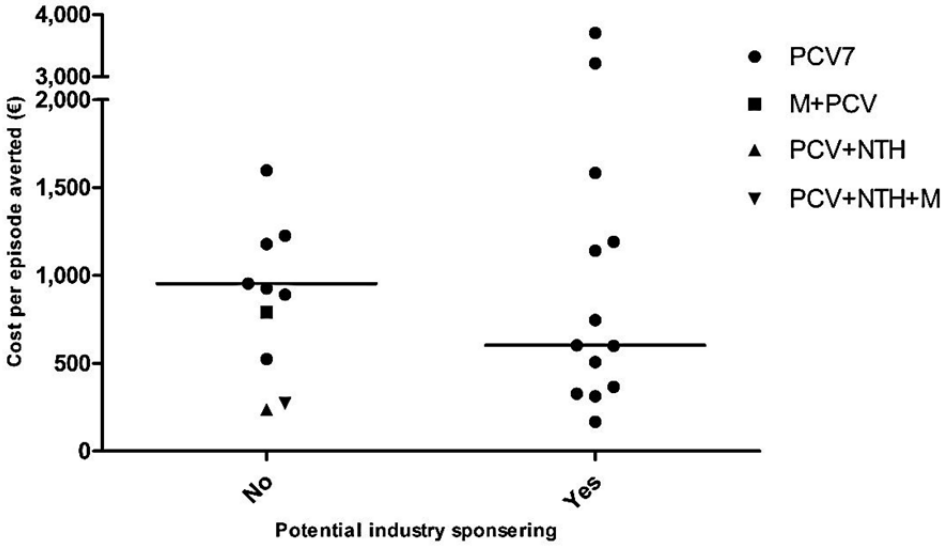
M = *Moraxella Catarrhalis*; NTH = non-typable *Haemophlius influenzae*; PCV = pneumococcal conjugate vaccines.

Figure 3.5. The relation between cost per AOM episode averted and the vaccine price in Euros



M = *Moraxella Catarrhalis*; NTH = non-typable *Haemophlius influenzae*; PCV = pneumococcal conjugate vaccines.

Figure 3.6. Influence of industry involvement on the cost per AOM episode averted



M = *Moraxella Catarrhalis*; NTH = non-typable *Haemophlius influenzae*; PCV = pneumococcal conjugate vaccines.
Black lines indicate the median of costs per AOM episode averted for the PCV7studies only.

Discussion

This review shows that cost per AOM episode averted by PCV varies considerably across studies, i.e. from €168 to €4,214. No difference was found when the studies were stratified to the used perspectives; the variation in costs per AOM episode averted was seen both in studies performed with a health care payer perspective (€ 367 - € 3,216) as in studies with a societal perspective (€ 168 - € 4,214).
The costs per averted AOM episode were mainly driven by the assumed AOM incidence, the number of averted AOM episodes per 100,000 children, and the assumed costs per AOM episode.
As far as we are aware, this is the first review on cost effectiveness of PCV against AOM, which is very important since many countries still have to decide whether they will include pneumococcal vaccination in their national immunization program. Others are discussing a potential switch towards either the newly licensed 13-valent

PCV or the combined 10-valent pneumococcal conjugate–NT*Hi* vaccine. And although PCV was originally introduced due to its effectiveness against invasive pneumococcal disease, their potential effectiveness against AOM appears to become a major economic driver for implementing these vaccines in national immunization programs. More information is therefore warranted on the costs per AOM episode averted and/or cost per AOM QALY. To allow for comparison of various cost-effectiveness studies, we indexed the costs to the same year and currency.

Some potential limitations should be discussed.

First, the effects of PCV on AOM are complex. They result from the direct protection against AOM provided by the vaccine (antibody mediated), but also from changes in the nasopharyngeal flora induced by the vaccine (reduction and replacement of pneumococcal serotypes), the effects on antibiotic resistance (reduction of the more resistant vaccine serotypes, potential emergence of non-vaccine pneumococcal serotypes, that may or may not become also antibiotic resistant and antibiotic use in the community), vaccine availability (or, more precisely, vaccine shortage), and successful implementation of vaccination programs.[35] Only one study [33] performed a sensitivity analysis for a potential waning effect due to replacement. Other studies did ignore waning due to replacement completely [15, 18, 21, 22, 27, 31] or decided not to include it because of lack of evidence on the impact of waning.[16, 17, 19, 20, 23-26, 30, 32, 34] Three studies did include a waning effect based on age and all assumed that the effect of vaccination would wane between the age of 2 and 5 years.[7, 28, 29]

Second, definitions of AOM vary and surveillance data regarding the incidence of AOM are lacking for most countries, therefore the assumptions used in the original models are uncertain. Similarly, real cost studies are scarce, especially regarding the indirect costs of AOM.

Third, assumptions regarding vaccine coverage varied from 70% up to 96%. In 11 studies the vaccine coverage is not mentioned, and is likely to be assumed at 100%. This may have lead to misleading estimates of the impact of immunization programs on both the burden of AOM and health care budgets.[36]

Fourth, some studies included herd immunity in their models, while others did not. Herd immunity is known to be important in conjugate vaccines like Meningococcal C and other vaccines like Rubella.[37] However, the herd immunity regarding AOM is unclear and very difficult to estimate.

Fifth, only 4 of the 21 included papers in this review reported on AOM-specific QALYs/DALYs. Previous studies on interventions in AOM have shown that effects reported as QALYs are very small, and may therefore not be as useful as for other conditions.[38] However, for the studies that did report on AOM-QALYs/ DALYs we calculated or extracted cost per QALY/DALY, and the results were in agreement with the results for 'cost per AOM episode averted'.
Sixth, almost all included studies reported on PCV7. Since no efficacy data against AOM are available for the newly licensed 10- and 13-valent pneumococcal vaccines, the current results may not be generalized to these vaccines. On the other hand, our results do show that current cost-effectiveness models depend on too many assumptions precluding firm conclusions.
Finally, as vaccine-related adverse events do not occur often [4, 9], and the associated cost are low, only seven of the included studies reported on costs for vaccine adverse events, of which two only in their sensitivity analyses. [7, 15, 18, 28, 29, 31, 33] Therefore, we did not include these costs in our equation for the cost per AOM episode averted. The influence of this specific costs on the total cost per AOM episode averted would have been small, € 0 [33] - € 21 [7].

In conclusion, we found that key assumptions regarding the incidence and costs of AOM episodes have major implications for the estimated cost effectiveness of PCV against AOM. Uniform methods for estimating direct and indirect costs of AOM should be agreed upon to reliably compare the cost effectiveness of the available and future pneumococcal vaccines against AOM.

Acknowledgements

No sources of funding were used to assist in the preparation of this review.
Prof. E.A.M. Sanders received unrestricted grants from Wyeth and Baxter for research, consulting fees for Wyeth and GlaxoSmithKline, lecturing fees from Wyeth and grant support from Wyeth and GlaxoSmithKline. Prof. dr. A.G.M. Schilder received honoraria from GlaxoSmithKline for participation in workshops and educational activities on otitis media. Dr. M.M. Rovers received honoraria from GlaxoSmithKline for an expert meeting at the ESPO in Budapest in 2008. Together with prof. dr. Schilder she received a grant for a study on the microbiology of otitis media from GlaxoSmithKline.

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Appendix 3.1. Search strategy

Pubmed	
#1	("Otitis Media"[Title/Abstract]) OR ("Otitis Media"[MeSH])
#2	(glue[Title/Abstract] AND (ear[Title/Abstract] OR ears[Title/Abstract])
#3	((((("OME"[Title/Abstract]) OR ("AOM"[Title/Abstract])) OR ("OM"[Title/ Abstract])) OR ("OMA"[Title/Abstract])) AND (glue[Title/Abstract] AND ("ear"[Title/Abstract] OR "ears"[Title/Abstract]))
#4	(((#1) OR #2) OR #3)
#5	(((((((Costs[Title/Abstract]) OR (Costing[Title/Abstract]) OR ("Burden"[Title/ Abstract])) OR ("direct costs"[Title/Abstract])) OR ("indirect costs"[Title/ Abstract])) OR (Price*[Title/Abstract])) OR (Expense*[Title/ Abstract])) OR (Fee*[Title/ Abstract])) OR (Charge*[Title/Abstract])) OR ("Monetary"Title/ Abstract]))
#6	(((((("Cost-effectiveness"[Title/Abstract]) OR ("Cost-benefit"[Title/Abstract])) OR ("Cost-utility"[Title/Abstract])) OR ("Review"[Title/Abstract])) OR ("Economic evaluation"[Title/Abstract])) OR ("Cost of illness"[Title/ Abstract])) OR ("Willingness to pay"[Title/Abstract])) OR ("Modelling"[Title/ Abstract]))
#7	#5 OR #6
#8	((((((((((Child*[Title/Abstract]) OR (Infant*[Title/Abstract])) OR ("Baby" [Title/ Abstract])) OR (Newborn*[Title/Abstract])) OR (Youngster*[Title/ Abstract])) OR (Adolescent*[Title/Abstract])) OR (Pediatric*[Title/Abstract])) OR ("Babies"[Title/ Abstract])) OR (Newborn*[Title/Abstract]) OR (Paediatric*[Title/Abstract])) OR (Neonat*[Title/Abstract]))
#9	((((((((((vaccin*[Title/Abstract]) OR Synflorix[Title/Abstract]) OR Prevenar [Title/Abstract]) OR 7vCRM[Title/Abstract]) OR 7-valent pneumococcal conjugate vaccine[Title/Abstract]) OR 11-valent pneumococcal conjugate vaccine[Title/Abstract]) OR PCV[Title/Abstract]) OR Pneumococ*[Title/ Abstract]) OR 7-valent[Title/ Abstract]) OR 10-valent[Title/Abstract]) OR 11-valent[Title/Abstract]) OR 13-valent[Title/Abstract]))
#10	((((#4) AND #7) AND #8) AND #9)
DARE, NHS-EED, HTA	
#1	MeSH Otitis Media EXPLODE 1
#2	Otitis AND Media
#3	#1 OR #2
#4	vaccine
#5	#3 AND #4

Appendix 3.1. Continued

Cochrane Central Register of Controlled Trials	
#1	(Otitis):ti,ab,kw AND (media):ti,ab,kw
#2	(glue):ti,ab,kw AND (ear*):ti,ab,kw
#3	(OME):ti,ab,kw OR(OM):ti,ab,kw OR (OMA):ti,ab,kw OR (AOM):ti,ab,kw
#4	(#1 OR #2 OR #3)
#5	(Cost*):ti,ab,kw OR (Burden):ti,ab,kw OR (Expense*):ti,ab,kw OR(Monetary): ti,ab,kw OR (Price*):ti,ab,kw OR (Fee*):ti,ab,kw OR (Charge*):ti,ab,kw OR (Direct costs): ti,ab,kw OR (Indirect costs):ti,ab,kw
#6	(Cost-effectiveness):ti,ab,kw OR (Cost-benefit):ti,ab,kw OR (Cost-utility): ti,ab,kw OR(Review):ti,ab,kw OR (Economic evaluation):ti,ab,kw OR (Cost of illness):ti,ab,kw OR (Willingness to pay):ti,ab,kw OR (Modelling):ti,ab,kw
#7	(#5 OR #6)
#8	(Child*):ti,ab,kw OR (Infant*):ti,ab,kw OR (Baby):ti,ab,kw OR(Babies):ti,ab,kw OR (Newborn*):ti,ab,kw OR (Youngster*):ti,ab,kw OR (Adolescent*):ti,ab,kw OR (Pediatric*):ti,ab,kw OR (Paediatric*):ti,ab,kw OR (Neonat*):ti,ab,kw
#9	(vaccin*):ti,ab,kw OR (Synflorix):ti,ab,kw OR (Prevenar):ti,ab,kw OR (7vCRM): ti,ab,kw OR (7-valent pneumococcal conjugate vaccine):ti,ab,kw OR (11-valent pneumococcal conjugate vaccine):ti,ab,kw OR (PCV):ti,ab,kw OR (Pneumococ*):ti,ab,kw OR (7-valent):ti,ab,kw OR (10-valent):ti,ab,kw OR (11-valent):ti,ab,kw OR (13-valent):ti,ab,kw
#10	(#4 AND #7 AND #8 AND #9)

Chapter 3

Chapter 4

Adenoidectomy in children with recurrent upper respiratory tract infections

Chapter 4

Chapter 4.1

Effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections: an open randomized controlled trial

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BMJ 2011;383:d5154

Chapter 4.1

Abstract

Objective: To assess the effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections (URTI).

Methods: Open randomised controlled trial (11 general hospitals and two academic centres), including 111 children aged 1-6 selected for adenoidectomy for recurrent URTI. They were randomised to a strategy of immediate adenoidectomy with or without myringotomy or a strategy of initial watchful waiting. The primary outcome measure was the number of URTI episodes per person year calculated from data obtained during the total follow-up (maximum 24 months). Secondary outcomes were days with URTI per person year, middle ear complaints with fever in episodes and days, days with fever, prevalence of URTI, and health related quality of life.

Results: During the median follow-up of 24 months, there were 7.91 URTI episodes per person year in the adenoidectomy group and 7.84 in the watchful waiting group (incidence rate difference 0.07, 95% confidence interval -0.70 to 0.85). No relevant differences were found for days with URTI and middle ear complaints with fever in episodes and days, nor for health related quality of life. The prevalence of URTI decreased over time in both groups. Children in the adenoidectomy group had significantly more days with fever than the children in the watchful waiting group. Two children had complications related to surgery.

Conclusion: In children selected for adenoidectomy for recurrent upper respiratory tract infections, a strategy of immediate surgery confers no clinical benefits over an initial strategy of watchful waiting.

Introduction

An acute upper respiratory tract infection (URTI) is the most common diagnosis in children in primary care: every year the diagnosis is made in one in every two children aged 0-4 and in one in 10 of those aged 5-9.[1] The true incidence of the condition in the community is much higher as usually parents do not consult their doctor when their child develops an URTI. URTIs not only affect children's health but also account for a large proportion of annual healthcare expenditure and high indirect costs for the family and society.[2-4] An estimated 20% of children experience *recurrent* URTI and many of these children are referred to the ear, nose, throat surgeon for surgery.[5-8] Adenoidectomy is one of the most commonly performed surgical procedures in children in western countries. In 2009 in the Netherlands 15,179 children (16.3 per 1000) aged 0-4 years, and 5,573 children (5.5 per 1000) aged 5-9 years underwent adenoidectomy.[9, 10] In 60% of these children, recurrent URTI was the indication for surgery.[11] In 2006 in the United States 129,540 children (1.76 per 1000) up to the age of18 underwent adenoidectomy. In 12% of these children the operation was performed because of chronic infections.[12] In both countries the figures remained stable over the past decade.[12, 13]

Remarkably, the adenoidectomy rate is more than 3 times higher in the Netherlands than in the United States, and the proportion of children operated on for chronic infections varies fivefold across these two countries, suggesting that there is no international consensus as to which children with URTI benefit from the operation.

Evidence for the effectiveness of adenoidectomy in children with recurrent URTI is indeed scarce and (inter)nationally accepted guidelines are lacking.

In our recent Cochrane review we showed that so far only two randomized controlled trials of adenoidectomy in children included URTI as an outcome measure.[14] One study was methodologically weak,[15] and the other was performed in children with recurrent acute otitis media rather than URTI.[16]

In this open multicenter randomized controlled trial we studied the effectiveness of adenoidectomy in children with recurrent URTI.

Chapter 4.1

Materials and methods

Patients

We performed an open, multicenter, randomized controlled trial between April 2007 and October 2010. Ear, nose, throat surgeons in 11 general hospitals and two academic centers were asked to complete a questionnaire on their patients aged 1-6 years who they selected for adenoidectomy with or without myringotomy. They were asked to list the indication for the operation and any previous ear, nose, throat surgery. Parents who had expressed interest in the trial were contacted by a member of our study team. Children were eligible to participate in the trial if they were selected for adenoidectomy for recurrent URTI. The parents were given detailed information about the trial, exclusion criteria were checked, and a standard demographic and disease specific questionnaire was completed. We excluded children who had previously undergone adenoidectomy or adenotonsillectomy and those with tympanostomy tubes (grommets) present or who had an indication for insertion of tympanostomy tubes. We also excluded children with Down's syndrome and craniofacial malformation.

Randomization

Children, whose parents gave informed consent, were randomly assigned to one of two strategies: adenoidectomy with or without myringotomy within 6 weeks or initial watchful waiting. For this purpose we used a computerized minimization strategy, i.e. a method of ensuring balance between prognostic factors in small samples;[17] factors that were taken into account were age (<2 years and ≥ 2 years) and hospital. Treatment allocation was concealed until formal informed consent was obtained and the child was included in the trial.

Baseline measurements

When children entered the study, the study doctor filled out a demographic and disease specific questionnaire including information on the number of URTI in the year before trial entry, previous ear, nose, and throat operations, and risk factors for URTI. Parents filled out two generic and three disease specific questionnaires on health related quality of life: the child health questionnaire[18, 19], the RAND general health rating index for children[20, 21], the sinonasal symptoms questionnaire[22], the OSA-18 quality of life questionnaire[23], and the otitis media-6 questionnaire[24]. All children

underwent an ear, nose, and throat examination including fiberoptic endoscopy of the nasopharynx. Adenoid size was graded as obstructing the choanae for 0-25%, 26-50%, 51-75%, or 76-100%. A blood sample was taken for the Phadiatop test, an allergen-specific IgE test to a panel of common food and aeroallergens in children with the result classified as positive or negative. Finally, data on nasopharyngeal flora, exhaled nitric oxide, and costs were collected at baseline and during follow-up. These results will be reported separately.

Follow-up

During the two year follow-up parents kept a diary, including specific symptoms of URTI: nasal stuffiness, mouth breathing, nasal discharge, sore throat, cough, and fever. They also noted middle ear complaints and absence from day-care or school because of URTI. They measured their child's temperature every day with a validated tympanic membrane thermometer. To avoid information bias, we had an electronic device built in which stored date and first temperature measurement of each day.[25]The study doctor collected the diary and thermometer data during the follow-up visits at 3, 6, 12, 18 and 24 months and examined the child's ear, nose and throat. At those visits parents also filled out questionnaires on health related quality of life.

Parents, general practitioners and ear-nose-throat surgeons of the participating children were encouraged to manage URTI during follow up according to their regular practice.

Primary and secondary outcomes

The primary outcome measure was the number of URTI episodes per person year calculated from data obtained during follow-up (maximum 24 months). The definition of URTI was two or more of the following: fever (a temperature of 38.0°C or higher as measured by a tympanic thermometer), diary scored symptoms of nasal stuffiness or mouth breathing, nasal discharge, sore throat, or cough. An episode ended when the child was free from symptoms for at least a day. A new episode was recorded after at least seven days without symptoms or fever.

Secondary outcome measures were days with URTI per person year, incidences of mild and severe URTI, and middle ear complaints with fever in episodes and days, days with fever, days of absence from day care or school because of URTI, prevalence of URTI, and health related quality of life. Mild URTI was defined as an URTI without fever and resolving within 10 days. Severe URTI was defined as an URTI

persisting for more than 10 days or an URTI accompanied by fever. Middle ear complaints were defined as acute otorrhea, earache, or pulling the ear, accompanied by fever. To measure the burden of URTI during follow-up we calculated the prevalence of URTI per week. Generic health related quality of life was assessed with the child health questionnaire [18, 19], and the RAND general health rating index for children[20, 21], and disease specific health related quality of life with the sinonasal symptoms questionnaire [22], the OSA-18 quality of life questionnaire [23], and the otitis media-6 questionnaire.[24]

Statistical analysis

Our sample size calculation was based on a clinically relevant reduction of URTI of 33%. Assuming a mean baseline incidence of six (SD three) URTI each year, and taking α=0.05 and a power of 0.90, we calculated that we would need 49 children in each group. To allow for 10% loss-to-follow up we aimed to include 110 children.

The effects of adenoidectomy on URTI episodes and days were calculated as incidence rate differences (IRD) and incidence rate ratios (IRR) per person year with 95% confidence intervals (95% CI). Scores on health related quality of life instruments were linearly transformed into 0-100 scales (with 100 being the best possible score) and presented per subscale. We used Student's *t* tests or Mann-Whitney U tests to evaluate differences between the two groups. Poisson regression analyses with a robust covariance matrix estimator were used to adjust for potential confounding (observed baseline differences in prognostic factors, such as sex, breast feeding for more than three months, family history of URTI, and passive smoking). The 95% CIs of the adjusted rate differences and ratios were addressed in R by means of bootstrapping for which we replicated the trial 10.000 times using random replacement samples.

Potential modification of the effect of adenoidectomy was evaluated with Poisson analyses including interaction terms for age (<2 versus $\geq$ 2), adenoid size (<75% versus $\geq$75% obstruction of the choanae), and Phadiatop (positive versus negative). Subgroups were further analysed only in case of significant interaction effects.

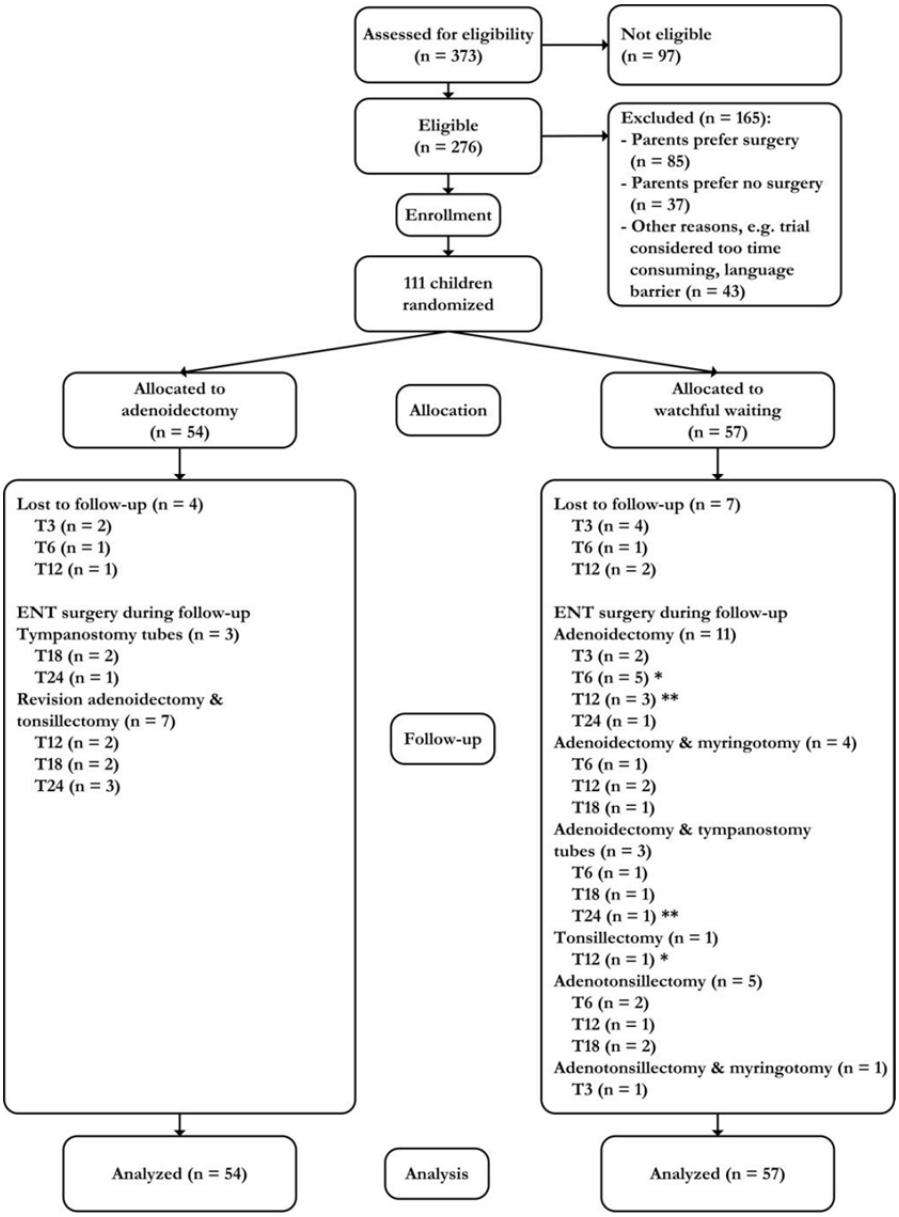
In addition to the intention-to-treat analysis, we also performed two sensitivity analyses: a *per protocol* analysis in which we excluded the children in the watchful waiting group who went on to have surgery, and an *as treated* analysis in which we added the children in the watchful waiting group who underwent surgery to the adenoidectomy group.

To study the external validity, we compared demographic and disease specific characteristics of the included children with those who were eligible to participate, but whose parents did not give informed consent. We used Pearson's Chi-square tests to compare these characteristics.
All analyses were performed according to the intention-to-treat principle, using SPSS version 17 (SPSS Inc., Chicago, Illinois), Rothman's Episheet version June 11, 2008 and R version 2.13.0 (April 13, 2011).

Results

Patients
Between April 2007 and April 2009, 373 children aged 1-6 selected for adenoidectomy for recurrent URTI were referred to our trial center. Of these, 262 (70%) were ineligible or excluded for various reasons (*Figure 4.1.1*) and 111 were randomly assigned to one of two strategies: 54 children to adenoidectomy with or without myringotomy within 6 weeks, and 57 children to initial watchful waiting.
Table 4.1.1 shows baseline characteristics. The mean age was 36 and 38 months and the median number of URTI episodes in the year before trial entry was 10 in the adenoidectomy group and nine in the watchful waiting group. Median follow-up was 24 months in both groups.
During the trial period, 11 (10%) children were lost to follow-up for non-medical reasons: four (7%) children from the adenoidectomy group and seven (12%) children from the watchful waiting group. All children allocated to adenoidectomy underwent adenoidectomy within six weeks: 48 (89%) had adenoidectomy alone and six (11%) had adenoidectomy and myringotomy. During follow-up seven (13%) children allocated to adenoidectomy underwent tonsillectomy and revision adenoidectomy and three (6%) had tympanostomy tubes inserted. During follow-up 17 (30%) children allocated to watchful waiting underwent adenoidectomy (in four (7%) children it was combined with myringotomy and in two (4%) with tympanostomy tubes; one (2%) child underwent adenoidectomy at 12 months and revision adenoidectomy with tympanostomy tubes at 24 months; one (2%) underwent adenoidectomy at six months and tonsillectomy at 12 months) and six (11%) underwent adenotonsillectomy (in one combined with myringotomy).

Figure 4.1.1. Flow of participants through trial of adenoidectomy in children with recurrent URTI



Footnote:
* one child underwent adenoidectomy at T6 and tonsillectomy at T12
** one child underwent adenoidectomy at T12 and revision adenoidectomy and tympanostomy tubes at T24

Table 4.1.1. Baseline characteristics of 111 children according to treatment allocation

	Adenoidectomy group N=54 (%)	Watchful waiting group N=57 (%)
Patient characteristics		
Age (SD), mo	35.7 (19.4)	37.6 (18.1)
Male sex	37 (68.5)	29 (50.9)
Breastfeeding ≥ 3 months	24 (44.4)	32 (56.1)
Positive Phadiatop test[a]	12 (23.5)	16 (30.2)
Positive family history for recurrent URTIs	31 (57.4)	41 (71.9)
Exposure to household nicotine smoke	19 (35.2)	13 (22.8)
Children with household pets	33 (61.1)	36 (63.2)
Children with siblings	42 (77.8)	38 (66.7)
Education level mother		
1) low	10 (18.5)	9 (15.8)
2) average	22 (40.7)	30 (52.6)
3) high	22 (40.7)	18 (31.6)
Day care attendance of children < 4 years	33 (80.5)	36 (87.8)
Disease characteristics		
Median number of episodes of URTI in the year before trial entry (IQR)	10.0 (2.75 to 16.5)	9.0 (2.0 to 17.0)
OSA score, median (IQR)[b]	-0.99 (-2.41 to 1.13)	-1.70 (-2.42 to 0.42)
Adenoid size 76-100%	13 (25.5)	11 (22.9)

Abbreviations:
IQR = interquartile range; URTI = upper respiratory tract infection; OSA = obstructive sleep apnea.

[a] Phadiatop is an allergen-specific IgE test to a panel of common food and aeroallergens in children; its result was classified as positive or negative.

[b] Brouilette Obstructive Sleep Apnea Score: 1.42 x difficulty breathing + 1.41 x apnea + 0.71 x snoring – 3.83. Range -3.83 to +3.5. Score greater than 3.5 is highly predictive of OSA; score between -1 and 3.5 indicates possible OSA; and score below -1 indicates no OSA.

Primary outcome

During the total follow-up the incidences of URTI episodes in the adenoidectomy and watchful waiting group were 7.91 and 7.84 per person year (IRD 0.07, 95% CI −0.70 to 0.85; *Table 4.1.2*). These incidences were 9.22 and 9.39 per person year (difference −0.17, −1.34 to 1.00), respectively, during the first year of follow-up and 6.55 and 6.17 per person year (difference 0.37, −0.62 to 1.37), respectively, during the second year of follow-up (*Table 4.1.3A*). Similar results were found after adjustment for observed baseline differences—that is, the adjusted rate differences for the total

follow-up, year one, and year two were −0.03 (−1.72 to 1.67), −0.14 (−1.76 to 1.68), and 0.13 (−2.05 to 2.32) (*Table 4.1.3B*).

Secondary outcomes

During the total follow up period there were 66.10 and 67.36 days with URTI per person year (IRD -1.27, 95% CI -3.52 to 0.99; *Table 4.1.2*) in the adenoidectomy and watchful waiting group, respectively.

Figure 4.1.2 shows that the proportion of children with an URTI (expressed as the prevalence per week) decreased over time in both groups. No differences were found between the two groups for mild and severe URTI episodes and days per person year during the total follow-up (*Table 4.1.2*).

Children in the adenoidectomy group had significantly more days with fever than the children in the watchful waiting group: 20.00 versus 16.49 days per person year in during the total follow-up period (IRD 3.51; 95% CI 2.33 to 4.69).

Table 4.1.2. Primary and secondary outcomes for the total follow-up period (maximum 24 months)

	Adenoidectomy 101 person years	**Watchful waiting** 101 person years	**Incidence rate difference** (95% CI)	**Incidence rate ratio** (95% CI)
Primary outcome				
URTI episodes	7.91	7.84	0.07 (-0.70 to 0.85)	1.01 (0.91 to 1.11)
Secondary outcomes				
URTI days	66.10	67.36	-1.27 (-3.52 to 0.99)	0.98 (0.95 to 1.01)
Severe URTI episodes	3.98	3.53	0.45 (-0.08 to 0.99)	1.13 (0.98 to 1.30)
Severe URTI days	48.11	46.56	1.55 (-0.35 to 3.44)	1.03 (0.99 to 1.08)
Mild URTI episodes	3.93	4.31	-0.38 (-0.94 to 0.18)	0.91 (0.80 to 1.04)
Mild URTI days	17.99	20.80	-2.81 (-4.03 to -1.60)	0.86 (0.81 to 0.92)
Fever days	20.00	16.49	3.51 (2.33 to 4.69)	1.21 (1.14 to 1.29)
Middle ear complaints with fever episodes	0.51	0.45	0.05 (-0.14 to 0.24)	1.11 (0.75 to 1.65)
Middle ear complaints with fever days	0.86	0.85	0.01 (-0.24 to 0.27)	1.01 (0.75 to 1.36)
Absence from day care or school	1.66	2.00	-0.33 (-0.71 to 0.04)	0.83 (0.68 to 1.02)

Abbreviations:
URTI = upper respiratory tract infection; PY = person years;
95% CI = 95% confidence interval

Table 4.1.3A. Primary and secondary outcomes for follow-up year 1 and year 2 separately

	Adenoi-dectomy	Watchful waiting	Incidence rate difference 95% CI	Incidence rate ratio 95% CI
	Year 1			
	52 PY	53 PY		
Primary outcome				
URTI episodes	9.22	9.39	-0.17 (-1.34 to 1.00)	0.98 (0.87 to 1.11)
Secondary outcomes				
URTI days	52.24	45.22	7.03 (4.35 to 9.71)	1.16 (1.09 to 1.22)
Severe URTI episodes	4.47	4.23	0.25 (-0.55 to 1.05)	1.06 (0.88 to 1.27)
Severe URTI days	39.17	31.39	7.78 (5.50 to 10.06)	1.25(1.17 to 1.33)
Mild URTI episodes	4.74	5.16	-0.42 (-1.27 to 0.44)	0.92 (0.77 to 1.09)
Mild URTI days	13.07	13.82	-0.75 (-2.16 to 0.66)	0.95 (0.85 to 1.05)
Fever days	20.78	16.51	4.27 (2.61 to 5.93)	1.26 (1.15 to 1.38)
Middle ear complaints with fever episodes	0.64	0.51	0.12 (-0.17 to 0.42)	1.24 (0.75 to 2.07)
Middle ear complaints with fever days	1.01	0.88	0.13 (-0.24 to 0.50)	1.15 (0.77 to 1.71)
Absence from day care or school	1.10	1.33	-0.23 (-0.65 to 0.19)	0.83 (0.58 to 1.17)
	Year 2			
	49 PY	49 PY		
Primary outcome				
URTI episodes	6.55	6.17	0.37 (-0.62 to 1.37)	1.06 (0.91 to 1.24)
Secondary outcomes				
URTI days	80.60	91.31	-10.71 (-14.38 to -7.03)	0.88 (0.85 to 0.92)
Severe URTI episodes	3.47	2.78	0.69 (-0.01 to 1.39)	1.25 (1.00 to 1.56)
Severe URTI days	57.47	62.96	-5.50 (-8.57 to -2.42)	0.91 (0.87 to 0.96)
Mild URTI episodes	3.08	3.40	-0.31 (-1.03 to 0.40)	0.91 (0.73 to 1.13)
Mild URTI days	23.14	28.34	-5.21 (-7.22 to -3.20)	0.82 (0.75 to 0.88)
Fever days	19.18	16.47	2.72 (1.04 to 4.39)	1.16 (1.06 to 1.28)
Middle ear complaints with fever episodes	0.36	0.39	-0.03 (-0.27 to 0.22)	0.93 (0.49 to 1.78)
Middle ear complaints with fever days	0.71	0.82	-0.11 (-0.46 to 0.23)	0.86 (0.55 to 1.36)
Absence from day care or school	2.25	2.72	-0.47 (-1.09 to 0.16)	0.83 (0.64 to 1.07)

Abbreviations:
URTI = upper respiratory tract infection; PY = person years; 95% CI = 95% confidence interval

Table 4.1.3B. Primary and secondary outcomes adjusted for observed baseline differences

	Adenoi-dectomy	Watchful waiting	Incidence rate difference 95% CI	Incidence rate ratio 95% CI
Total follow-up				
	101 PY	101 PY		
Primary outcome				
URTI episodes	7.86	7.89	-0.03 (-1.72 to 1.67)	1.00 (0.80 to 1.23)
Secondary outcomes				
URTI days	66.25	67.20	-0.95 (-20.50 to 14.48)	0.99 (0.73 to 1.31)
Severe URTI episodes	3.97	3.54	0.42 (-0.63 to 1.52)	1.12 (0.84 to 1.48)
Severe URTI days	48.49	46.20	2.28 (-15.62 to 20.17)	1.05 (0.71 to 1.52)
Mild URTI episodes	3.89	4.35	-0.46 (-1.31 to 0.35)	0.89 (0.73 to 1.09)
Mild URTI days	17.80	21.01	-3.21 (-7.85 to 1.17)	0.85 (0.66 to 1.06)
Fever days	20.16	16.36	3.80 (-6.75 to 14.20)	1.23 (0.68 to 2.12)
Middle ear complaints with fever episodes	0.53	0.44	0.09 (-0.26 to 0.43)	1.20 (0.56 to 2.36)
Middle ear complaints with fever days	0.91	0.81	0.10 (-0.61 to 0.77)	1.13 (0.48 to 2.60)
Absence from day care or school	1.75	1.90	-0.15 (-0.78 to 0.48)	0.92 (0.64 to 1.30)
Year 1				
	52 PY	53 PY		
Primary outcome				
URTI episodes	9.23	9.37	-0.14 (-1.76 to 1.68)	0.99 (0.82 to 1.20)
Secondary outcomes				
URTI days	52.21	45.24	6.97 (-13.24 to 27.51)	1.15 (0.74 to 1.72)
Severe URTI episodes	4.55	4.16	0.40 (-0.68 to 1.48)	1.10 (0.85 to 1.40)
Severe URTI days	39.18	31.39	7.79 (-11.19 to 26.89)	1.25 (0.71 to 2.13)
Mild URTI episodes	4.68	5.23	-0.55 (-1.62 to 0.48)	0.90 (0.72 to 1.10)
Mild URTI days	13.03	13.86	-0.83 (-5.10 to 3.28)	0.94 (0.68 to 1.28)
Fever days	20.70	16.57	4.13 (-10.99 to 18.38)	1.25 (0.49 to 2.66)
Middle ear complaints with fever episodes	0.68	0.48	0.20 (-0.28 to 0.67)	1.41 (0.60 to 3.07)
Middle ear complaints with fever days	1.09	0.81	0.28 (-0.66 to 1.18)	1.34 (0.49 to 3.61)
Absence from day care or school	1.21	1.22	-0.01 (-0.64 to 0.61)	0.99 (0.57 to 1.63)

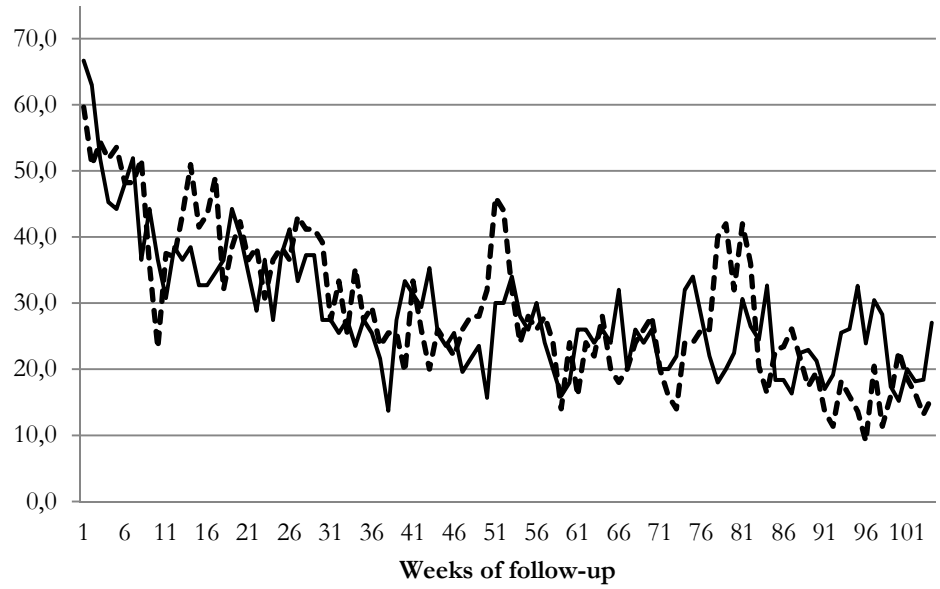
Table 4.1.3B. Continued

	Adenoi-dectomy	Watchful waiting	Incidence rate difference 95% CI	Incidence rate ratio 95% CI
Year 2				
	49 PY	49 PY		
Primary outcome				
URTI episodes	6.43	6.30	0.13 (-2.05 to 2.32)	1.02 (0.71 to 1.42)
Secondary outcomes				
URTI days	79.60	89.39	-9.79 (-35.55 to 12.91)	0.89 (0.67 to 1.16)
Severe URTI episodes	3.34	2.88	0.47 (-0.98 to 1.93)	1.16 (0.71 to 1.82)
Severe URTI days	57.13	61.70	-4.57 (-26.06 to 16.37)	0.93 (0.64 to 1.32)
Mild URTI episodes	3.08	3.40	-0.32 (-1.35 to 0.65)	0.90 (0.66 to 1.23)
Mild URTI days	22.54	27.64	-5.10 (-11.86 to 1.39)	0.82 (0.61 to 1.05)
Fever days	19.01	15.81	3.20 (-5.09 to 12.05)	1.20 (0.73 to 1.94)
Middle ear complaints with fever episodes	0.35	0.41	-0.05 (-0.44 to 0.33)	0.87 (0.18 to 2.08)
Middle ear complaints with fever days	0.71	0.82	-0.11 (-0.98 to 0.69)	0.86 (0.18 to 2.27)
Absence from day care or school	2.31	2.57	-0.26 (-1.24 to 0.73)	0.90 (0.59 to 1.35)

Abbreviations:
URTI = upper respiratory tract infection; PY = person years; 95% CI = 95% confidence interval

During the total follow up there were 0.51 episodes of middle ear complaints with fever per person year in the adenoidectomy group and 0.45 in the watchful waiting group (IRD 0.05, 95% CI -0.14 to 0.24). Children in the adenoidectomy group had 0.86 days per person year of middle ear complaints with fever and children in the watchful waiting group had 0.85 (IRD 0.01, 95% CI -0.24 to 0.27). Days of absence from day care or school because of an URTI were 1.66 and 2.00 (IRD -0.33, 95% CI -0.71 to 0.04) in the adenoidectomy and watchful waiting group, respectively. *Table 3A* shows the results for follow-up year one and two separately. After adjustment for observed baseline differences, we found no significant differences (*Table 4.1.3B*).

Figure 4.1.2. Proportion of children with an URTI (prevalence / week) in the adenoidectomy (black line) and watchful waiting (dashed line) group



Health related quality of life as measured by generic (child health questionnaire [18, 19], and RAND [20, 21]) and disease specific (sinonasal symptoms questionnaire [22], OSA-18 quality of life questionnaire [23], and otitis media-6 questionnaire.[24]) questionnaires, did not differ statistically significant between both groups over time. Exact numbers and figures are available in appendix 4.1.1..

As we found no significant interaction terms, we did not further analyse any subgroup of patient.

Table 4.1.4A. Results for the per protocol and as treated analyses

	Adenoi-dectomy	Watchful waiting	Incidence rate difference 95% CI	Incidence rate ratio 95% CI
Per protocol				
	101 PY	61 PY		
Primary outcome				
URTI episodes	7.91	8.04	-0.13 (-1.02 to 0.77)	0.98 (0.88 to 1.10)
Secondary outcomes				
URTI days	66.10	57.63	8.47 (5.99 to 10.95)	1.15 (1.10 to 1.19)
Severe URTI episodes	3.98	3.50	0.48 (-0.13 to 1.09)	1.14 (0.96 to 1.34)
Severe URTI days	48.11	35.42	12.69 (10.67 to 14.70)	1.36 (1.29 to 1.43)
Mild URTI episodes	3.93	4.54	-0.60 (-1.26 to 0.06)	0.87 (0.74 to 1.01)
Mild URTI days	17.99	22.21	-4.22 (-5.66 to -2.77)	0.81 (0.76 to 0.87)
Fever days	20.00	15.11	4.88 (3.58 to 6.19)	1.32 (1.22 to 1.43)
Middle ear complaints with fever episodes	0.51	0.46	0.05 (-0.17 to 0.27)	1.10 (0.69 to 1.75)
Middle ear complaints with fever days	0.86	0.87	-0.10 (-0.39 to 0.19)	0.89 (0.63 to 1.26)
Absence from day care or school	1.66	1.83	-0.17 (-0.59 to 0.25)	0.91 (0.71 to 1.15)
As treated				
	141 PY	61 PY		
Primary outcome				
URTI episodes	7.81	8.04	-0.23 (-1.08 to 0.62)	0.97 (0.87 to 1.08)
Secondary outcomes				
URTI days	70.67	57.63	13.04 (10.69 to 15.40)	1.23 (1.18 to 1.27)
Severe URTI episodes	3.93	3.50	0.42 (-0.15 to 1.00)	1.12 (0.96 to 1.31)
Severe URTI days	52.49	35.42	17.07 (15.16 to 18.99)	1.48 (1.41 to 1.55)
Mild URTI episodes	3.94	4.54	-0.59 (-1.22 to 0.03)	0.87 (0.75 to 1.00)
Mild URTI days	18.18	22.21	-4.03 (-5.40 to -2.65)	0.82 (0.77 to 0.87)
Fever days	19.59	15.11	4.48 (3.26 to 5.70)	1.30 (1.20 to 1.40)
Middle ear complaints with fever episodes	0.49	0.46	0.03 (-0.17 to 0.24)	1.07 (0.69 to 1.66)
Middle ear complaints with fever days	0.85	0.87	-0.02 (-0.30 to 0.26)	0.98 (0.71 to 1.35)
Absence from day care or school	1.83	1.83	0.00 (-0.41 to 0.40)	1.00 (0.80 to 1.25)

Abbreviations:
URTI = upper respiratory tract infection; PY = person years; 95% CI = 95% confidence interval

Table 4.1.4B. Results for the per protocol and as treated analyses adjusted for observed baseline differences

	Adenoi-dectomy	Watchful waiting	Incidence rate difference 95% CI	Incidence rate ratio 95% CI
Per protocol				
	101 PY	61 PY		
Primary outcome				
URTI episodes	7.89	8.01	-0.19 (-2.27 to 1.83)	0.97 (0.75 to 1.26)
Secondary outcomes				
URTI days	66.23	57.44	8.78 (-12.98 to 30.34)	1.15 (0.81 to 1.63)
Severe URTI episodes	3.97	3.53	0.44 (-0.82 to 1.72)	1.12 (0.81 to 1.60)
Severe URTI days	48.34	35.15	13.19 (-6.31 to 32.62)	1.38 (0.86 to 2.23)
Mild URTI episodes	3.92	4.56	-0.63 (-1.68 to 0.33)	0.86 (0.67 to 1.08)
Mild URTI days	17.89	22.40	-4.58 (-10.31 to 0.72)	0.80 (0.60 to 1.04)
Fever days	20.36	14.69	5.67 (-4.76 to 15.43)	1.39 (0.77 to 2.45)
Middle ear complaints with fever episodes	0.52	0.44	0.08 (-0.36 to 0.47)	1.18 (0.50 to 3.08)
Middle ear complaints with fever days	0.90	0.81	0.09 (-0.91 to 0.87)	1.11 (0.41 to 3.84)
Absence from day care or school	1.73	1.72	0.01 (-0.71 to 0.74)	1.01 (0.67 to 1.56)
As treated				
	141 PY	61 PY		
Primary outcome				
URTI episodes	7.78	8.10	-0.31 (-2.16 to 1.47)	0.96 (0.77 to 1.21)
Secondary outcomes				
URTI days	71.02	56.98	14.04 (-4.35 to 31.87)	1.25 (0.94 to 1.68)
Severe URTI episodes	3.84	3.55	0.29 (-0.82 to 1.39)	1.08 (0.81 to 1.49)
Severe URTI days	52.84	34.90	17.93 (0.34 to 34.44)	1.51 (1.02 to 2.33)
Mild URTI episodes	3.94	4.54	-0.60 (-1.56 to 0.32)	0.87 (0.70 to 1.08)
Mild URTI days	18.19	22.17	-3.99 (-9.48 to 1.13)	0.82 (0.63 to 1.06)
Fever days	19.71	14.90	4.81 (-4.42 to 13.28)	1.32 (0.78 to 2.23)
Middle ear complaints with fever episodes	0.49	0.45	0.04 (-0.34 to 0.37)	1.10 (0.53 to 2.63)
Middle ear complaints with fever days	0.86	0.84	0.02 (-0.87 to 0.72)	1.03 (0.44 to 3.30)
Absence from day care or school	1.87	1.75	0.12 (-0.54 to 0.75)	1.07 (0.75 to 1.56)

Abbreviations:
URTI = upper respiratory tract infection; PY = person years; 95% CI = 95% confidence interval

Cross-overs

We found no statistically significant differences in baseline variables nor in the number of URTI during the first year of follow-up between those children in the control group who did and did not crossover (data not shown).

The per protocol and as treated analyses (*Table 4.1.4A*) yielded the same results as the intention-to-treat analysis regarding our primary outcome, that is URTI episodes during the total follow-up. For example, the IRD for episodes of URTI was -0.13 (95% CI -1.02 to 0.77) for the per protocol analysis and -0.23 (95% CI -1.08 to 0.62) for the as treated analysis. The adjusted IRDs also showed no significant differences for the primary outcome (*Table 4.1.4B*).

Generalizability

To assess the external validity of our results we compared demographic and disease specific characteristics of the children participating in the trial with those of the 165 (60%) children who were eligible for the trial but did not participate for various reasons. In the trial participants and eligible but

non-participating children, respectively, the mean age at referral was 36 and 34 months, 59% and 56% were boys, 57% and 45% had symptoms of snoring or obstructive apnoea, 78% and 84% had nasal discharge on examination, and 67% and 69% had nasal obstruction on examination. Importantly, none of these variables differed significantly.

Adverse events

Two (4%) children in the adenoidectomy group experienced an adverse event: one child was admitted to hospital for an asthma exacerbation during follow-up and in one child a primary tooth was broken when the mouth gag was inserted. One (2%) child in the watchful waiting group who underwent adenotonsillectomy during follow-up was admitted to hospital for a postoperative haemorrhage.

Discussion

In children selected for adenoidectomy for recurrent URTI, a strategy of immediate surgery did not reduce the number of URTI episodes compared with a strategy of initial watchful waiting. The prevalence of URTI decreased similarly over time in both

groups, suggesting that the contribution of surgery to the favourable natural course of URTI is trivial.
We found no relevant differences between the two strategies for days of URTI, days and episodes of mild and severe URTI and middle ear complaints with fever, days of absence from day care or school, and health related quality of life. There was a significant difference for days with fever.
Forty per cent of children in the initial watchful waiting group underwent surgery during the course of the trial. These children, however, were not more severely affected by URTI than the 60% who did not undergo surgery nor did they do better after surgery.

Comparison with literature
So far, most trials of adenoidectomy have been performed in children with recurrent acute otitis media or persistent otitis media with effusion, and otitis media was studied as the primary outcome. These studies showed a benefit of adenoidectomy regarding the resolution of middle ear effusion and also a small benefit regarding hearing, but did not observe a beneficial effect on recurrence of acute otitis media.[26]
The one study (n=76) that did include children selected for adenoidectomy because of frequent URTI showed that at 12 months' follow-up 75% of children in the adenoidectomy group and 73% of children in the control group improved during follow-up regarding common colds (risk difference (RD) 2%, 95% CI -18% to 22%). At 24 months follow-up these figures were 77% and 88%, respectively (RD -11%, 95% CI -28% to 7%).[15] Another study (n=180) of adenoidectomy versus chemoprophylaxis and placebo in children with recurrent acute otitis media, included days with rhinitis as a secondary outcome. Children in the adenoidectomy group had four fewer days with rhinitis during six months follow-up than those in the control groups (95% CI -13 to 7 days).[16]
All trials of adenoidectomy performed so far had methodological limitations.[14, 26] Firstly, only three trials provided a power analysis and included adequate numbers. As the other trials included relatively few patients, their power might have been too low, leading to a type II error. Secondly, most studies had significant loss to follow-up. This can be associated with either good or poor outcome. Thirdly, three studies were analysed per protocol rather than by intention to treat. Per protocol analyses underestimate the treatment effect as in surgical trials only children in the watchful waiting group with persisting complaints can change treatment group, whereas

children of the surgical group, who might experience similar complaints, cannot change treatment group. Fourthly, information bias might have been considerable because trials on adenoidectomy, as most surgical trials, cannot be performed in a true double blind fashion. Such bias will overestimate the effect of the intervention. None of the trials tried to minimise information bias by choosing an objective outcome measure, such as fever. Finally, the generalisability of the trials can be questioned as only a small proportion of children undergoing
adenoidectomy were included in the trials.

Possible limitations

Our trial has several limitations. First, we emphasize that our trial compares two strategies (immediate adenoidectomy and initial watchful waiting). As in other surgical trials, such as our previous study on adenotonsillectomy,[27] the fact that some patients in the surgery group undergo additional surgical interventions and some patients in the watchful waiting group eventually undergo adenoidectomy mimics daily practice.[28, 29] This is part of the two strategies we compared. We studied whether the children in the control group who went on to undergo adenoidectomy were more severely affected than those who did not. There were no significant differences in baseline variables nor in the number of URTI during the first year of follow-up between those children in the control group who did and did not crossover (data not shown). Furthermore, the per protocol and as treated analyses yielded the same results as the intention-to-treat analysis regarding our primary outcome, that is the number of URTI episodes during the total follow-up.

Secondly, we chose for 33% as indicating a clinically relevant difference (in absolute terms a decrease from six to four URTI a year) as the incidence of URTI in young children is high, and is known to decrease over time spontaneously. Nevertheless, we have looked into the probability that given our results a difference of 20-25%, that is a difference of 1.5 URTI per year, could have occurred. Looking at the confidence interval of the total follow-up, the value -1.5 is not within the 99% confidence interval, which means, that we can also confidently rule out a difference of 1.5 episodes. Therefore, it seems unlikely that the results and conclusions would change if we had chosen another clinically relevant difference in our power calculation.

Thirdly, we question can whether our results are generalizable to all children with recurrent URTI. As we found no statistical differences between the trial participants and those eligible but non-participating, and none of the studied characteristics

modified the effect of adenoidectomy, we thinks that these are generalizable to all children selected for adenoidectomy for recurrent URTI.

Strengths of the study

As our randomised controlled trial of adenoidectomy focused on children with recurrent URTI, it provides important evidence for the many children selected for adenoidectomy for this indication. To our knowledge this is the first randomised controlled trial focusing specifically on these children. We included an objective method to study the effect of adenoidectomy—that is, fever measured daily by a validated thermometer that automatically stored data. Fever is an important physical sign in childhood infections, and most episodes of fever in young children aged under 8 are related to URTI.[30, 31]

For the randomization process we applied a minimization strategy that accounted for age and hospital. As such, we ensured that the children within each center were equally distributed over the two groups. Therefore potential bias from possible differences in "traditions" of treating these children is precluded.

Conclusion

In children selected for adenoidectomy for recurrent URTI, an strategy of immediate surgical confers no clinical benefits over an strategy of initial watchful waiting.

Acknowledgements

We thank the participants and their parents; Nelly van Eden for secretarial support, Nicole Boekema for data management and Rolf Groenwold for assistance with the bootstrap analysis. We also thank our colleagues at the participating hospitals: Flevoziekenhuis Almere, Meander Medisch Centrum Amersfoort, Gelre Ziekenhuis Apeldoorn and Zutphen, Wilhelmina Ziekenhuis Assen, Albert Schweitzer Ziekenhuis Dordrecht, Universitair Medisch Centrum Groningen, Diakonessenhuis Meppel, St. Antonius Ziekenhuis Nieuwegein, Vlietland Ziekenhuis Schiedam, MESOS Medisch Centrum Utrecht and the Universitair Medisch Centrum Utrecht. Finally we thank the members of the executive steering committee: E.H. van den Akker, M.J.M. Bonten, K. Fischer, E.A.M. Sanders, and R. van Weissenbruch.

Funding

ZonMw - the Netherlands Organisation for Health Research and Development, Health Care Efficiency Research Programme, sub-programme Effects & Costs 2007 no. 80-007022-98-07901. The funder had no role in the study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication. All authors were independent from the funder and had access to all the data.

Trial Register

The trial was registered in the Dutch Trial Register in May 2007 with the title "Effectiveness of adenoidectomy in children with recurrent URTI" NTR968; ISRCTN03720485.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that MTAvdA, CWBB, MMR, AWH, AGMS have no relationships with companies that might have an interest in the submitted work in the previous 3 years; their spouses, partners, or children have no financial relationships

that may be relevant to the submitted work; and MTAvdA, CWBB, MMR, AWH, AGMS have no non-financial interests that may be relevant to the submitted work. AGMS and MMR have participated in workshops and educational activities on otitis media organized by GlaxoSmithKline and have received a grant from GlaxoSmithKline for a study on the microbiology of otitis media in 2009.

Ethics approval

This study was approved by the Medical Ethics Committees of the University Medical Center Utrecht and all participating hospitals and was monitored according to Good Clinical Practice.
Informed consent: informed consent was obtained from all participants.

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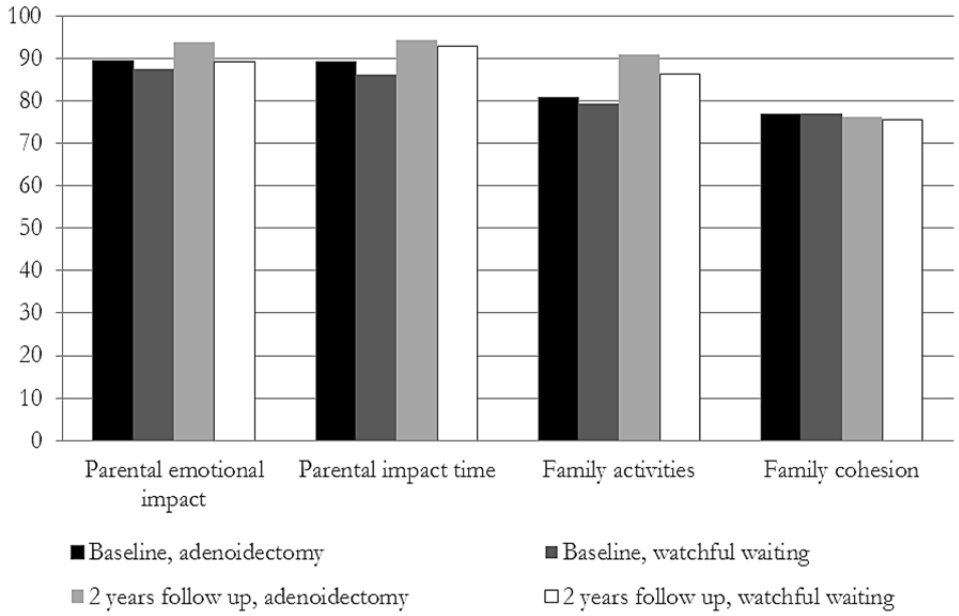
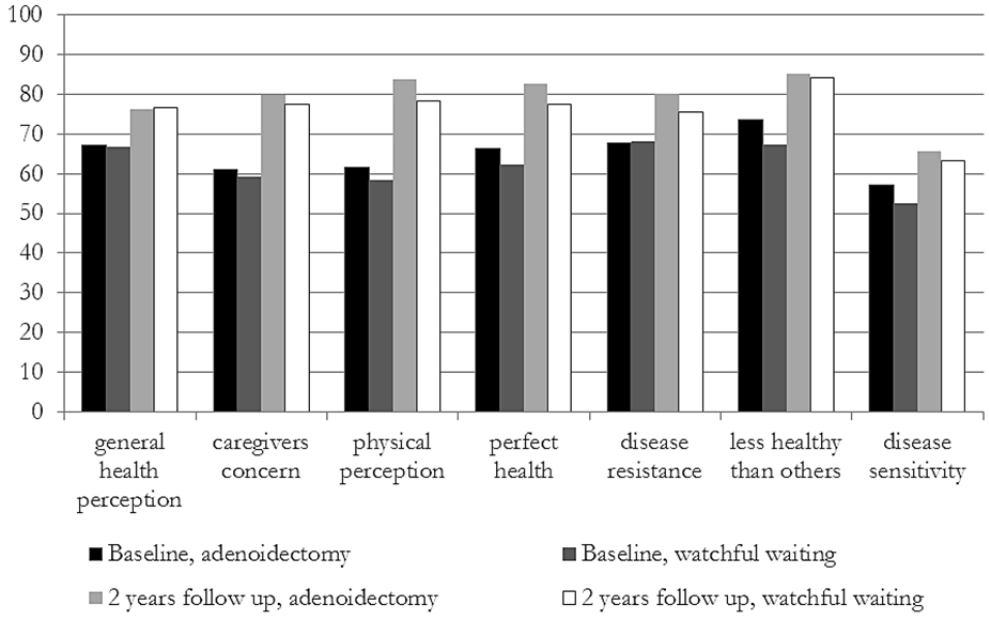
Appendix 4.1.1. Figures and tables for generic and health related quality of life

Figure 4.1.3A. Child Health Questionnaire at baseline and 2 year follow-up



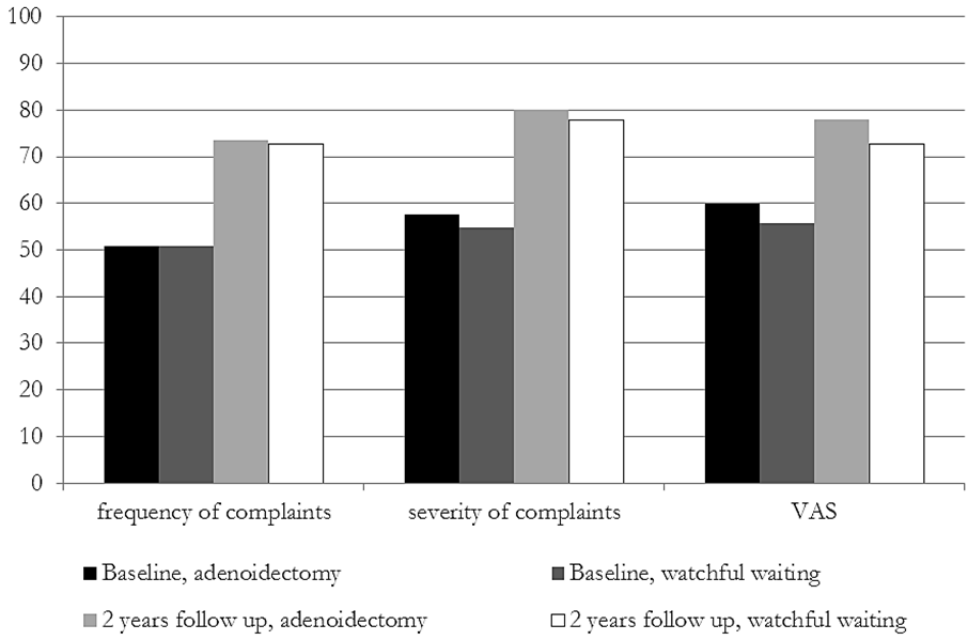
	Adenoidectomy	Watchful waiting	Difference	95% CI
	Inclusion			
Parental emotional impact	89.5	87.4	2.1	(-1.5 to 5.6)
Parental impact time	89.1	86.3	2.8	(-2.0 to 7.4)
Family activities	80.8	79.3	1.5	(-4.3 to 7.3)
Family cohesion	76.9	77.0	-0.1	(-6.4 to 6.3)
	2 year follow-up			
Parental emotional impact	93.7	89.2	4.5	(-1.3 to 10.3)
Parental impact time	94.4	92.9	1.5	(-4.2 to 7.2)
Family activities	90.8	86.2	4.6	(-1.6 to 10.8)
Family cohesion	76.1	75.5	0.6	(-5.5 to 6.8)

Figure 4.1.3B. RAND at baseline and 2 year follow-up



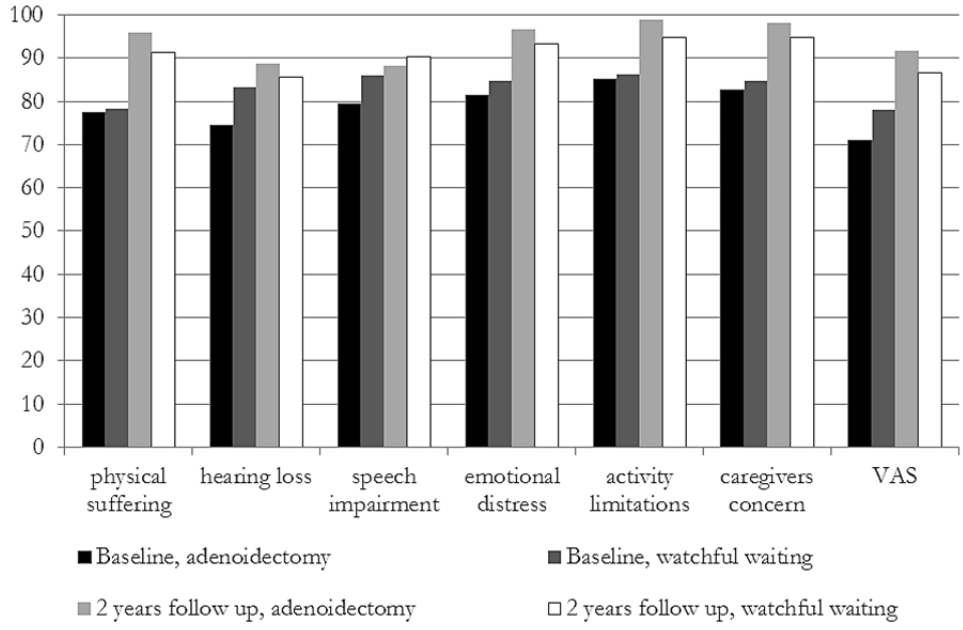
	Adenoidectomy	Watchful waiting	Difference	95% CI
	Inclusion			
General health perception	67.2	66.7	0.5	(-4.8 to 5.8)
Caregivers concern	61.1	59.3	1.8	(-6.2 to 10.0)
Physical perception	61.5	58.3	3.2	(-5.5 to 11.9)
Perfect health	66.2	62.2	4.0	(-2.8 to 10.7)
Disease resistance	67.7	68.1	-0.4	(-7.8 to 6.9)
Less healthy than others	73.5	67.4	6.1	(-3.1 to 15.2)
Disease sensitivity	57.0	52.6	4.4	(-4.6 to 14.0)
	2 year follow-up			
General health perception	76.1	76.7	-0.6	(-6.2 to 4.9)
Caregivers concern	79.9	77.3	2.6	(-6.9 to 12.2)
Physical perception	83.7	78.4	5.3	(-4.0 to 4.6)
Perfect health	82.6	77.3	5.3	(-0.9 to 11.6)
Disease resistance	80.0	75.5	4.5	(-3.2 to 12.3)
Less healthy than others	85.2	84.1	1.1	(-8.2 to 10.4)
Disease sensitivity	65.7	63.2	2.5	(-7.2 to 12.1)

Figure 4.1.3C. Sinonasal symptoms questionnaire (domain: sinus infection) at baseline and 2 year follow-up



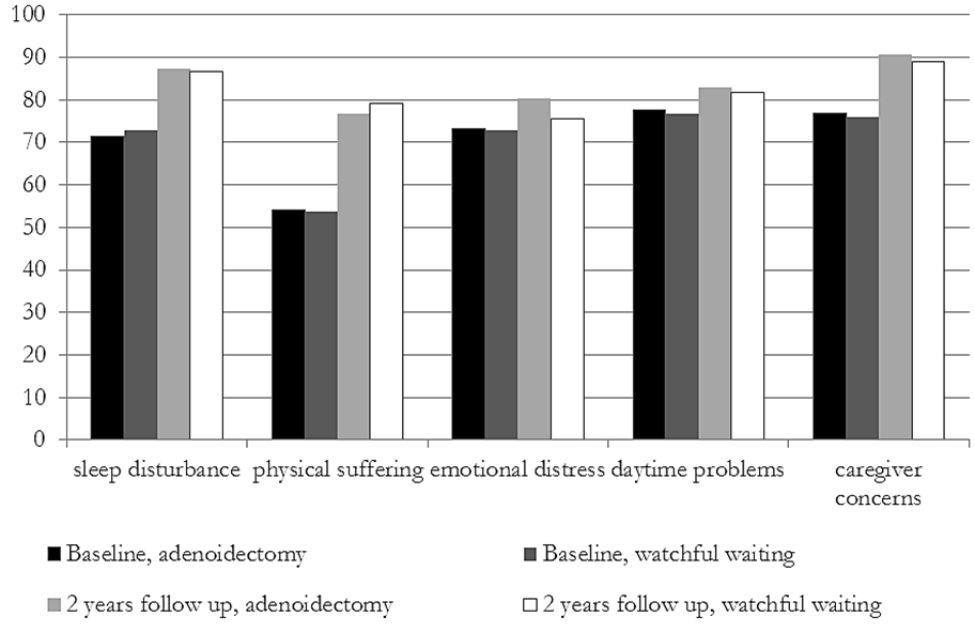
	Adenoidectomy	Watchful waiting	Difference	95% CI
	Inclusion			
Frequency of complaints	50.8	50.8	0.0	(-7.8 to 7.9)
Severity of complaints	57.7	54.8	2.9	(-4.9 to 10.8)
VAS	60.0	55.7	4.3	(-3.2 to 11.7)
	2 year follow-up			
Frequency of complaints	73.6	72.7	0.9	(-9.9 to 11.6)
Severity of complaints	80.1	77.9	2.2	(-7.0 to 11.4)
VAS	78.0	72.7	5.3	(-3.3 to 14.0)

Figure 4.1.3D. Otitis Media-6 at baseline and 2 year follow-up



	Adenoidectomy	Watchful waiting	Difference	95% CI
	Inclusion			
Physical suffering	77.5	78.3	-0.8	(-11.3 to 9.6)
Hearing loss	74.5	83.3	-8.8	(-18.5 to 0.7)
Speech impairment	79.3	86.0	-6.7	(-15.5 to 2.0)
Emotional distress	81.3	84.7	-3.4	(-11.6 to 4.9)
Activity limitations	85.2	86.2	-1.0	(-8.9 to 6.7)
Caregivers concern	82.7	84.7	-2.0	(-10.3 to 6.3)
VAS	71.0	78.0	-7.0	(-16.8 to 2.8)
	2 year follow-up			
Physical suffering	96.0	91.2	4.8	(-1.6 to 11.0)
Hearing loss	88.8	85.7	3.1	(-4.8 to 11.0)
Speech impairment	88.3	90.3	-2.0	(-9.9 to 5.8)
Emotional distress	96.6	93.2	3.4	(-2.4 to 9.2)
Activity limitations	98.8	94.8	4.0	(-0.2 to 8.1)
Caregivers concern	98.1	94.8	3.3	(-1.0 to 7.6)
VAS	91.6	86.6	5.0	(-2.1 to 12.0)

Figure 4.1.3E. OSA-18 at baseline and 2 year follow-up



	Adenoidectomy	Watchful waiting	Difference	95% CI
	Inclusion			
Sleep disturbance	71.3	72.9	-1.6	(-0.8 to 4.9)
Physical suffering	54.1	53.7	0.4	(-6.4 to 7.2)
Emotional distress	73.3	72.9	0.4	(-6.5 to 7.2)
Daytime problems	77.7	76.7	1.0	(-4.8 to 6.9)
Caregiver concerns	76.7	76.0	0.7	(-5.2 to 6.6)
	2 year follow-up			
Sleep disturbance	87.4	86.7	0.7	(-4.2 to 5.8)
Physical suffering	76.6	79.1	-2.5	(-10.6 to 5.5)
Emotional distress	80.4	75.5	4.9	(-10.6 to 5.5)
Daytime problems	82.8	81.7	1.1	(-5.1 to 7.3)
Caregiver concerns	90.5	89.0	1.5	(-3.6 to 6.7)

Chapter 4.1

Chapter 4.2

Immediate adenoidectomy as compared to an initial watchful waiting strategy in children with recurrent upper respiratory tract infections: an economic evaluation

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Submitted

Abstract

Objective: To compare the costs associated with two clinical strategies in children with recurrent upper respiratory tract infections: immediate adenoidectomy versus an initial watchful waiting strategy.

Methods: A cost-minimization analysis from a societal perspective, including both direct and indirect costs alongside an open randomized controlled trial with a two year follow-up. The trial was multicenter, including eleven general and two university hospitals in the Netherlands. 111 children aged 1 through 6 years, selected for adenoidectomy for recurrent upper respiratory tract infections according to current clinical practice were randomized to a strategy of immediate adenoidectomy with or without myringotomy or a strategy of initial watchful waiting. The main outcome measure was the difference in median costs during two year follow-up.

Results: The median total of direct and indirect costs in the adenoidectomy and watchful waiting group were € 1,385 (US$ 1,995) and € 844 (US$ 1,216) per patient, respectively. The extra costs in the adenoidectomy group are primarily attributable to surgery and visits to the otorhinolaryngologist. Other costs did not differ significantly between the groups.

Conclusion: In children selected for adenoidectomy for recurrent upper respiratory tract infections, immediate adenoidectomy results in an increase in costs, whereas it confers no clinical benefit over an initial watchful waiting strategy.

Introduction

In a recent randomized controlled trial we compared two common clinical strategies in children with recurrent upper respiratory tract infections: immediate adenoidectomy versus initial watchful waiting.[1] We found no relevant differences between both strategies in the incidence of upper respiratory tract infections and middle ear problems, or health related quality of life. We concluded that immediate adenoidectomy confers no clinical benefits over an initial watchful waiting strategy.
In clinical practice, the decision for either of these treatment strategies is made by both the physician and parents and based on careful consideration of anticipated benefits and risks and personal preference. Costs should be part of this decision process as well.[2] So far, no information is available on the costs involved with immediate surgery or initial watchful waiting in children with recurrent upper respiratory tract infections. This is relevant as in both strategies costs may be considerable. Besides costs related to immediate or delayed surgery, there are those related to doctor's visits, use of medication for upper respiratory tract infections and indirect costs, e.g. related to parental absence from work. We set out to compare the costs associated with both strategies.

Material and Methods

Study design
A cost-minimization study was carried out alongside an open multicenter RCT in eleven general and two academic hospitals in the Netherlands between April 2007 and October 2010. The study was approved by the medical ethics committee of the University Medical Center Utrecht. The design of the study has been reported previously.[3] In brief, children aged 1 through 6 years selected for adenoidectomy for recurrent upper respiratory tract infections were eligible for the study. Children with previous adenoidectomy or adenotonsillectomy, and with tympanostomy tubes present or an indication for insertion of tympanostomy tubes in combination with adenoidectomy were excluded from the study. Children with Down's syndrome or craniofacial malformation were also excluded. After obtaining informed consent children were randomly assigned to either a) adenoidectomy with or without myringotomy within 6 weeks, or b) an initial watchful waiting strategy.

Follow-up

Parallel to clinical symptoms, parents recorded resources used in diaries, such as doctor's visits, medication, hospital admissions and surgical interventions, as well as out-of-pocket expenses for over-the-counter drugs, babysitting and traveling to medical appointments during the 2-year follow-up period. The study doctor collected diary data during the scheduled follow-up visits at 3, 6, 12, 18 and 24 months. Where relevant, diary entries were verified by data from the medical records.

During follow-up, parents, family physicians and otorhinolaryngologists of the participating children were encouraged to manage episodes of upper respiratory tract infections according to their regular practice, including antibiotics and ear-nose-throat surgery.

Outcome measures

The primary outcome measure of this cost-minimization study was the difference in median costs between the two strategies during the full two years of follow-up. To study short term effects, the secondary outcome was the difference in median costs in the first year of follow-up. These costs included both direct and indirect costs, and were estimated at patient level in Euros (€) for 2009.

Costs

Cost prices were estimated from a societal perspective according to the guidelines for economic evaluation in health care research. Costs of surgery were retrieved from available data from a previous costing study.[4] Costs of diagnostic tests were retrieved from the Dutch diagnostic formulary.[5] Costs of medication, were derived from the Dutch Formulary[5], and a pharmacist's fee was added.[6] Costs of over-the-counter drugs and alternative medicines were based on average retail prices. Costs of consulting a family physician or medical specialist, day case surgery, other procedures and hospitalizations were based on current Dutch guidelines for pharmaco-economic evaluation.[6] Indirect costs to society associated with leave or absence from work of the parents were estimated using the friction cost method.[7] Costs associated with absence of professional day-care were estimated as the compensation for professional day care as provided by the government. Costs for informal babysitting were estimated using standard rates of the Dutch National Institute for Family Finance Information, NIBUD.[8] According to the guidelines for economic evaluation in health

care research, Euros were converted to US Dollars using the exchange rate of 31 December 2009 (€1 = US$1.4406).[9]

Analysis

We used a short time horizon for all analyses and therefore took no time preference or discount rate into account. Differences in costs were compared between both randomization groups. Where relevant, differences were tested by non parametric Mann-Whitney tests, as costs always have a skewed distribution. Uncertainty was addressed by means of bootstrapping[10] for which we replicated the trial 1,000 times using random replacement samples. All analyses were performed on the basis of intention to treat; also because we aimed to compare the costs of two *strategies;* adenoidectomy versus initial watchful waiting (the latter may include surgery later during follow-up).Sensitivity analyses were conducted by (1) excluding the children in the initial watchful waiting group that underwent ear-nose-throat surgery during follow-up (per protocol analysis) or by counting these children in the adenoidectomy group (as treated analysis), to compare the costs of adenoidectomy versus no adenoidectomy, rather than of the two strategies.

Results

Study group

In total, 111 children were enrolled in the study between April 2007 and April 2009; 54 were allocated to adenoidectomy within 6 weeks, and 57 were allocated to an initial watchful waiting strategy. Mean age was 36 months in the adenoidectomy group and 38 month in the watchful waiting group. The median number of episodes of upper respiratory tract infections in the previous year was 10 in the adenoidectomy group and 9 in the watchful waiting group. The median follow up was 24 months in both groups. Overall, 11 children were lost to follow-up for non-medical reasons, 4 from the adenoidectomy group and 7 from the watchful waiting group. All children allocated to adenoidectomy underwent adenoidectomy within 6 weeks: 48 adenoidectomy alone and 6 adenoidectomy and myringotomy. During follow-up 7 children (13.0%) allocated to adenoidectomy underwent tonsillectomy and revision adenoidectomy and three (5.6%) had tympanostomy tubes inserted. During the course of the trial 17 children (29.8%) allocated to initial watchful waiting underwent adenoidectomy (in 4 children combined with myringotomy and in 2 with

tympanostomy tubes; one child underwent adenoidectomy in the first year of follow-up and revision adenoidectomy with tympanostomy tubes in the second year of follow-up; 1 child underwent adenoidectomy in the first 6 months of follow-up and tonsillectomy in the 6 months thereafter) and 6 (10.5%) children underwent adenotonsillectomy (in 1 combined with myringotomy).

Costs

Table 4.2.1 shows a detailed overview of the most relevant cost estimates. The median costs per patient during the full two- year follow-up period were € 1,385 (IQR 806 – 2,386) (US$ 1,995, IQR 1,162 - 3,437) in the adenoidectomy group and € 844 (416 – 1,994) (US$ 1,215 IQR 600 - 2,873) in the watchful waiting group, i.e. an immediate surgical strategy costs € 541 (US$ 779) more than an initial watchful waiting strategy. (*Table 4.2.2A*) Bootstrapping yielded the same results, which means that there is no uncertainty regarding the median costs. Children in the adenoidectomy group had higher median costs related to surgery ($p < 0.001$) and visits to the otorhinolaryngologist ($p = 0.03$). Other costs, such as those of visits to the family physician, of (over-the-counter) drugs and parental leave of absence did not differ significantly between the groups. The median costs during the first year of follow-up were € 959 (IQR 632 – 1,658) (US$ 1,382 IQR 911 - 2,388) in the adenoidectomy group and € 505 (105 – 1,194) (US$ 728, IQR 151 - 1,720) in the watchful waiting group (*Table 4.2.2B*). Again bootstrapping yielded the same results.

Sensitivity analysis

Per protocol analysis resulted in a difference in median cost between the adenoidectomy and initial watchful waiting group of € 778 (US$ 1,121) during two year of follow-up ($p <0.001$). As treated analysis resulted in a difference in median costs between the two groups of € 777 (US$ 1,119) during two year of follow-up ($p<0.001$). (*Table 4.2.3*)

Table 4.2.1. Resources used and cost estimates in € and US$ for 2009

Resources	Cost Estimate, €	Cost Estimate, US$ [a]	Source
Adenoidectomy	336.54	484.82	Cost study
Adenoidectomy and myringotomy	567.39	817.38	Cost study
Adenoidectomy and insertion of tympanostomy tubes	717.02	1032.94	Cost study
Adenotonsillectomy	379.01	546.00	Cost study
Adenotonsillectomy and myringotomy	609.85	878.55	Cost study
Adenotonsillectomy and insertion of tympanostomy tubes	759.48	1094.11	Cost study
Tonsillectomy	357.78	515.42	Cost study
Insertion of tympanostomy tubes	380.47	548.11	Cost study
Diagnostic tests	Several	Several	Guideline
Hospitalization per day	358.68	516.71	Guideline
Consultation ORL / pediatrician	61.40	88.45	Guideline
Consultation family physician	20.79	29.95	Guideline
Consultation other medical professional	25.72	37.05	Guideline
Parental leave of absence (per hour)	35.99	51.85	Guideline
Absence of day-care (per hour)	6.10	8.79	Government
Babysitting (per hour)	5.70	8.21	NIBUD
Pharmacist fee (per prescription)	7.28	10.49	Guideline
Prescribed medication	Several	Several	Dutch formulary
Over-the-counter drugs and CAM	Several	Several	Retail prices

Abbreviations:
Guideline: Dutch guidelines for pharmacoeconomic research [5]
NIBUD: Dutch National Institute for Family Finance Information [8]
ORL: otorhinolaryngologist
CAM: complementary and alternative medication
[a] Exchange rate 31-12-2009 1 € = 1.4406 US$

Table 4.2.2A. Median costs in € and US$ during two year follow up

	Adenoidectomy (n = 54)	**Watchful waiting (n = 57)**
	Median (€) (IQR)	Median (€) (IQR)
Surgery and hospitalization	336.54 (336.54 – 599.35)	0.00 (0.00 – 379.01)
Prescribed medication	8.55 (0.72 – 30.35)	6.64 (0.00 – 21.50)
Over-the-counter drugs and CAM	8.36 (2.36 – 28.98)	12.41 (2.03 – 36.78)
Consultations otorhinolaryngologist	61.40 (0.00 – 122.80)	0.00 (0.00 – 107.45)
Consultation other specialist	0.00 (0.00 – 63.53)	0.00 (0.00 – 57.62)
Consultation family physician	72.96 (18.24 – 117.09)	72.96 (20.79 – 172.01)
Absence of day-care	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
Parental leave of absence	359.90 (53.99 – 899.75)	251.93 (0.00 – 701.81)
Babysitting	0.00 (0.00 – 47.03)	0.00 (0.00 – 45.60)
Other costs (including travel costs)	80.40 (24.58 – 171.45)	80.40 (26.09 – 201.62)
Total	€ 1,384.84 (806.48 – 2,385.51) US$ 1,995.00 (1,161.82 – 3,436.57)	€ 843.56 (416.40 – 1,994.03) US$ 1,215.23 (599.87 – 2,872.60)

Abbreviations:
CAM: complementary and alternative medication
IQR: interquartile range

Table 4.2.2B. Median costs in € and US$ during the first year of follow up

	Adenoidectomy (n = 54)	**Watchful waiting (n = 57)**
	Median (€) (IQR)	Median (€) (IQR)
Surgery and hospitalization	336.54 (336.54 – 336.54)	0.00 (0.00 – 336.54)
Prescribed medication	6.47 (0.07 – 16.48)	3.36 (0.00 – 13.23)
Over-the-counter drugs and CAM	5.27 (0.97 – 18.17)	8.81 (1.19 – 29.48)
Consultations otorhinolaryngologist	61.40 (0.00 – 69.08)	0.00 (0.00 – 61.40)
Consultation other specialist	0.00 (0.00 – 57.62)	0.00 (0.00 – 47.30)
Consultation family physician	31.38 (0.00 – 62.47)	31.38 (5.30 – 93.95)
Absence of day-care	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
Parental leave of absence)	287.92 (0.00 – 863.76)	0.00 (0.00 – 431.88)
Babysitting	0.00 (0.00 – 45.60)	0.00 (0.00 – 17.10)
Other costs (including travel costs)	47.66 (19.17 – 81.50)	41.58 (7.80 – 121.98)
Total	€ 959.24 (632.12 – 1657.80) US$ 1,381.88 (910.63 – 2,388.23)	€ 505.40 (104.68 – 1193.66) US$ 728.08 (150.80 – 1,719.59)

Abbreviations:
CAM: complementary and alternative medication
IQR: interquartile range

Table 4.2.3. Sensitivity analyses on total costs in € and US$ during two year of follow up

	Adenoidectomy Median (IQR)	Watchful waiting Median (IQR)	Difference in median costs
Excluding cross-overs	€ 1,384.84 (806.48 – 2,385.51)	€ 606.61 (136.47 – 1,478.55)	€ 778.23
	US$ 1,995.00 (1,161.79 – 3,436.57)	US$ 873.88 (196.60 – 2,130.00)	US$ 1,121.12
Analysing cross-overs as treated	€ 1,383.54 (756.97 – 2,276.46)	€ 606.61 (136.47 – 1,478.55)	€ 776.93
	US$ 1,993.13 (1,090.49 – 3,279.47)	US$ 873.88 (196.60 – 2,130.00)	US$ 1,119.25

Discussion

This study shows that in children selected for adenoidectomy for recurrent upper respiratory tract infections, an immediate surgical strategy costs € 541 (US$ 799) more than an initial watchful waiting strategy during two year of follow up. This is an increase of 64%, whereas immediate surgery confers no clinical benefit over an initial watchful waiting strategy. The extra costs are related to surgery and visits to the otorhinolaryngologist. Other costs did not differ significantly between the groups.

The results of our study are in agreement with three other studies that reported higher costs for surgical strategies in children with upper respiratory tract infections, i.e. adenotonsillectomy in children with mild to moderate throat infections[4], and tympanostomy tubes in children with otitis media with effusion.[11, 12] To our knowledge, this is the first economic evaluation of adenoidectomy in children with recurrent upper respiratory tract infections.

The major strength of our study is that we measured costs prospectively alongside a randomized controlled trial, and used a societal perspective that included all relevant costs.
Some potential limitations should also be taken into consideration. First, 23 (40%) children from the initial watchful waiting group underwent adenoidectomy during the course of the trial. We performed an intention to treat analysis as our primary analysis since our aim was to compare clinical *strategies,* and not to compare adenoidectomy versus no adenoidectomy per se. For the latter, we performed per protocol and as treated analyses, which however may suffer from confounding, because the baseline comparability of prognosis, achieved through randomization may be lost.

Interestingly, the per protocol and as treated analyses did not change the clinical results, confirming the lack of benefit following adenoidectomy, but the differences in costs were substantially higher, € 778 (US$ 1,121) and € 777 (US$ 1,119) after 1 and 2 years follow-up, respectively. This larger negative economic effect can be explained by the fact that in the sensitivity analyses children with higher costs (mostly due to surgery) were excluded from the watchful waiting group.
Second, we originally planned this study as a cost-effectiveness study, dividing the difference in costs by the difference in effects. Because our trial showed comparable clinical effectiveness of an immediate surgical strategy and an initial watchful waiting strategy in children with recurrent upper respiratory tract infections, we decided to perform a cost-minimization study comparing the costs of both strategies.
Third, generalizing the results of economic evaluations to other countries might be challenging due to differences in healthcare systems and prices. Although the absolute (differences in) costs might indeed not be generalizable, the ratio between the costs in the adenoidectomy and the watchful waiting group will remain applicable to other countries, i.e. we expect that in other countries adenoidectomy is also about 1.5 times more costly than watchful waiting.
Finally, we indexed costs of surgery from a previous costing study [4], because recent cost figures could not be extracted from the current Dutch 'Diagnosis Treatment Combination' system (DBC-system) introduced in 2005.[13] This system is based on diagnostic classifications rather than on an internationally recognized therapeutic classification system. A DBC can be defined as a predefined average package of care with, in most cases, a fixed price depending on the diagnosis. By using the indexed costs from our previous costing study[4], instead of a DBC price, our cost prices and final results are comparable to those of previous and future economic evaluations.

Conclusion

In children selected for adenoidectomy for recurrent upper respiratory tract infections, immediate adenoidectomy results in an increase in costs, whereas it confers no clinical benefit over an initial watchful waiting strategy.

Acknowledgements

We thank Ardine de Wit for advising us regarding the design of the study.

Funding

The study was funded by a grant from ZonMw - the Netherlands Organisation for Health Research and Development, Health Care Efficiency Research Programme, sub-programme Effects & Costs 2007 no. 80-007022-98-07901. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. All authors were independent from the funder and had access to all the data.

Conflict of interest

Prof. dr. A. Schilder and Dr. M. Rovers received honoraria from GlaxoSmithKline for participation in expert meetings a workshop and educational activities on otitis media. They also received a grant for a study on the microbiology of otitis media from GlaxoSmithKline. All other authors have no relationships with companies that might have an interest in the submitted work; neither do they have non-financial interests that may be relevant to the submitted work.

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Chapter 5

From design to publication

Chapter 5

Chapter 5.1

Selective reporting of primary outcomes: A comparison of grant applications and publications

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Submitted

Abstract

Background: Outcome reporting bias, which is defined as the selection for publication of a subset of the original reported outcome variables on the basis of the results, may not only impact the interpretation of individual studies but also of any subsequent systematic review or meta-analysis.

Objective: To assess discrepancies between primary outcomes specified in grant proposals, trial registries and subsequent publications, the influence of the statistical significance and the impact factor of the journal of publication.

Methods: We investigated all finalised research projects (n = 79) awarded by the ZonMw "Health Care Efficiency Research Program" as from 2001, along the pathway from grant application, trial registration, published protocol, final report to scientific publication.

Results: Agreement between primary outcomes in trial registries, final reports and scientific publications as compared to those in the grant proposals were 68%, 70% and 37%. In 22 of the 62 (36%) projects with a scientific publication, a primary outcome specified in the grant proposal was not included in the publication. In general, no explanation for the discrepancies was provided. Agreement between grant proposal and scientific publication was higher for high (45%) than for low (29%) impact factor journals RD 16% (95% confidence interval -8% ; 40%). The chance of an original primary outcome being included in the scientific publication was 2.8 times higher (95% confidence interval 1.2; 6.6) for outcomes that were statistically significant.

Conclusion: Reporting of primary outcomes in the trial registry and final publication is often inconsistent with that in the original grant proposal, and is biased favouring statistical significance. Guidelines like the CONSORT statement need to be updated and include the statement that all outcomes specified in the grant proposal should be fully reported.

Introduction

Selective publication of studies with statistically significant results is a widely recognized source of bias.[1-3] Outcome reporting bias refers to selective reporting of a subset of the originally defined outcome variables, typically based on the study findings.[4-6] This may not only affect interpretation of an individual study but also of any systematic review or meta-analysis including the study.[4, 7, 8] Since the direction and magnitude of the average effects as reported in meta-analysis guide clinical guidelines and consequently clinical decisions, publication of all results rather than a selection is essential.

So far, most studies comparing outcomes as defined in study protocols with those in published reports focused on protocols submitted to either scientific journals or ethics committees. These protocols may, however, already differ from those submitted for funding. So far, only Chan et al compared awarded grant proposals with the resulting scientific publications.[9] They showed that primary outcomes differed between protocols and publications for 40% of the trials. This study was performed in 2002, whereas in 2004 it became compulsory to register trials and subsequently many high impact journals require protocol submission preferably at an early stage of the study and minimally as co-submission with a scientific paper. It is unclear whether this policy has improved completeness of outcome reporting and decreased potential bias.

We were in the unique position to have access to and study outcomes in both grant proposals, trial registries, final reports and scientific publications of a clinical research program of the Dutch grant agency ZonMW. We first assessed differences in primary outcomes as specified in grant proposals, trial registries and subsequent publications. In addition, we studied whether such discrepancies were affected by the statistical significance of the original primary outcome and by the impact factor of the scientific journal in which the paper was published.

Chapter 5.1

Materials and methods

Grant applications, trial registrations and scientific publications
All grants awarded by the Health Care Efficiency Research Program of the Netherlands Organization for Health Research and Development (ZonMw) (i.e. the Dutch "National Institutes of Health") from 2001 up to 2006 were eligible for inclusion in this study. They were included when the final report, i.e. the report for the program committee, was received by ZonMw before March 1, 2010.

The grant applications and final reports were retrieved from the paper files at ZonMw office. The trial registries (www.clinicaltrials.gov, www.isrctn.org, www.trialregister.nl) were then searched for registration of these studies. Using the final reports specifying the scientific products, and the names of the researchers, relevant scientific publications were retrieved by a literature search (PubMed, EMBASE, and Cochrane Library), with the last search performed on Augusts 13, 2011. We used standardized, pilot-tested forms to extract the following data from the grant proposals, trial registry, final reports and scientific publications: study design, type of research, sample size, length of follow-up, research institute, primary and secondary outcomes, and the number of scientific publications. With regard to the primary outcomes, the following characteristics were extracted: stage at which they were first mentioned, power calculation for that specific primary outcome, and the corresponding overall effect estimate. The type of research was categorized as intervention, diagnostic, prognostic, or other type of studies.

Statistical analysis
We compared the primary outcome measures reported in the grant proposal with those in trial registries, published protocols and final publications. We used a modified classification of Chan et al [10]:

1. Reported primary outcome(s) were in complete agreement with the grant proposal
2A. At least one primary outcome was omitted from the trial register, final report or scientific publication
2B. A primary outcome of the grant proposal was downgraded to a secondary outcome in the trial register, final report or scientific publication.

3A. A new primary outcome was introduced in the trial registration, final reports or scientific publication

3B. A secondary outcome in the grant proposal was upgraded to a primary outcome in the trial register, final report or scientific publication.

For each study we tabulated all primary outcomes in a 2x2 table relating this modified classification of Chan et al to the statistical significance of the primary outcome in the grant proposal (yes vs no). In this analysis, outcomes were classified as ineligible if their statistical significance was unknown. For every trial an odds ratio was calculated from the 2x2 table: an odds ratio above 1 indicates that a statistically significant primary outcome had a higher odds of being reported than non-significant primary outcomes. We also calculated a pooled odds ratio for all studies to provide an overall estimate of this potential outcome reporting bias.

All analyses were also stratified regarding the impact factor of the scientific journals in which the outcomes were published (higher or lower than the median impact factor of 5.1). All data were analyzed with SPSS, version 15 (SPSS, Inc., Chicago, Illinois).
This study received no external funding.

Results

Of the 79 projects that could be evaluated, the majority were intervention studies (63%), followed by diagnostic (23%), prognostic (8%), and other (6%) studies (*Table 5.1.1*). Most projects were randomized controlled trials (60%), and almost all were conducted at a university or university medical center (94%). Of the 47 randomized controlled trials, 43 (92%) were registered in a trial register; 39 (83%) were registered before the end of the trial and 9 (19%) before the first patient was enrolled. All studies that started after 2004 were registered before the first patient was enrolled.
Across the 79 studies, we identified 661 outcomes (median 8.5 outcomes per study protocol, range 1-19) in the grant proposals, trial registries, final reports or scientific publications. Of all outcomes 229 were reported as a primary outcomes somewhere during the process from grant application to final publication. The number of specified *primary* outcomes ranged from 1 to 7 (mean 1.8).

Table 5.1.1. Characteristics of the 79 included projects

	All included studies N = 79		Studies registered in trial register N = 47		Studies with a published study protocol N = 21		Studies with a scientific publication N = 62	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Type of study								
Intervention	50	63.3	38	80.9	17	81.0	43	69.4
Diagnostic	18	22.8	8	17.0	3	14.3	15	24.2
Prognostic	6	7.6	1	2.1	1	4.8	3	4.8
Other	5	6.3	0	0	0	0	1	1.6
Design								
Randomized controlled trial	47	59.5	43	91.5	19	90.5	40	64.5
Cohort	13	16.5	3	6.4	2	9.5	12	19.4
Modeling	10	12.7	0	0	0	0	5	8.1
Other	9	11.4	1	2.1	0	0	5	8.1

Trial register versus grant application

In 32 of the 47 projects (68%) that were registered in a trial register, the registered primary outcomes agreed completely with those in the grant proposal (*Table 5.1.2, Figure 5.1.1*). In 10 registered studies (21%) a primary outcome was not included as such (in 7 studies at least one primary outcome was not included at all and in 6 studies a primary outcome was downgraded to a secondary outcome). In 12 studies (26%) a new primary outcome was introduced or a secondary outcome was upgraded to a primary outcome.

Final report versus grant application

In 55 of the 79 projects (70%) the primary outcomes reported in the final report were in complete agreement with those in the grant proposal (*Table 5.1.2, Figure 5.1.1*). In 19 studies (24%) a primary outcome was not included as such (in 13 studies at least one primary outcome was not included at all and in 6 studies a primary outcome was downgraded to a secondary outcome). In 15 studies (19%) a new primary outcome was introduced or a secondary outcome was upgraded to a primary outcome.

Table 5.1.2. Comparison of primary outcomes in trial registers, published protocols, final reports, scientific publications and the grant proposal (comparator)

	Trial register N = 47		Published protocol N = 21		Final report N = 79		Scientific publications N = 62	
	N	%	N	%	N	%	N	%
Complete agreement with grant proposal regarding primary outcomes	32	68.1	12	57.1	55	69.6	23	37.1
Primary outcome from grant proposal omitted or downgraded in text or trial registration	10	21.3	6	28.6	19	24.1	32	51.6
Primary outcome of the grant proposal omitted in text or trial registration	7	14.9	4	19.0	13	16.5	22	35.5
Primary outcome of the grant proposal downgraded to secondary outcome in text or trial registration	6	12.8	3	14.3	6	7.6	14	22.6
New primary outcome introduced or secondary outcome of the grant proposal upgraded to primary outcome in text or trial registration	12	25.5	6	28.6	15	19.0	28	45.2
New primary outcome introduced in text or trial registration	1	2.1	2	9.5	7	8.9	17	27.4
Secondary outcome of the grant proposal upgraded to primary outcome in text or trial registration	11	23.4	3	14.3	8	10.1	12	19.4
Discrepancy in primary outcome favouring statistically significant result? [a]								
Yes	NA	NA	NA	NA	12	15.2	30	48.4
Impossible to conclude					0	0	1	1.6

[a] A discrepancy in primary outcome was said to favour a statistically significant result when a new, statistically significant outcome was introduced or upgraded in the article or when a statistically non-significant primary outcome was omitted or downgraded in the published article

In 8 of the 24 projects (33%) with a discrepancy in primary outcomes between the grant application and final report some explanation was provided, notably progressive insights (n=3) or recruitment problems (n=5),resulting in a premature termination of the study and a subsequent decision to use another (intermediate) outcome as the primary outcome.

Scientific publication versus grant application

In 23 of the 62 projects (37%) with a scientific publication, the reported primary outcomes completely agreed with those in the grant proposal (*Table 5.1.2, Figure 5.1.1*). In 32 studies (52%) a primary outcome was not included as such (in 22 studies at least one primary outcome was not included at all and in 14 studies a primary outcome was downgraded to a secondary outcome). *Figure 5.1.2* shows the association between the number of omitted or downgraded primary outcomes in the scientific publications and the total number of primary outcomes defined in the grant application. In 28 studies (45%) a new primary outcome was introduced or a secondary outcome was upgraded to a primary outcome.

Two of the 39 projects (5%) with a discrepancy in primary outcomes between the grant application and scientific publication provided an explanation, i.e. recruitment problems.

Association between reporting and statistical significance

The chance of a primary outcome being reported in the final report was 3.3 times higher if that primary outcome was statistically significant as compared to a non-significant outcome (pooled odds ratio 3.3 (95% confidence interval 0.9; 12.5)). For the scientific publications the pooled odds ratio was 2.8 (95% confidence interval 1.2; 6.6).

Impact factors

Complete agreement between the grant application and scientific publication occurred in 9 out of 31 studies (29%) published in a journal with an impact factor lower than the median (5.1), and in 14 out of 31 studies (45%) published in a journal with an impact factor of 5.1 or larger (RD 16%; 95% confidence interval -8% ; 40%).

Figure 5.1.1. Complete agreement regarding primary outcomes

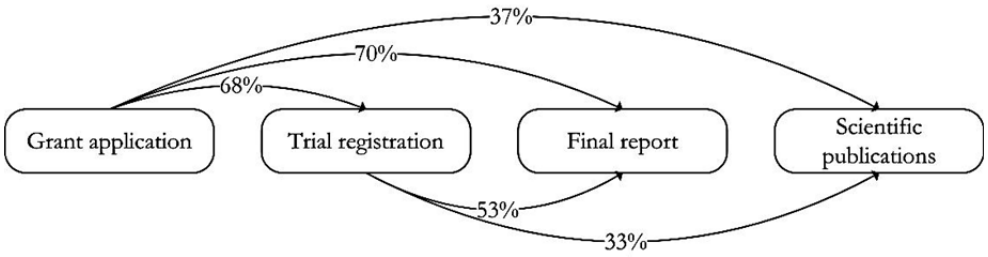
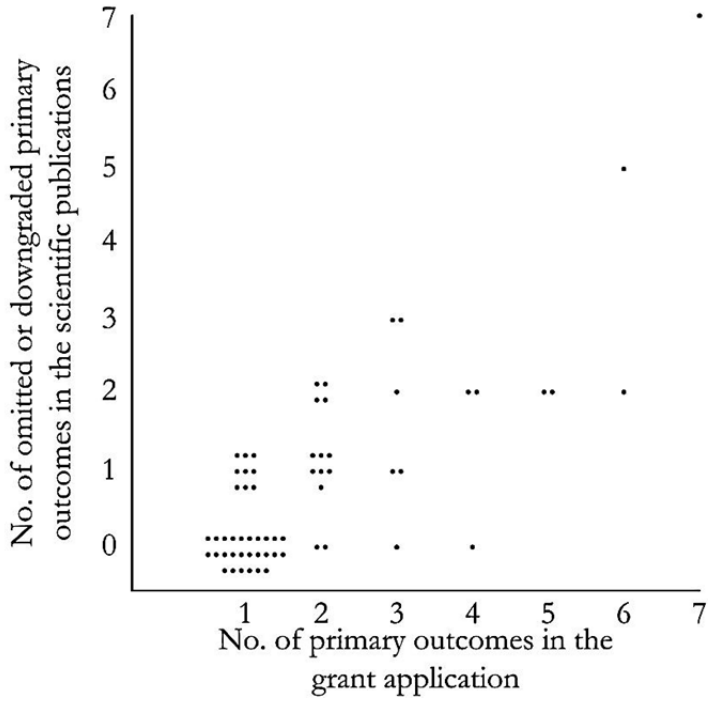


Figure 5.1.2. Number of omitted or downgraded primary outcomes in the scientific publications, displayed according to total number of primary outcomes defined in the grant application



Legend Figure 5.1.2
Each individual study (n = 62) is represented by a dot.

Discussion

Research funding agencies emphasize the importance of adherence to the grant proposal and protocol in their guidelines and request that amendments to the protocol should be kept to a minimum, and if they do occur, they should be reported.[11] For example, both the ICH E3 [International Conference on Harmonisation: ICH Topic E3] guideline [12] and the Medicines and Healthcare products Regulatory Agency (MHRA) [13] state that changes in outcomes should be reported in journal articles.
However, our results show that the agreement between primary outcomes in the scientific publication and grant application was only 37%, whereas mostly no

explanation for these discrepancies was provided. These results are consistent with those of earlier studies comparing protocols with scientific publications [9, 14-16] and thus suggest that the policy of the research funding agencies and trial registries have not improved completeness of outcome reporting and decreased potential bias.

The major strength of our study is that we had access to and could report on (dis) agreements in primary outcomes as specified across all stages of research from grant proposal, trial registration, final reporting to scientific publication. Several potential limitations of our study should also be mentioned. First, scientific publications regarding the final results were not (yet) available for all projects. A comparison of the grant proposals and final reports with a scientific publication versus those without a scientific publication did not show large differences (data not shown). Bias due to missing scientific publications is therefore unlikely.
Second, we excluded studies for which odds ratios could not be calculated due to missing data in the 2x2 table, from the analysis on the association between completeness of reporting and statistical significance. Consequently, studies were more likely to be included in the analysis if they varied in the level of reporting and/or statistical significance, i.e. the reported odds ratio probably is an underestimation of the real effect. A sensitivity analysis, in which all reported and non reported outcomes without a known significance level were scored as not significant, resulted in an OR of 6.2 (1.8 ; 21.6) for the final reports and an OR of 3.5 (1.5 ; 7.9) for the scientific publications.
Third, our results might not be directly generalizable to studies without funding or to other countries or funders as each has its own standards. However, the process of a peer-review grant application process will be similar for various organizations.

One can think of several reason for discrepancies between the primary outcomes in the grant proposals and in the trial registry, final reports and scientific publications, such as logistical barriers to measure the original primary outcome, lower event rates than anticipated, new evidence that invalidates the original primary outcome, or supports the use of a more appropriate outcome. At best, such amendments were made independently of the study findings, but our finding that the chance of a primary outcome being reported in a scientific publication was around 3 times higher if this primary outcome was statistically significant, suggests that the modifications were conducted to highlight the "most interesting" results. Furthermore, there was a remarkable difference between the percentage agreement with the grant proposal

between the final report for the funding agency (70%) and the scientific publications (34%). Researchers appear to be more aware of the importance of reporting all primary outcomes as specified in the grant application while they are writing their final report for the funding agency as compared to their scientific publications. It is, however, also possible that reviewers and editors have had their influence on the primary outcomes that were reported in the scientific publications, e.g. in studies with more than one primary outcome.

Since the ZonMw "Health Care Efficiency Research Program" is a federal funding agency, our results indicate that selective reporting of outcomes is also present in government-funded studies and not only in industry-sponsored trials.
As this outcome reporting bias may impact the direction and magnitude of the average effects reported in meta-analysis, which are often used to guide clinical decisions, the consequences of selective reporting may be substantial. We believe that publication of all results is essential to make well-informed decisions. Deviations from grant proposals should therefore be limited or at least be addressed in the published reports so that readers can assess the potential for bias.

In conclusion, discrepancies between primary outcomes specified in the original grant proposal, and those in trial registries and final publications are common and biased favoring statistically significance. Guidelines like the CONSORT statement need to be updated and include the statement that all outcomes specified in the grant proposal should be fully reported.

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Chapter 5.2

A comparison of subgroup analyses in grant applications and publications

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American Journal of Epidemiology, 2011 Jul 15;174(2):219-25

Chapter 5.2

Abstract

Background: One of the most important recommendations of the available guidelines on studying and reporting subgroup analyses, is to pre-specify subgroups rather than define them post hoc. We therefore studied both grant proposals and their publications and compared the subgroup analyses that were pre-specified in the grant proposal to those that were finally published.

Methods: Grants awarded by the 'Netherlands Organization for Health Research and Development' from 2001 onward that were finalized before March 1, 2010, were studied. We analyzed whether or not projects mentioned subgroups in their grant application and related publications (i.e. the final report and scientific publications). The main outcome measure was the proportion of studies in which the publications were completely in agreement with the grant proposal, i.e. subgroups that were pre-specified in the grant proposal were reported and no new subgroup analyses were introduced in the publications. Of all individual subgroups that could be identified in the included projects, we analyzed if they were pre-specified or a post-hoc finding.

Results: Subgroups were mentioned in 49 (62%) grant applications and in 53 (67%) publications. In 20 (25%) of the 79 included projects, publications were completely in agreement with the grant proposal. Of the 149 pre-specified subgroups, 46 (31%) were reported in the final report or scientific publications, and 143 of the 189 (76%) reported subgroups were based on post-hoc findings. For 77% of the subgroup analyses in the publications, there was no mention whether these were pre-specified or post-hoc. Justification for subgroup analysis and methods to study subgroups were rarely reported.

Conclusion: There is a large discrepancy between grant applications and final publications regarding subgroup analyses. Both non-reporting pre-specified subgroup analyses and reporting post-hoc subgroup analyses are common

Introduction

One of the challenges of physicians in practicing evidence-based medicine lies in judging whether the treatment effects estimated in empirical studies are indeed applicable to the patients he or she encounters in daily clinical practice or even to an individual patient. Moreover, the treatment effects may be modified by certain patient characteristics (i.e., vary across patient subgroups). Patients and clinicians will thus benefit from knowledge on which patient characteristics should be taken into account in the decision to initiate treatment. Such knowledge on relevant subgroup effects will enable treatment decisions to be individualized as much as possible.[1-3]

Subgroup analyses can be valuable when there is consensus that a clinically relevant subgroup is studied in an appropriate way. However, when subgroup analyses are underpowered or analyzed in an incorrect way, they can lead to incorrect conclusions, that is, false positive or false negative results. As such, treatment may be either withheld from those most likely to benefit or targeted at a subgroup of patients unlikely to profit from it.[4-7] Currently, inappropriate subgroup analyses are common.[4-8] It has been especially suggested that investigators who are disappointed by their initial overall negative findings search for subgroups of patients in whom the treatment is beneficial after all.[9, 10]

Several publications have observed the problem of reporting inappropriate subgroup analyses.[4, 7, 11-14] However, when properly planned, reported, and interpreted, subgroup analyses can provide valuable information.[15] One of the most important recommendations of the available guidelines is to prespecify subgroups rather than define them post hoc. Publications so far on the pros and cons of subgroup analyses, however, are based on published studies only[4, 8, 11, 13, 15-22], and therefore the authors were unable to establish whether subgroup analyses were indeed prespecified in the design of the study or reported in only the methods section of an article. We had the unique opportunity to study both grant proposals and their final reports and publications to compare the subgroup analyses that were prespecified in the grant proposal with those that were finally published.

Chapter 5.2

Materials and methods

Grant applications and scientific publications

All grants awarded by the Health Care Efficiency Research Program of the Netherlands Organization for Health Research and Development (ZonMw) (i.e., the Dutch "National Institutes of Health") from 2001 were eligible for inclusion in this study. They were included when the final report (i.e., a report for the program committee in which researchers provide their results to confirm that they have met the grant conditions) was received by ZonMw before March 1, 2010.

The grant applications and final reports were retrieved from the ZonMw office. PubMed was used to search for the related scientific publications, with the last search on June 1, 2010.

We used standardized, pilot-tested forms to extract the following data: study design, type of research, sample size, length of follow-up, research institute, primary and secondary outcomes, the number of scientific publications, and the presence of a question regarding the diversity of the study population (in the grant application form and/or the final report). With regard to the subgroup analyses, the following characteristics were extracted: number, type, stage of the process first mentioned, justification, methods used, power calculation for that specific subgroup, and the results (both the overall effect estimate and the subgroup results).

The type of research was categorized as one of the following: intervention, diagnostic, prognostic, or other. We classified 5 types of subgroups: patient characteristics (e.g., age, gender, or ethnicity); disease characteristics (e.g., severity); intervention characteristics (e.g., dose or adjuvant interventions); household characteristics (e.g., socioeconomic status, smoking, or family history); and other characteristics. The justification for the subgroup analyses was categorized as literature, clinical experience, biologic mechanism, or no justification at all.

Statistical analysis

We first analyzed whether or not projects mentioned subgroups in their grant application and their related publications (i.e., both the final report and the scientific publications). The main outcome measure was the proportion of studies in which the publications were completely in agreement with the grant proposal; that is, subgroups that were prespecified in the grant proposal were reported and no new subgroup analyses were introduced in the publications. For this main outcome measure, we also

performed stratified analysis per type of research (i.e., interventions studies vs. other types of research) and research design (randomized controlled trials vs. other designs). Second, we compared published study protocols with the grant proposal and final publications.

Of all individual subgroups that could be identified in the included projects, we analyzed if they were first mentioned in the grant application (i.e., prespecified) or in the publications (i.e., post-hoc finding). Prespecified subgroups were defined as any subgroup mentioned in the grant application; neither the categories of the subgroup variable nor the direction or outcome had to be specified. We also calculated the percentage of subgroup analyses performed on nonsignificant or inconclusive overall effect estimates.

A subgroup analysis was defined as significant when the researchers reported a significant effect by either 1) providing a significant P value for the interaction test and/or 2) reporting the results of the stratified analyses, whereby confidence intervals differed significantly between the subgroups, and/or 3) stating that there was a significant subgroup effect without providing the actual numerical values.

All data were analyzed anonymously with SPSS, version 15 (SPSS, Inc., Chicago, Illinois), by using descriptive and comparative statistics. Continuous variables were presented as medians and ranges and/or interquartile ranges. Categorical and dichotomous variables were presented as proportions.

Results

Of the 79 projects that could be evaluated, the majority were intervention studies (63.3%), followed by diagnostic (22.8%), prognostic (7.6%), and other (6.3%) studies (*Table 5.2.1*). Most projects comprised randomized controlled trials (59.5%), and almost all were conducted at a university or university medical center (93.7%). Sixty-four projects (81.0%) mentioned at least one subgroup during any stage of the process from grant application to final report and/or scientific publications.

Table 5.2.1. Characteristics of the 79 included projects

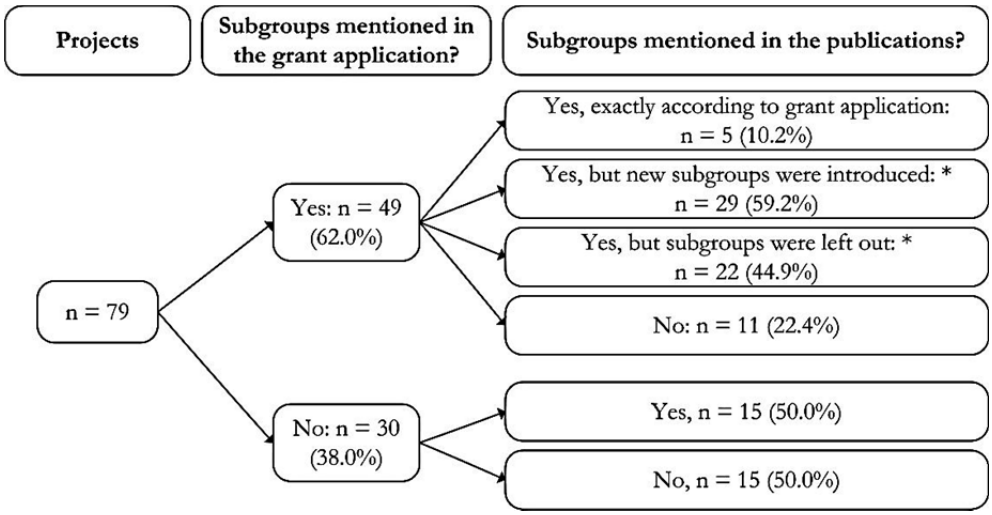
	All Included Studies (n = 79)			Studies With Subgroup Analyses (n = 64)		
	No.	%	Median (Range)	No.	%	Median (Range)
Type of study						
Intervention	50	63.3		44	68.8	
Diagnostic	18	22.8		13	20.3	
Prognostic	6	7.6		5	7.8	
Other	5	6.3		2	3.1	
Design						
Randomized controlled trial	47	59.5		40	62.5	
Cohort	13	16.5		10	15.6	
Modeling	10	12.7		6	9.4	
Other	9	11.4		8	12.5	
Research institute						
University/university medical center	74	93.7		60	93.7	
General hospital	1	1.3		0	0	
Other	4	5.1		4	6.3	
No. of scientific publications per project			4 (0–21)			5 (0–21)
No. of publications on effectiveness per project			1 (0–9)			2 (0–9)
Total no. of subgroups per project						
0	15	19.0		NA	NA	
1	10	12.7		10	15.6	
2	14	17.7		14	21.9	
≥3	40	50.6		40	62.5	
			3 (0–20)			4 (1–20)

Abbreviation: NA, not applicable.

In 20 of the 79 projects (25%), the final publications were in agreement with the grant proposal; that is, subgroups that were prespecified in the grant proposal were reported and no new subgroup analyses were introduced in the publications. *Figure 5.2.1* shows that 49 (62%) and 53 (67%) projects mentioned subgroups in their grant application and related publications (i.e., final report and/or scientific publications), respectively. Only 5 of the 49 projects (10.2%) that specified subgroups in their grant application reported on exactly the same subgroups in their publications. Eleven of the 49 projects (22.4%) with intended subgroup analyses did not report on subgroups at all, whereas the other 33 projects (67.3%) added and/or omitted subgroups in the

publications. Half of the 30 studies that did not prespecify any subgroup did report subgroups in their publications. When restricted to the 8 studies that justified at least one of their subgroups in the grant proposal, 1 (12.5%) did not report on subgroups at all, whereas the other 7 (87.5%) added extra subgroups in the publications; 4 (50.0%) also omitted subgroups in the publications.

Figure 5.2.1. The process of mentioning subgroups in research projects



Publications consist of both the final report and the scientific publications.
*****18 studies that mentioned subgroups in the grant application both added and omitted subgroups in their publications

For 21 of the 79 studies, a published protocol was available, and 13 (62%) of these were completely similar to the grant proposal regarding the planned subgroup analyses. When we compared the 21 published protocols with the scientific publication, 8 (38%) were completely similar regarding the planned and reported subgroup analyses. This percentage is somewhat higher than the 25% of the grant proposals that were in complete agreement with the scientific publications.
In 11 of the 50 (22%) intervention studies, the final publications were in agreement with the grant proposal and, for the other studies, this was 9 out of 29 (31%). When stratified on design, agreement was seen in 11 of the 47 randomized controlled trials (23%) and in 9 of the 32 remaining designs (28%).

Within the 64 projects that did report on subgroups, a total of 292 subgroups were identified. Only 46 (30.9%) of the 149 a priori (i.e., in the grant application) specified subgroups were also reported in either the final report and/or the publication. Of the 189 subgroups reported in either the final report or publication, 143 (75.6%) were post-hoc findings (i.e., first introduced in the report or publications). For 77% of the subgroup analyses reported in the scientific publications, it was not mentioned whether they were based on either prespecified subgroup analyses or post-hoc findings.

Eighty-five of the 120 (70.8%) subgroup analyses in the scientific publications were performed on a nonsignificant or inconclusive overall effect estimate, whereas 35 (29.2%) were performed on a significant overall effect estimate. Of the subgroup analyses performed on nonsignificant or inconclusive results, 20 became significant (23.5%); of those performed on a significant overall result, 34.4% remained significant.

In 6 of the 36 (17%) studies that reported on subgroups in their scientific publications, subgroup analyses were performed on a "new" primary outcome, that is, not the one mentioned in the grant proposal, and in 3 studies (8%), subgroup analyses were performed on a "new" secondary outcome.

Table 5.2.2 shows the characteristics of subgroup analyses mentioned during the process from grant application to final publications on the project level. More than 80% of the projects did not justify any of their subgroups, but if justified it was mostly based on literature. Interaction tests, which are recommended to study subgroup effects 6, were not reported in the grant application at all and in only 4 (9%) final reports and 8 (22%) scientific publications.

None of the final reports or scientific publications reported exact details regarding the interaction tests used. In 3 of the 4 final reports that used interaction tests, subgroup effects were reported only for significant interaction tests; the other final report reported all subgroup effects, including those with a nonsignificant interaction test.

In 2 of the 8 scientific publications that used interaction tests, the results of the interaction tests were not presented. Two other scientific publications reported both significant and nonsignificant results on the interaction test. The last 4 scientific publications that used interaction tests reported only nonsignificant interaction tests.

Table 5.2.2. Characteristics of subgroup analyses on project level during the process from grant application to final publications

	Grant Application[a] (n = 49)			Final Report (n = 44)			Scientific Publications (n = 36)		
	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)
No. of subgroups									
1	14	28.6		9	20.5		13	36.1	
2	9	18.4		15	34.1		7	19.4	
≥3	26	53.1		20	45.5		16	44.4	
			1 (1–3)			1 (1–3)			2 (1–3)
No. of newly introduced subgroups									
0	NA	NA		9	20.5		16	44.4	
1	NA	NA		10	22.7		7	19.4	
2	NA	NA		14	31.8		7	19.4	
≥3	NA	NA		11	25.0		6	16.7	
			NA			1 (0–2)			0 (0–1.5)
Only subgroup analyses mentioned in this stage of the process? (yes)[b]	11	17.2		4	6.3		3	4.7	
Specification of earlier mentioned subgroups? (yes)	NA	NA		7	15.9		5	13.9	
Type of subgroups [c]									
Patient characteristics	35	71.4		29	65.9		18	50.0	
Disease characteristics	25	51.0		25	56.8		24	66.7	
Intervention characteristics	4	8.2		4	9.1		6	16.7	
Household characteristics	11	22.4		8	18.2		11	30.6	
Other characteristics	11	22.4		13	29.5		13	36.1	
Not specified, only mentioned that subgroup analyses will be/were performed	15	30.6		1	2.3		1	2.8	
Justification [c]									
Not mentioned at all	41	83.7		38	86.4		29	80.6	
Mentioned for at least one subgroup	8	16.3		6	13.6		7	19.4	
Literature	8	16.3		5	11.4		6	16.7	
Clinical experience	1	2.0		1	2.3		3	8.3	
Biologic mechanism	3	6.1		2	4.5		0	0	
Statistical methods used for subgroup analyses [c]									
Not mentioned at all	34	69.4		29	65.9		14	38.9	
Mentioned for at least one subgroup	15	30.6		15	34.1		22	61.1	

Table 5.5.2. Continued

	Grant Application [a] (n = 49)			Final Report (n = 44)			Scientific Publications (n = 36)		
	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)
Interaction test	0	0		4	9.1		8	22.2	
Stratified analyses	15	30.6		13	29.5		17	47.2	
Power calculation for subgroup? (yes)	6	12.2		4	9.1		1	2.8	

Abbreviation: IQR, interquartile range; NA, not applicable.

Legend table 5.2.2

[a] Grant application consists of the following: preproposal, official grant application, and rebuttal.

[b] As percentage of those studies that mentioned a subgroup anywhere in the process (n = 64).

[c] Total number can be higher than the total number of studies, as all subgroups in the same stage of the process were combined but where type, justification, and method were mentioned for each subgroup separately.

Discussion

To our knowledge, we are the first to compare subgroup analyses as outlined in grant proposals with those included in final publications. In 25% of the projects, the final publications were in complete agreement with the grant proposal (i.e., subgroups that were prespecified in the grant proposal were reported and no new subgroup analyses were introduced in the publications). Only 31% of the subgroups that were prespecified in the grant proposal were reported in the final report or publication, and 76% of the finally reported subgroup effects were post-hoc findings. Justification of subgroup analysis, the statistical methods used, and power calculations were very rarely reported.

Two-thirds of the projects in our study reported on subgroups in their final publication, which is in agreement with most reviews that have been performed so far in which the proportion of subgroups ranged from 57% to 70%.[4, 7, 11, 15, 18-20, 22.] The number of subgroups reported in our study ranged from 1 to 16, with a median of 2. In previous studies, the median number of subgroups ranged from 2 to 4[4, 7, 11, 17], and the maximum number of subgroups ranged from 15 up to 50.[4, 7, 11, 12, 17, 19] Other studies also found that justification of subgroup analyses, the methods used to perform subgroup analyses, and power calculations for performing subgroup analyses

are often not reported.[4, 7, 8, 11, 12, 15-19, 21, 22] Nineteen percent of the projects included in our study justified at least one of the subgroups on which they report in the scientific literature. This is in line with other studies performed so far that also found that clinical or scientific justification is rare.[8, 11, 12, 16] Sixty-one percent of our studies reported a statistical method for at least one of their subgroup analyses; 36% used the interaction test (22% of total), and 77% used stratified analyses (47% of total). Most studies performed so far focused on the use of the interaction test, and the proportion of studies that used the interaction test for at least one of their subgroups ranged from 10% to 56%[4, 7, 8, 11, 12, 15-19, 21, 22], which is comparable with our findings. So far, only 3 studies have mentioned the power of the subgroup analyses; all reported that the studies were underpowered for detecting subgroup effects.[4, 11, 21] This is in agreement with our findings that, in only 5% of the studies with a scientific publication, a power calculation was performed for one of the reported subgroups.

Several potential limitations of our study should also be taken into consideration. First, scientific publications regarding the final results were not (yet) available for all projects because some projects were only finished recently (n = 14), and others were discontinued because of recruitment problems (n = 5). A comparison of the grant proposals and final reports of the completely finished (i.e., with scientific publication) projects and those without the scientific publication did not show large differences. Bias due to missing publications is therefore unlikely. Second, reporting bias cannot be precluded; that is, subgroup effects in scientific publications might be influenced by the opinions of reviewers and editors. We did not, however, find large differences between the final reports, which are due to time constraints mostly written before the scientific publication, and the scientific publications. We therefore think that reporting bias is also unlikely. Third, in the analyses we pooled the data of different types of research (e.g., diagnostic and therapeutic research) and study designs (e.g., randomized controlled trials and cohort studies). Because the analyses might differ, we also performed sensitivity analyses stratified for type of research and study design, which showed similar results. We therefore decided that pooling was indeed allowed. Fourth, our results might not be directly generalizable to other countries or grant-awarding organizations as each grant-awarding organization has its own standards. However, the process of a peer-review grant application process will very likely be the same for all organizations. Fifth, as most studies mentioned multiple subgroups, a clustering effect may occur for reporting on justification and methods. We therefore reported the results on project instead of individual subgroup level.

Furthermore, the implications for practice are still unclear, because we do not know how often reported subgroups led to incorrect conclusions, with the potential consequence that treatment is either withheld from those most likely to benefit or that the treatment is targeted at a subgroup of patients unlikely to profit from it. We also do not know yet whether the subgroup results will be implemented in daily practice.
Despite all the recommendations available regarding the prespecification, justification, and methods for subgroup analyses[4, 5, 14-16, 23-30], the items are still underreported. The development of one, generally accepted, guideline for performing subgroup analyses should therefore be encouraged. This guideline should then be implemented in guidelines regarding the quality improvement of such publications as the Consolidated Standards of Reporting Trials (CONSORT), the Standards for the Reporting of Diagnostic Accuracy Studies (STARD), and the Quality of Reporting of Meta-Analyses Standards (QUOROM), as this seems the only option to really improve the analysis, reporting, and claim of subgroup effects in clinical research.
In conclusion, there is a large discrepancy between the grant applications and the final publications regarding subgroup analyses. Both nonreporting prespecified subgroup analyses and reporting post-hoc subgroup analyses are common. More guidance is clearly needed.

Acknowledgements

This study received no external funding. We thank ZonMw for its approval of using anonymous project data and Dr. Elsbeth Steenland (ZonMw) for her comments on this article.
Conflict of interest: none declared.

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Chapter 6

Adenoidectomy in children with otitis media with effusion: an individual patient data meta-analysis

In preparation

Abstract

Objective: To study the effects of adenoidectomy with or without tympanostomy tubes on hearing in children with otitis media with effusion (OME), and to identify subgroups of children with OME that may benefit more than others from this treatment.

Methods: We performed a meta-analysis using individual patient data from three randomised controlled trials on the effect of adenoidectomy with or without tympanostomy tubes in children with OME. Individual patient data of 567 children aged 0 to 9 years were validated and re-analysed. The primary outcome was mean hearing level at 12 months, and the secondary outcomes were hearing levels at 6, 18 and 24 months. Subsequently, we studied whether the effect of the intervention on hearing level was modified by specific patient characteristics, such as baseline hearing level.

Results: At 12 months follow up, the mean hearing level of children treated with adenoidectomy with (either a unilateral or bilateral) tympanostomy tubes was 3.2 dB (95% CI 0.7 – 5.6) better than the hearing level in the watchful waiting group, and 3.5 dB (95% CI 1.7 – 5.2) better than in children treated with only unilateral or bilateral tympanostomy tubes. The differences between the groups were also statistically significant at 6, 18 and 24 months follow up. For the primary outcome (hearing level at 12 months) the effect of adenoidectomy with or without tympanostomy tubes was not modified by the patient characteristics studied (interaction term p-values >0.05).

Conclusions: Adenoidectomy with tympanostomy tubes improved hearing up to 3 dB for up to 24 months. No clinically relevant subgroups of children with OME could be identified that benefit more than others from this treatment.

Introduction

Otitis media with effusion (OME) is one of the most common paediatric diagnoses in primary care. OME refers to an accumulation of fluid in the middle ear cavity behind an intact tympanic membrane without signs and symptoms of an acute infection. The functional effect of OME is a conductive hearing loss, which has been thought to result in impairment of speech, language, and cognitive development.[1] In general, OME is self-limiting, but about one in five children suffers from recurrent or persistent OME and half of these children are referred to an ear, nose and throat (ENT) surgeon. Many of these children are selected for an ENT operation, typically tympanostomy tubes and / or adenoidectomy.[2]

We recently performed a Cochrane review, which showed a significant beneficial effect of adenoidectomy with or without tympanostomy tubes as compared to watchful waiting or tympanostomy tubes alone on the *resolution* of middle ear effusion in children with OME. The beneficial effect on hearing was small[3] , but might indicate that some children might benefit more than others (i.e. some may have a large beneficial effect whereas other do not benefit at all). Furthermore, the high referral and surgery rates in day-to-day general practice may also illustrate that both general practitioners and ear-nose-throat (ENT)-surgeons believe that certain subgroups of patients may benefit most from adenoidectomy with or without tympanostomy tubes. Indeed, some studies suggest that specific subgroups might benefit more from treatment than others. For example, one randomised controlled trial (RCT) suggested a possible interaction between hearing level at baseline and treatment effect – that is, children with a larger hearing loss at baseline appear to benefit more from treatment than children with a smaller hearing loss[4] while another RCT indicated gender as a possible relevant subgrouping variable.[5]
Reliable identification of subgroups of children more or less likely to benefit from adenoidectomy with or without tympanostomy tubes based on individual trials has not proven to be successful, because most trials were too small for valid and reliable subgroup analyses. A meta-analysis of the individual data from original trials however provides the opportunity to reliably identify patient subgroups most likely to benefit.[6-13] In this paper we performed such an individual patient data (IPD) meta-analysis.

Chapter 6

Methods

Selection of the trials and quality assessment

For this IPD-meta-analysis the same search strategy was used as in our Cochrane review.[3] In short, we searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL,*The Cochrane Library* Issue 1, 2009); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; *m*RCT (Current Controlled Trials); ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform); ClinicalStudyResults.org and Google. We used the following keywords with their synonyms: 'adenoidectomy' and 'otitis' (see Appendix for complete search strategy). We checked the bibliography of all relevant studies and reviews in order to identify supplemental studies. We imposed no language restriction on the searches. Two reviewers performed the final selection of eligible studies and the quality assessment; disagreement was resolved by discussion. For the quality assessment we used the Cochrane Collaboration's tool for assessing risk of bias[14] including a judgment on sequence generation, allocation concealment (whether or not assignment to the intervention or control group could be foreseen by the participants or the investigators), blinding, incomplete outcome data, selective outcome reporting and evaluation of other possible bias. The primary investigators of all selected trials were asked for the raw data of their trials. The obtained data were thoroughly checked for consistency, plausibility, and integrity of randomisation and follow up. Any queries were resolved by contacting the responsible trial investigator.

Types of studies

We considered all RCTs comparing adenoidectomy with or without tympanostomy tubes to either watchful waiting or tympanostomy tubes alone for inclusion in this meta-analysis. Trials in which the method of randomisation was not specified in detail were included, but we excluded quasi-randomised trials (e.g. allocation by date of birth or record number). Studies with a follow-up period of less than 6 months were excluded. Desirable time points for outcome assessment were 6, 12, 18, and 24 months.

Types of interventions

To evaluate the effects of adenoidectomy with or without tympanostomy tubes we intended to compare the following interventions: 1) adenoidectomy versus watchful waiting, 2) adenoidectomy versus tympanostomy tubes, 3) adenoidectomy with tympanostomy tubes versus watchful waiting, 4) adenoidectomy with tympanostomy tubes versus tympanostomy tubes, and 5) adenoidectomy with tympanostomy tubes versus adenoidectomy.

Outcome variables

The primary outcome measure was hearing level (measured by pure-tone audiometry) at 12 months. Secondary outcomes were hearing level at 6, 18 and 24 months follow up. Hearing level was expressed as a mean hearing level (if possible averaged over 500, 1000, 2000, and 4000 Hz) measured where possible by air conduction, pure tone audiometry. In the analyses at child level, the binaural average of the mean hearing level over these frequencies was used in the analyses for all children. Trials that inserted tympanostomy tube unilaterally and therefore randomised ears rather than children were analysed at ear level, i.e. the mean hearing level in each ear was used in the analyses. However, to pool the results of the ear studies with those of the child study, we also calculated the binaural average of the mean hearing level in the ear studies. Patient characteristics that could be included in the IPD as potential modifiers of the effect of the interventions were: age, gender, season, siblings, household smoking, history of breast feeding, history of acute otitis media, age at first episode of acute otitis media, and baseline hearing loss. As the pathogenesis of otitis media is known to be multifactorial, children with more than one potential effect modifier may have more persistent or severe disease and hence might benefit more from treatment with adenoidectomy with or without tympanostomy tubes than children with only one such potential effect modifier. To study this possibility, we also studied combinations of effect modifiers.

Analyses and statistics

All analyses were performed as randomised (so called "intention-to-treat" principle). First, pooled results were calculated. Differences in mean hearing levels between the treatment groups were tested with generalized linear models. By including a dummy for the particular study to the model, the pooled effects were corrected for study. Second, fixed effect regression analyses were performed with treatment group, the

potential subgroup, a dummy for the particular study, and an interaction term (treatment group*potential modifier) as independent variables, and hearing level as dependent variable. If a significant interaction effect ($p < 0.05$) was identified, we performed stratified analyses of the difference in the effect on the mean hearing level within each stratum of the effect modifier, i.e. the actual subgroups. All analyses were first performed for the primary outcome, i.e. hearing level at 12 months follow up. Subsequently, the analyses were performed for the secondary outcomes, i.e. hearing level at 6, 18 and 24 months. All data were analyzed with SPSS, version 15 (SPSS, Inc., Chicago, Illinois).

Results

The literature search identified 18 randomised trials that compared adenoidectomy with or without the insertion of tympanostomy tubes with watchful waiting or insertion of tympanostomy tubes alone in children with OME. Thirteen trials were excluded from the meta-analyses because, hearing level was not measured (k = 7)[15-21], all children underwent adenoidectomy (k=4)[22-25], or randomisation was inadequate (k=2).[26, 27] The data of one trial[28] was not available and four triallists provided their data at the first author's (CB) disposal.[4, 5, 29, 30] One trial was excluded from the analyses after the data was obtained, as it appeared impossible to distract the results as presented in the article.[4] Of the three included trials, 1 trial[29] was not published yet. This study randomized children (n = 376) to receive either adenoidectomy with bilateral tympanostomy tubes, bilateral tympanostomy tubes alone or watchful waiting. In the other two trials[5, 30] a tympanostomy tubes were inserted in one ear with the contralateral ear as the comparison (n = 191) (see also *Figure 6.1*). The quality of the included studies was good and *Table 6.1* presents the main characteristics of the three included trials. *Table 6.2* presents the baseline characteristics of the 567 patients in the three included studies. At child level adenoidectomy with tympanostomy tubes could be compared with both watchful waiting and tympanostomy tubes, at ear level also comparisons with adenoidectomy as a single intervention were possible (*Figure 6.2).*

Figure 6.1. Flow chart of the studies included in the IPD meta-analysis

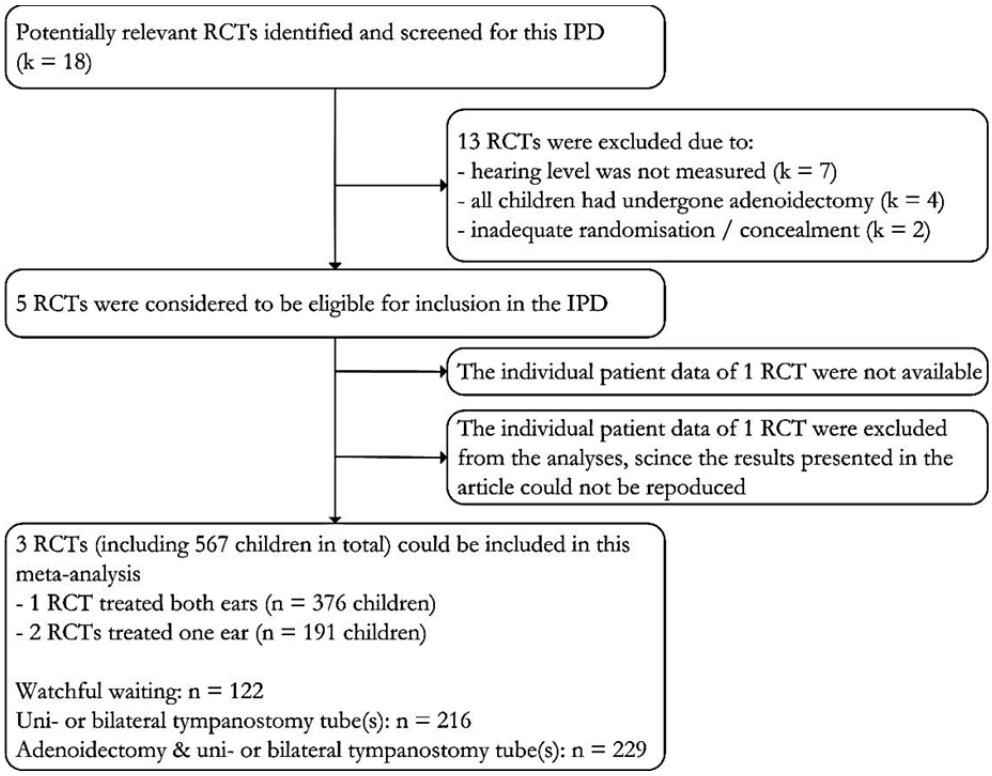


Table 6.1 Characteristics of the four included trials in the IPD meta-analysis

Trial	No. of patients	Inclusion criteria	Age (y)	Interventions	Outcome measurements	Potential subgroups	Follow up
Dempster (1993)[5]	72	Bilateral type B tymp ≥ 25 dB HL > 3 months	3 - 12	Unilateral TT Ad + unilateral TT	Audiometry Tympanometry Otoscopy	1, 2, 3	6 and 12 months
TARGET (2001)[30]	376	Bilateral type B/C2 tymp >20 dB HL & ABG >10 >3 months	3.5 - 7	WW Bilateral TT Ad + bilateral TT	Audiometry Tympanometry Otoscopy Symptom scores Behaviour Child QoL Parental QoL	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	3, 6, 12, 18, and 24 months
Maw (1986/1993)[15]	225	Referred to ORL Bilateral type B tymp >25 dB HL	2 - 9	Unilateral TT Ad + unilateral TT ATE + unilateral TT* * Not included in meta-analysis	Audiometry Tympanometry Otoscopy	1, 2, 3, 4, 6, 7, 8, 9,10	6,12 and 18 months, 2, 3, 4, 5, 6, 7, 8, 9, 10 years

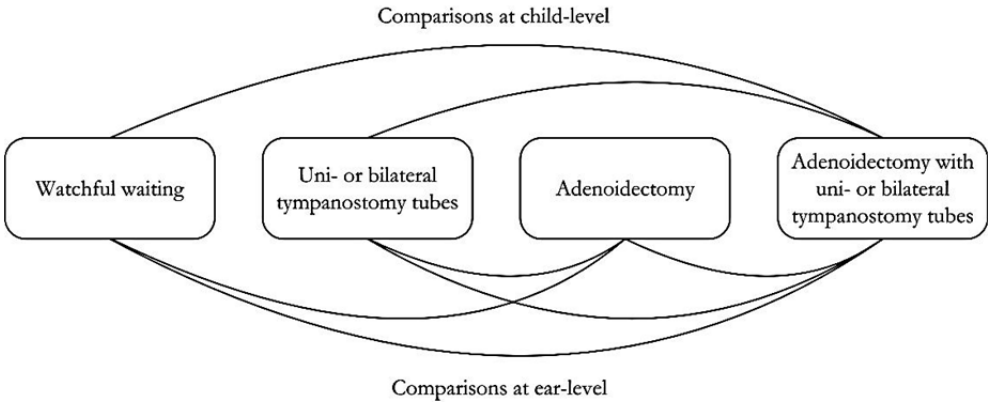
Legend table 6.1
1 = age, 2 = gender, 3 = hearing level acute otitis media (AOM) in history, 4 = age at first AOM, 5 = duration of deafness, 6 = season, 7 = siblings, 8 = smoking, 9 = breastfeeding, 10 = acute otitis media (AOM) in history
Ad = Adenoidectomy ATE = adenotonsillectomy TT = tympanostomy tube(s)
WW = watchful waiting (non surgical strategy) HL = hearing level OME = otitis media with effusion

Table 6.2. Baseline characteristics of the 567 patients in the three included trials

	Adenoidectomy with unilateral or bilateral tympanostomy tubes N = 229, k = 3	**Unilateral or bilateral tympanostomy tubes** N = 216, k = 3	**Watchful waiting** N = 122, k = 1
Age in years, mean (SD) range	5.4 (1.1) 2.5 – 9.0	5.3 (1.0) 3.3 – 9.0	5.2 (0.9) 3.5 – 7.0
< 4 years	20 (8.7%)	22 (10.2%)	11 (9.0%)
Gender: male	127 (55.5%)	115 (53.2%)	62 (50.8%)
Tubes			
No tubes	NA	NA	122 (100%)
Unilateral	101 (44.1%)	90 (46.7%)	NA
Bilateral	128 (55.9%)	126 (58.3%)	NA
Autumn / Winter at time of surgery	84 (43.8%)	79 (43.6%)	54 (44.3%)
Siblings (yes)	171 (90.0%)	152 (84.9%)	101 (83.5%)
Household smoking (yes)	93 (51.7%)	82 (48.8%)	53 (49.5%)
Breastfeeding (yes)	92 (48.7%)	81 (45.8%)	56 (45.9%)
Age in months at first AOM, mean (SD) / range	23.6 (0.7 – 70.0)	26.2 (18.0) 0.0 - 68.0	24.2 (18.5) 2.0 – 69.0
Number of AOM episodes in the past 12 months	1.8 (2.6) 0 – 15	2.0 (2.5) 0 – 12	2.2 (2.6) 0 – 12
Number of AOM episodes in past			
None	82 (44.6%)	62 (36.0%)	42 (36.2%)
1-3 episodes	71 (38.6%)	73 (42.4%)	49 (42.2%)
4 or more	31 (16.8%)	37 (21.5%)	25 (21.6%)
Average hearing level dB (SD) range	31.5 (7.2) 13.1 – 65.0	31.8 (14.4) 14.4 – 47.5	33.5 (6.4) 20.6 – 50.0
< 25 dB	42 (19.0%)	29 (13.9%)	9 (7.4%)
≥ 25 dB	179 (81.0%)	179 (86.1%)	113 (92.6%)

Data are numbers (%), unless otherwise specified.
Percentages do not always add to 100% because of missing data for some characteristics.

Figure 6.2. Possible comparisons at child- and ear-level



Analyses at child level

The average binaural mean hearing levels could be studied in 540 children at 6, 12, 18 and 24 months. At 12 months follow up, the mean hearing level in the adenoidectomy with unilateral or bilateral tympanostomy tubes group was 17.0 dB HL (95% CI 15.8 – 18.2), in the unilateral or bilateral tympanostomy tubes group 20.5 dB HL (95% CI 19.1 – 21.8) and in the watchful waiting group 20.2 dB HL (95% CI 18.1 – 22.2. The mean hearing level of children treated with adenoidectomy with unilateral or bilateral tympanostomy tubes was 3.2 dB (95% CI 0.7 – 5.6) better than the hearing level in the watchful waiting group, and 3.5 dB (95% CI 1.7 – 5.2) better than in children treated with unilateral or bilateral tympanostomy tubes. These differences were also statistically significant at 6, 18 and 24 months follow up (*Table 6.3*).

Analyses at ear level

Hearing levels could be studied in 382 ears at 6 and 12 months. At 12 months follow up, the mean hearing level in the adenoidectomy with an unilateral tympanostomy tube group was 16.0 dB (95% CI 14.3 – 17.8), in the adenoidectomy group 17.5 dB (95% CI 15.3 – 19.6), in the unilateral tympanostomy tube group 17.7 dB (5% CI 15.4 – 20.0) and in the watchful waiting group 21.4 dB (95% CI 18.9 – 23.9). At 12 months hearing levels were significantly better in both the adenoidectomy, and the adenoidectomy with a unilateral tympanostomy tube group than in the watchful waiting group. Other comparisons did not show significant effects at 12 months. At 6 months, the mean hearing level was significantly better in all surgical groups as compared to the watchful waiting group. Hearing levels in the adenoidectomy only

Table 6.3. Average hearing levels during follow up, pooled over all three trials

	Adenoidectomy with unilateral or bilateral tympanostomy tubes	Unilateral or bilateral tympanostomy tubes	Watchful waiting
	N = 248, k = 3	N = 244, k = 3	N = 122, k = 1
6 months, mean HL dB (95% CI)	15.9 (14.8 – 17.1)	18.1 (16.9 – 19.3)	23.8 (21.8 – 25.8)
12 months, mean HL dB (95% CI)	17.0 (15.8 – 18.2)	20.5 (19.1 – 21.8)	20.2 (18.1 – 22.2)
18 months, mean HL dB (95% CI)	15.8 (14.6 – 16.9)	20.8 (19.3 – 22.4)	19.5 (17.4 – 21.7)
24 months, mean HL dB (95% CI)	15.0 (13.8 – 16.2)	19.5 (18.3 – 20.9)	18.8 (17.1 – 20.4)

Analyses were adjusted for study

Table 6.4. Hearing levels during follow up, pooled for the two studies that treated ears

	Adenoidectomy with unilateral tympanostomy tube	Adenoidectomy	Unilateral tympanostomy tube	Watchful waiting
	N ears = 90	N ears = 90	N ears = 101	N ears = 101
6 months, mean HL dB (95% CI)	14.6 (12.8 – 16.5)	18.6 (16.0 – 21.3)	15.1 (12.9 – 17.3)	23.9 (21.4 – 26.4)
12 months, mean HL dB (95% CI)	16.0 (14.3 – 17.8)	17.5 (15.3 – 19.6)	17.7 (15.4 – 20.0)	21.4 (18.9 – 23.9)

Analyses were adjusted for study

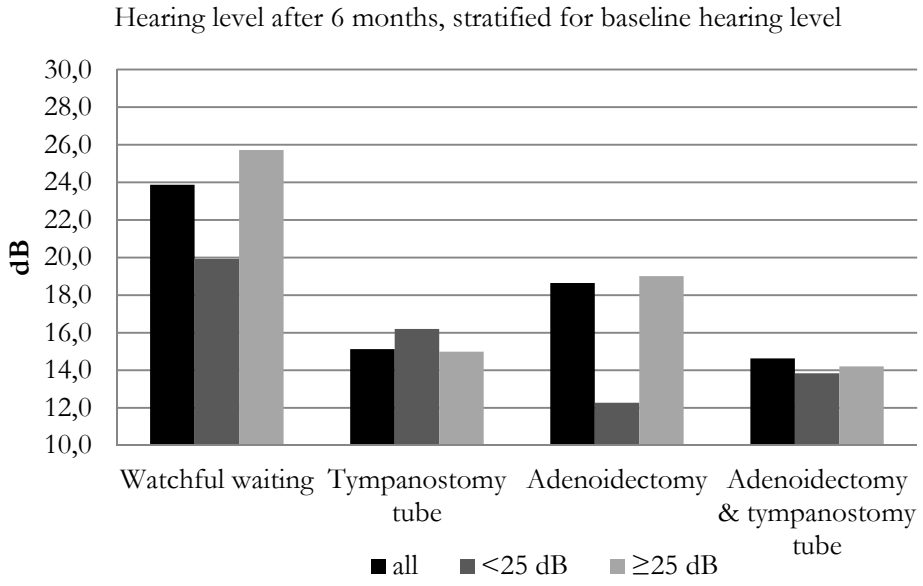
group were worse than in both the unilateral tympanostomy tube group and the adenoidectomy with an unilateral tympanostomy tube group. (*Table 6.4*).

Interaction between baseline patient characteristics and the effect on the outcomes

No significant interaction was found between any of the patient characteristics and the primary outcome hearing level at 12 months or the secondary outcomes at 18 or 24 months. At ear level (i.e. those treated with a tympanostomy tube in one ear using the untreated ear as comparator) there was a significant interaction ($p = 0.04$) between hearing level at 6 months and hearing level at baseline when this was dichotomized at 25 dB. Compared to watchful waiting, the effect of a unilateral tympanostomy tube alone or in combination with adenoidectomy was 6 dB better for children with a baseline hearing level of 25 dB or greater than for children with a baseline hearing level smaller than 25 dB. Compared to adenoidectomy alone, the effect of a unilateral

tympanostomy tube alone or in combination with adenoidectomy was 7 dB better in children with a baseline hearing level of 25 dB or greater than for children with a baseline hearing level smaller than 25 dB (*Figure 6.3*).

Figure 6.3. Stratified results regarding the interaction between baseline hearing level and treatment in the trials that randomized ears after 6 months follow up



Discussion

The pooled results show that, at 12 months, the mean hearing level of children treated with adenoidectomy with unilateral or bilateral tympanostomy tubes was 3.2 dB (95% CI 0.7 – 5.6) better than the hearing level in the watchful waiting group, and 3.5 dB (95% CI 1.7 – 5.2) better than in children treated with unilateral or bilateral tympanostomy tubes. This effect lasts up to 24 months after surgery. Patient characteristics did not modify the treatment effect for the primary outcome; hearing level at 12 months. However, at 6 months follow up a significant interaction between baseline hearing level (<25/≥25 dB) and treatment was found in those studies that randomised ears. A larger baseline hearing level resulted in a larger treatment effect.

The main strengths of our study were that, by re-analysing the data of three trials, we were able to include a relative large number of 567 children. This enabled us to more precisely estimate the main effect of adenoidectomy with or without tympanostomy tubes compared to watchful waiting or tympanstomy tubes alone. It also offered an opportunity to study subgroups of children that may benefit more from treatment with adenoidectomy with or without tympanostomy tubes.

Some potential limitations should also be discussed.

First, only 3 of the 5 eligible studies could be included in our meta-analysis. The other two studies did not report absolute hearing levels; one reported change scores only[4] and the other[28] reported the time with a hearing level of ≥20 dB during their two year follow up period. The conclusions of these studies were, however, in agreement with our results. We therefore believe that that inclusion of data from these trials would not have changed the results of our IPD meta-analysis.

Second, to study the pooled effect of the by ear and by child studies we used the binaural average mean hearing level, because hearing loss will affect a child and not an ear. This might, however, have underestimated the effect of the unilateral inserted tympanostomy tube.

Third, subgroups that benefitted more from treatment than others were only found in the studies that used a unilateral tympanostomy tube and randomised ears instead of children, and only at 6 months follow up. To be relevant for clinical practice, subgroups should preferably be found at both child and ear level and be persistent over time. A possible explanations for the fact that only studies that randomised ears showed a significant interaction with baseline hearing, may be the low number of children with a baseline hearing level of 25 dB or greater in the trial randomised at the child level. Consequently, the power of the subgroup analysis with a cut-off around 25 dB was larger in the analysis at the ear level. The adjustment for individual variance by analysing treatment effects within subjects, reducing measurement error might be another explanation. On the other hand, chance cannot be precluded either since the effect was only found at 6 months follow up, and only in 1 variable whereas we tested 8 subgrouping variables and their combinations.

Fourth, children with speech or language delays, behaviour and learning problems, Down's syndrome, or cleft palate, could not be studied in this IPD meta-analysis as these subgroups were excluded in the individual trials. The experience of many clinicians that these subgroups of children benefit more from treatment with adenoidectomy with tympanostomy tubes has not yet been evidenced in RCTs. As the

question whether to treat these children is very relevant for clinical practice, future trials studying these specific subgroups are justified.

Since the effect of adenoidectomy with tympanostomy tubes on hearing is small (3 dB hearing benefit after 12 months; pooled results), the question arises whether this benefit outweighs the potential adverse effects of adenoidectomy and tympanostomy tubes .[31-34] Furthermore, our findings suggest that tympanostomy tubes seem to improve hearing while present and patent in the short term (see *Figure 6.3*), whereas the combination with adenoidectomy appears to be associated with a more sustainable effect for up to 24 months (see *Table 6.3)*. This is consistent with the results of a Canadian-database study, that showed that the risk for re-insertion tympanostomy tubes was reduced by 50% in children who underwent the insertion of tympanostomy tubes with adjuvant adenoidectomy compared to those without the adjuvant adenoidectomy.[35]

In conclusion, adenoidectomy with tympanostomy tubes improved hearing up to 24 months. No clinically relevant subgroups of children with OME could be identified that benefit more than others from this treatment.

Funding

The study was funded by a grant from NHS HTA Project 10/124/01

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Appendix 6.1. Search strategies

CENTRAL	
#1	MeSH descriptor Adenoidectomy explode all trees
#2	MeSH descriptor Adenoids explode all trees with qualifier: SU
#3	adenoidectom* or adenotonsillectom* or adenotonsilectom* or adeno NEXT tonsillectomy* or adeno NEXT tonsilectom*
#4	(#1 OR #2 OR #3)
#5	MeSH descriptor Adenoids explode all trees
#6	adenoid* or adenotonsil*
#7	(#5 OR #6)
#8	MeSH descriptor Surgical Procedures, Operative explode all trees
#9	(surg*:ti or operat*:ti or excis*:ti or extract*: ti or remov*:ti or dissect*:ti or ablat*: ti or coblat*:ti or laser*:ti)
#10	(#8 OR #9)
#11	(#7 AND #10)
#12	(#4 OR #11)
#13	(nose OR nasal) NEAR (symptom* OR discharg* OR secret* OR obstruct*)
#14	rhinorrhea OR rhinorrhoea
#15	MeSH descriptor Nasal Obstruction explode all trees
#16	airway* AND obstruct*
#17	breath* AND impair*
#18	MeSH descriptor Otitis Media explode all trees
#19	middle NEXT ear NEXT (infect* OR inflam* OR disease*)
#20	otitis OR aom OR ome
#21	glue AND ear
#22	(#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23	(#12 AND #22)
PubMed	
#1	"Adenoidectomy"[Mesh]
#2	"Adenoids/surgery"[Mesh]
#3	adenoidectom* [tiab] OR adenotonsillectom* [tiab] OR adenotonsilectom* [tiab]OR "adeno tonsillectomy" [tiab]OR "adeno tonsilectom" [tiab]
#4	#1 OR #2 OR #3
#5	"Adenoids"/[Mesh]
#6	adenoid* [tiab] OR adenotonsil* [tiab]
#7	#5 OR #6
#8	"Surgical Procedures, Operative"[Mesh]
#9	"surgery"[Subheading]

Appendix 6.1. Continued

PubMed	
#10	surg* [tiab] OR operat* [tiab] OR excis* [tiab] OR extract* [tiab] OR remov* [tiab] OR dissect* [tiab] OR ablat* [tiab] OR coblat* [tiab] OR laser* [tiab]
#11	#8 OR #9 OR #10
#12	#7 AND #11
#13	#4 OR #12
#14	(nose [tiab] OR nasal [tiab]) AND (symptom* [tiab] OR discharg* [tiab] OR secret* [tiab] OR obstruct* [tiab])
#15	rhinorrhea [tiab] OR rhinorrhoea [tiab]
#16	"Nasal Obstruction"[Mesh]
#17	airway* [tiab] AND obstruct* [tiab]
#18	breath* [tiab] AND impair* [tiab]
#19	"Otitis Media"[Mesh]
#20	middle [tiab] AND ear [tiab] AND (infect* [tiab] OR inflam* [tiab] OR disease* [tiab])
#21	otitis [tiab] OR aom [tiab] OR ome [tiab]
#22	glue [tiab] AND ear [tiab]
#23	#14 OR #15 OR #16
EMBASE (Ovid)	
1	adenoidectomy/
2	(adenoidectom* or adenotonsillectom* or adenotonsilectom* or "adeno tonsillectomy*" or "adeno tonsilectom*").tw.
3	1 or 2
4	*Adenoid/
5	(adenoid* or adenotonsil*).ti.
6	4 or 5
7	(surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*).ti.
8	exp *Surgery/
9	8 or 7
10	6 and 9
11	3 or 10
12	nose obstruction/or rhinorrhea/
13	*airway obstruction/or *upper respiratory tract obstruction/
14	((nose or nasal) and (symptom* or discharg* or obstruct* or secret*)).tw.
15	(rhinorrhea or rhinorrhoea).tw.
16	(airway* and obstruct*).tw.
17	(breath* and impair*).tw.
18	exp Middle Ear Disease/

Appendix 6.1. Continued

EMBASE (Ovid)	
19	(middle and ear and (infect* or inflamm* or disease*)).tw.
20	(otitis or aom or raom or ome).tw.
21	(glue and ear).tw.
22	21 or 17 or 12 or 20 or 15 or 14 or 18 or 13 or 16 or 19
23	22 and 11
CINAHL (EBSCO)	
S1	(MH "Adenoidectomy")
S2	(MH "Adenoids/SU")
S3	adenoidectom* or adenotonsillectom* or adenotonsilectom* or "adeno tonsillectomy*" or "adeno tonsilectom*"
S4	(MM "Adenoids")
S5	TI adenoid* or adenotonsil*
S6	TI surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*
S7	(MH "Surgery, Operative")
S8	S6 or S7
S9	S4 or S5
S10	S8 and S9
S11	S1 or S2 or S3 or S10
Web of Science	
#1	TS=(adenoidectom* or adenotonsillectom* or adenotonsilectom* or "adeno tonsillectomy*" or "adeno tonsilectom*")
#2	TI=(adenoid* or adenotonsil*)
#3	TI=(surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*)
#4	#2 AND #3
#5	#1 OR #4
#6	TS=((nose or nasal) and (symptom* or discharg* or obstruct* or secret*))
#7	TS=(rhinorrhea or rhinorrhoea)
#8	TS=(airway* and obstruct*)
#9	TS=(breath* and impair*)
#10	TS=(middle and ear and (infect* or inflamm* or disease*))
#11	TS=(otitis or aom or raom or ome)
#12	TS=(glue and ear)
#13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	#5 AND #13

Appendix 6.1. Continued

	BIOSIS Previews / CAB Abstracts (Ovid)
1	(adenoidectom* or adenotonsillectom* or adenotonsilectom* or "adeno tonsillectomy*" or "adeno tonsilectom*").tw.
2	(adenoid* or adenotonsil*).ti.
3	(surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*).ti.
4	((nose or nasal) and (symptom* or discharg* or obstruct* or secret*)).tw.
5	(rhinorrhea or rhinorrhoea).tw.
6	(airway* and obstruct*).tw.
7	(breath* and impair*).tw.
8	(middle and ear and (infect* or inflamm* or disease*)).tw.
9	(otitis or aom or raom or ome).tw.
10	(glue and ear).tw.
11	3 and 2
12	11 or 1
13	8 or 6 or 4 or 7 or 10 or 9 or 5
14	13 and 12

Chapter 7

General discussion: How to put evidence into practice?

Chapter 7

The main aim of this thesis is to study several crucial steps in the research cycle from clinical questions to implementation in clinical practice. Several of these steps were illustrated by specific, research projects in the field of upper respiratory tract infections in children. The results of these separate projects were discussed in chapters 2-6. In this last chapter, we aim to highlight the process of putting research into practice from a broader perspective and discuss the role of the researcher, the funding agencies, and the journal editors in minimizing discrepancies between grant applications and publications and maximizing adherence to intentional, and funded, research ideas.

A major finding of this thesis is the discrepancy in primary outcome parameters and subgroup analyses between the grant application, trial registration, study report and published manuscripts in many studies (*Chapters 5.1 and 5.2).* Primary outcomes and subgroup analyses seem to appear and disappear along the way, often without any apparent reason. This selected reporting may not only affect interpretation of an individual study but also of any subsequent systematic review or meta-analysis including this study.[1-3] Since the direction and magnitude of the average effects as reported in meta-analyses guide clinical guidelines and consequently clinical decisions to further improve tailored care, publication of all results rather than a selection is essential.

Readers of scientific publications (such as physicians, health policy makers and patients) may not be aware of this phenomenon of selective reporting and therefore can not judge the clinical value of the reported result in the light of the intentional research idea for which the grant was awarded. This grant application has been critically reviewed by experts in the field who approved its methodology and clinical relevance. Research funding agencies therefore emphasize the importance of adherence to the grant proposal and protocol in their guidelines. They request that changes to the crucial parts of the study methods (e.g. outcome parameters or subgroup analyses) should be kept to a minimum, and if they do occur, they should be explicitly presented and the underlying reasons revealed.[4] At best, such amendments are made independently of the study findings. A statistically insignificant result certainly should not be a reason not to report an outcome, and vice versa should a statistically significant finding not be a reason to report a outcome or subgroup analysis that was not pre-specified. Our findings, however, suggest that most changes to primary outcomes and subgroup analysis are introduced to highlight the "most interesting" results, which may undermine the validity and clinical applicability of a

study. However, other reasons for discrepancies between grant applications and publications may not undermine the validity and applicability of the study, or may even improve it. These include lower event rates than anticipated, an a priori decision to publishing some of the results separately, and new evidence that invalidates the original primary outcome, or supports the use of a more appropriate outcome.

For example, we ourselves did not include all secondary outcomes of our trial on the effectiveness of adenoidectomy in children with upper respiratory tract infections as listed in the Dutch Trial Register (NTR968: ISRCTN03720485) in the manuscript of the main trial results submitted to the British Medical Journal (BMJ) (*Chapter 4.1,*[5]). Its reason being an a priori decision to report some of the outcomes in separate manuscripts to limit the scope of the major report to outcomes most relevant for practicing physicians. However, we failed to acknowledge this in the manuscript submitted to the BMJ. Such a comment was added only after the BMJ editor pointed out the discrepancy between the secondary outcomes in the submitted manuscript and the trial registry.

Since most patient oriented research is performed to improve clinical decision making, performing studies as planned and publishing all of its results is important. Acknowledgement of and reasons for changes in essential design and analytical features is also important. Researchers, funding agencies, reviewers and editors should be aware of this during each step, i.e. from the design of a new study up to publication. Several measures could be taken by researchers, funding agencies, and editors to minimize discrepancies between grant applications and publications, and subsequently maximize the adherence to the intentional research ideas. Researchers could 1) limit of the number of (primary) outcomes, 2) follow publication recommendations, and 3) enable data sharing. Funding agencies could register the study design of their approved grants, and editors could 1) ask for co-submission of the approved grant application and the protocol, and 2) enable authors to report all outcomes (electronically).

Each of these possible measures along the pathway from grant application to publication will be elaborated on below (see also *Table 7.1*).

1. Researchers: Limit the number of (primary) outcomes

In the grant applications we studied the number of primary outcomes ranged from 1 to 7. Secondary outcomes were even more numerous. The higher the number of outcomes included in a grant application or protocol, the greater the chance that they were reported selectively, affecting the interpretation of study results. Researchers should therefore reduce the number of (primary) outcomes and include only the most clinically relevant outcome as the primary outcome. Obviously, sample size calculations should be based on that outcome.

2. Funding agencies: Register approved grant applications

In 2004 the International Committee of Medical Journal Editors declared that researchers had to register their protocols of randomised controlled trials in a public repository at inception.[6] For other types of research no such registration is obligatory. However, many projects are voluntarily registered, and mandatory registration of observational studies is being discussed.[7] The advantages of study registration are clear. With trial registration every trial's existence will be known, providing research transparency and precluding unnecessary duplication of studies. Furthermore, it may prevent non-reporting of negative studies. Nevertheless, non-reporting of complete trials and selective reporting of individual outcomes still occurs. Trial registration at least provides the ability to adequately address this publication bias and selective reporting.[1, 8-11]

The studies included in this thesis showed that already at the trial registration stage outcomes and subgroups as listed in the approved grant applications are adapted. Registration of the approved grant application along with the trial protocol could therefore be helpful to a) ensure that the intentional research ideas become publically available and b) to make clear which adaptations are made between grant approval and the actual study protocol. The reasons for this adaptations (e.g. progressive insight, less resources provided which requires adaptation of the original study design, and logistic problems) could be added as well.

Currently, only structured abstracts (i.e. restricted items) of protocols are registered in trial registries to avoid issues of intellectual property, copyright and competition. Since these pros en cons also apply to registration of approved grant applications, we suggest to register only a structured summary of the approved application.

To ensure transparency the responsibility for this registration could be best assigned to the funding agencies rather than to the researchers.

3. Researchers: Follow publication guidelines

In recent years, reporting guidelines, of which CONSORT, STROBE, STARD and QUORUM are well-known examples,[8-12] have been developed and updated to improve reporting practices.[13-17] These guidelines specify a minimum set of items required to clearly and transparently describe what was done and found in the study.[18-21] Also issues that might introduce bias are reflected in these guidelines. Extension of these guidelines to cover some of the issues mentioned above, pertaining to the process from grant application up to published report, could further improve the reporting of study findings. For example, adding an item that researchers should report all outcomes (primary, secondary and subgroup analyses) as *approved in their grant application*, irrespective of the statistical significance of the results seems useful. Another valuable item that could be added is the recommendation to report all adaptations made to essential features of the grant application (e.g. separate reporting of secondary outcomes, new evidence that support the use of a more appropriate outcome).

4. Editors: Ask for co-submission of the approved grant application and protocol

While researchers are responsible for performing their study as planned, journal editors should ensure integrity of the peer-reviewed literature, as peer review provides manuscripts with a stamp of approval.[22, 23] Currently, some mostly higher impact journals request authors of trials to submit the study protocol with their manuscript. Editors and reviewers use these to ensure that the outcomes listed in the manuscript are in agreement with those specified in the trial protocol and registry.

When *all* journals request co-submission of approved grant application (or the original protocol for non-funded projects) for all types of studies in addition to protocols, editors and reviewers will even have better insight in the complete process from the intentional research ideas up to the manuscript submitted for publication. Obviously, this requires issues of confidentiality (including intellectual property) to be dealt with beforehand. To reduce the additional workload of reviewers and editors, a checklist could be developed by which researchers provide their initial primary and secondary outcomes, pre-specified subgroup analyses, and reasons for adaptations.

5. Editors: Enable authors to report all outcomes (electronically)

Sometimes editors and reviewers advise researchers to exclude certain outcomes because of word limits, and as such unintentionally introduce selective reporting.

With the vast majority of journals now being available online, it should be possible to publish additional information as online supplements. The advantage of reporting research in such a complete manner, is evident as readers can make better judgements regarding the clinical relevance of the findings and potential bias.[13] There is, however, also a disadvantage of reporting all outcomes in one publication; readers may get lost in the large number of findings presented. Authors could therefore acknowledge that some of the outcomes will be reported in separate manuscripts to limit the scope of the major report to those outcomes that are clinically most relevant.

6. Researchers: Enable data sharing

The rapid growth of the internet and related technologies has already had an tremendous impact on all steps of clinical research, from design up to scientific publication.[24] It has provided the opportunity for research registration, enabling others to check the registries before initiating a new study, and it decreases the chance of non-reporting of negative trials. Furthermore, online data collection facilitates the conduct of studies, and online publication of the main study results and relevant additional information is now possible. It has also been suggested that depositing research data into public repositories will increase the quality of publications,[13, 24-26] with the ability to review the quality of the data and the encouragement to share data with other researchers as the most important reasons.[24] In combination with the registration of grant applications, the online publication of (raw) research data will indeed bring researchers to publish all results as described in the grant application. However, free access to all raw study data could lead to unintended confusion for decision makers, and potential damage to studies. First, unfettered post hoc analyses could lead to confusion; which analyses should policy makers, practitioners, the authors of systematic reviews and the public rely on. Second, knowing that their individual data will be posted publicly might deter some people from taking part in trials. Even with re-assurance that data will not be identifiable, some people may worry about the fact that anyone could access the trial data and read their personal information (even if this is not actually the case). In our opinion research data are a public good, and like the Organisation for Economic Co-operation and Development (OECD) recommends,[27] should be openly and completely available . This does, however, require careful management of the data sharing process and proper handling of the data itself. Our preference therefore would be for governments and others to facilitate sharing of data between bona fide researchers, and potentially developing a

data repository or clearing house, with due consideration given to the logistic and resource implications of such an approach.

Table 7.1 Measures that could be taken to minimize discrepancies between grant applications and publications, and maximize adherence to the intentional research ideas

Step	Measures that could be taken	Who is responsible?
Study design	- Limit the number of (primary) outcomes	Researchers
Registration	- Register structured abstracts of approved grant applications	Funding agencies
Publication	- Follow publication guidelines	Researchers
	- Acknowledge that some of the outcomes will be reported in separate manuscripts to limit the scope of the major report to those outcomes that are clinically most relevant.	
	- Ask for co-submission of the approved grant application or the first version of the protocol for non-funded projects) and the protocol for all types of studies.	Editors
	- To reduce the additional workload of reviewers and editors, a checklist could be developed in which researchers provide their initial primary and secondary outcomes, pre-specified subgroup analyses, and reasons for adaptations.	
	- Enable authors to report all outcomes (electronically)	
	- Update guidelines with adding two items:	Publication
	1. Report all outcomes (primary, secondary and subgroup analyses) as *approved* in their *grant application*, irrespective of the statistical significance of the results seems useful.	guideline developers
	2. Report all adaptations made to essential features of the grant application (e.g. postponing reporting on secondary outcomes, changes made with respect to improved insight).	
After publication	- Enable data sharing	Researchers

In conclusion, we have shown that selective reporting occurs on a large scale. This may lead to incorrect interpretation of study findings and subsequent non-evidence based decision making. Adherence to intentional research ideas is therefore important. The proposed measures will increase research transparency and researchers' awareness of research integrity. With shared effort we should be able to apply higher-quality evidence in daily practice.

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Chapter 8

Summary
Samenvatting
Dankwoord
Curriculum vitae

Chapter 8

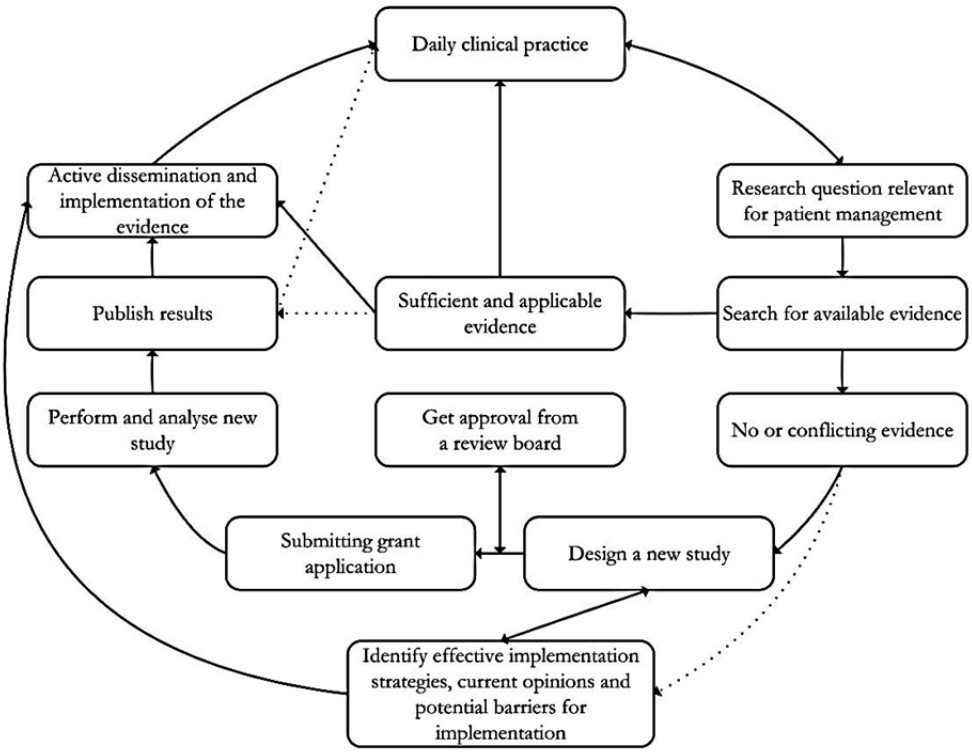
Summary

8

Chapter 8

Transfer of evidence into practice is often slow and therefore remains an important challenge. Factors influencing this process include awareness and agreement with available evidence, feelings about the applicability of the evidence to one's own patients and pressure from patients to start or refrain from a particular treatment. The best chance of bridging the gap between health research and implementation in daily clinical practice is created by optimizing all steps of the research cycle (*Figure 8.1*).

Figure 8.1 The clinical research cycle



Potential barriers in this process include skipping some of these essential steps, focussing on an irrelevant research question, ignoring the available evidence, making unrealistic assumptions, not involving patients in defining relevant outcomes, presenting a grand mean which is not applicable to individual patients, and lack of notion of the most effective implementation strategies.

In this thesis we use the example of management of children with upper respiratory tract infections (URTI) to study several of the crucial steps in the research cycle.
With URTIs, like rhinitis and otitis media, being so common in children, national and international variation in its management strategies, and available evidence regarding preventive and therapeutic management strategies accumulating, it served as a relevant and illustrative example of the steps that could be taken from the design of a new study up to successful implementation of its results.

In *chapter 2* we analysed which strategies are used to promote the uptake of evidence-based interventions in children with URTI in daily practice. (*Figure 8.1*: "Identify effective implementation strategies")
We identified ten studies, mostly aiming at changing antibiotic prescribing behaviour in children with acute otitis media (AOM). All strategies used (i.e. computer interventions, educational sessions with or without education materials, collaborative development of guidelines and a training video in combination with a risk factor checklist) were effective in changing health care professionals' practice regarding children with URTI. Multifaceted and computer strategies appear to work best. Computer interventions reduced antibiotic prescribing by 4% to 34%, and increased guideline compliance by 41%. Educational sessions combined with education materials reduced inappropriate antibiotic prescription by 2% to 17% and increased knowledge of compliance enhancing strategies by 28% to 29%. Collaborative guideline development combined with educational materials reduced inappropriate antibiotic prescription by 24% to 40%. Finally, by combining a training video and a risk factor checklist appropriate referrals by the GP to the otolaryngologist increased by 37%. Since the costs associated with these interventions were not explicitly mentioned in the articles, we could not draw any conclusions on their cost-effectiveness. We concluded that multifaceted and computer strategies appeared to be most effective to promote the uptake of evidence into practice in the area of URTI in children.

In *chapter 3* we answered the question 'What is the balance between costs and effects of pneumococcal conjugate vaccinations (PCV) against AOM in children?' (*Figure 8.1*: "Search for available evidence")
While PCV have shown to be highly effective against invasive pneumococcal disease, their potential effectiveness against AOM is becoming a major economic driver for

implementing these vaccines in national immunization programmes. However, the relationship between the costs and benefits of available vaccines in AOM remains a controversial topic. We therefore systematically reviewed the literature on the cost effectiveness of PCV against AOM in children and identified a total of 21 studies. The quality of these studies was moderate to good. The cost per AOM episode averted varied from € 168 to € 4,214, and assumed incidence rates varied from 20,952 to 118,000 per 100 000 children aged 0–10 years. Assumptions regarding direct and indirect costs varied between studies. The assumed vaccine efficacy of the 7-valent pneumococcal CRM197-conjugate vaccine was mainly adopted from two trials, which reported 6–8% efficacy. Others however only included AOM episodes caused by serotypes included in the vaccine, which resulted in efficacy rates varying from 12% to 57%. Costs per AOM episode averted were inversely related to the assumed incidence rates of AOM and to the estimated costs per AOM episode. The median costs per AOM episode averted tended to be lower in industry-sponsored studies. We concluded that key assumptions regarding the incidence and costs of AOM episodes have major implications for the estimated cost effectiveness of PCV against AOM. Uniform methods for estimating direct and indirect costs of AOM should be agreed upon to reliably compare the cost effectiveness of available and future pneumococcal vaccines against AOM.

In *chapter 4* we presented the results of our randomised controlled trial on the (cost-) effectiveness of adenoidectomy as compared to watchful waiting in children with recurrent URTIs. (*Figure 8.1*: "Design a new study")
In this open randomised controlled trial, 111 children aged 1-6 years selected for adenoidectomy for recurrent URTI were included. They were randomised to a strategy of immediate adenoidectomy with or without myringotomy or a strategy of initial watchful waiting, and were monitored for 2 years. The primary outcome was the number of URTI episodes per person year during the total follow up. Secondary outcomes were days with URTI per person year, prevalence of URTI, middle ear complaints with fever days with fever, health related quality of life and costs.
The clinical results of the trial were presented in *chapter 4.1*. During the 2 years follow-up, children in the adenoidectomy group had 7.91 URTI episodes per person year and children in the watchful waiting group 7.84 episodes (incidence rate difference 0.07, 95% confidence interval −0.70 to 0.85). We found no relevant differences for days of URTI or middle ear complaints with fever, nor for health related quality of life. The

prevalence of URTI decreased over time in both groups. Children in the adenoidectomy group had significantly more days with fever than the children in the watchful waiting group (difference 3,51; 95% confidence interval 2,33 to 4,69). In addition to the intention-to-treat analysis, we also performed two sensitivity analyses: a per protocol analysis in which we excluded the 23 children (40%) in the watchful waiting group who went on to have surgery, and an as treated analysis in which we added the children in the watchful waiting group who underwent surgery to the adenoidectomy group. These analyses yielded the same results as the intention-to-treat analysis regarding our primary outcome. For example, the incidence rate difference for episodes of URTI was -0.13 (95% CI -1.02 to 0.77) for the per protocol analysis and -0.23 (95% CI -1.08 to 0.62) for the as treated analysis. Two (4%) children in the adenoidectomy group experienced an adverse event: one child was admitted to hospital for an asthma exacerbation during follow-up and in one child a primary tooth was broken when the mouth gag was inserted. One (2%) child in the watchful waiting group who underwent adenotonsillectomy during follow-up was admitted to hospital for a postoperative haemorrhage.
The cost associated with both treatment strategies were compared in *chapter 4.2*. The median total of direct and indirect costs in the adenoidectomy and watchful waiting group were € 1,385 (US$ 1,995) and € 844 (US$ 1,216) per patient, respectively, i.e. adenoidectomy implied 1.6 times higher costs (64% increase). The extra costs in the adenoidectomy group were primarily attributable to surgery and visits to the otorhinolaryngologist. Other costs did not differ significantly between the groups.
We therefore concluded that in children selected for adenoidectomy for recurrent URTI, immediate adenoidectomy results in an increase in costs, whereas it confers no clinical benefit over an initial watchful waiting strategy.

In *chapter 5* we studied the process from design to publication of clinical research in general in all projects awarded by the Health Care Efficiency Research Program of the Netherlands Organization for Health Research and Development (ZonMw) (i.e., the Dutch "National Institutes of Health") between 2001 and 2006. (*Figure 8.1*: "Submitting grant application" and "Publish results")
In *chapter 5.1* we compared the primary outcomes reported in the grant application, the trial registry, and their related publications. Agreement between primary outcomes in trial registries, final reports and scientific publications as compared to those in the grant applications were 68%, 70% and 37%. In 22 of the 62 (36%) projects that

resulted in a scientific publication, a primary outcome specified in the grant application was not included in the publication. In general, no explanation for the discrepancies was provided. Agreement between grant application and scientific publication was higher for high (45%) than for low (29%) impact factor journals (RD 16% (95% confidence interval -8% ; 40%). The chance for an original primary outcome to be included in the scientific publication was 2.8 times higher (95% confidence interval 1.2 ; 6.6) for outcomes that were statistically significant. In *chapter 5.2* we compared the subgroup analyses as reported in grant applications with those presented in the related publications. Subgroups were mentioned in 49 (62%) grant applications and in 53 (67%) publications. In 20 of the 79 projects (25%), the publications were completely in agreement with the grant application; that is, subgroups that were pre-specified in the grant application were reported and no new subgroup analyses were introduced in the publications. Of the 149 pre-specified subgroups, 46 (31%) were reported in the final report or scientific publications, and 143 of the 189 (76%) reported subgroups were based on post-hoc findings. For 77% of the subgroup analyses in the publications, there was no mention of whether these were pre-specified or post hoc. Justification for subgroup analysis and methods to study subgroups were rarely reported.
We concluded that there is a large discrepancy between grant applications and publications regarding both primary outcomes and subgroup analyses, which is biased favouring statistical significance. As publication of all intended outcomes is the ethical obligation of researchers to the patients participating in their studies, we felt that publication guidelines need to be updated to include the statement that all outcomes specified in the grant application should be fully reported.

In *chapter 6* we presented the results of an Individual Patient Data meta-analysis pooling the original data of 3 trials on the effectiveness of adenoidectomy with or without tympanostomy tubes in children with otitis media with effusion (OME). (*Figure 8.1*: "Search for available evidence")
With this meta-analysis we aimed to identify subgroups of children with OME who will most likely benefit from adenoidectomy and as such facilitate clinical decisions about surgery in OME. We performed this meta-analysis using individual patient data of 567 children aged 0 to 9 years. The primary outcome was mean hearing level at 12 months, and the secondary outcomes were hearing levels at 6, 18 and 24 months. Subsequently, we studied whether the effect of the intervention on hearing was

modified by specific patient characteristics, such as baseline hearing level. At 12 months follow up, the mean hearing level of children treated with adenoidectomy with (either a unilateral or bilateral) tympanostomy tubes was 3.2 dB (95% CI 0.7 – 5.6) better than the hearing level in the watchful waiting group, and 3.5 dB (95% CI 1.7 – 5.2) better than in children treated with only unilateral or bilateral tympanostomy tubes. The differences between the groups were also statistically significant at 6, 18 and 24 months follow up. For the primary outcome (hearing level at 12 months) the effect of adenoidectomy with or without tympanostomy tubes was not modified by the patient characteristics studied (interaction term p-values >0.05).
We concluded that adenoidectomy combined with tympanostomy tubes improved hearing up to 3 dB for up to 24 months. No clinically relevant subgroups of children with OME could be identified that benefit more than others from this treatment.

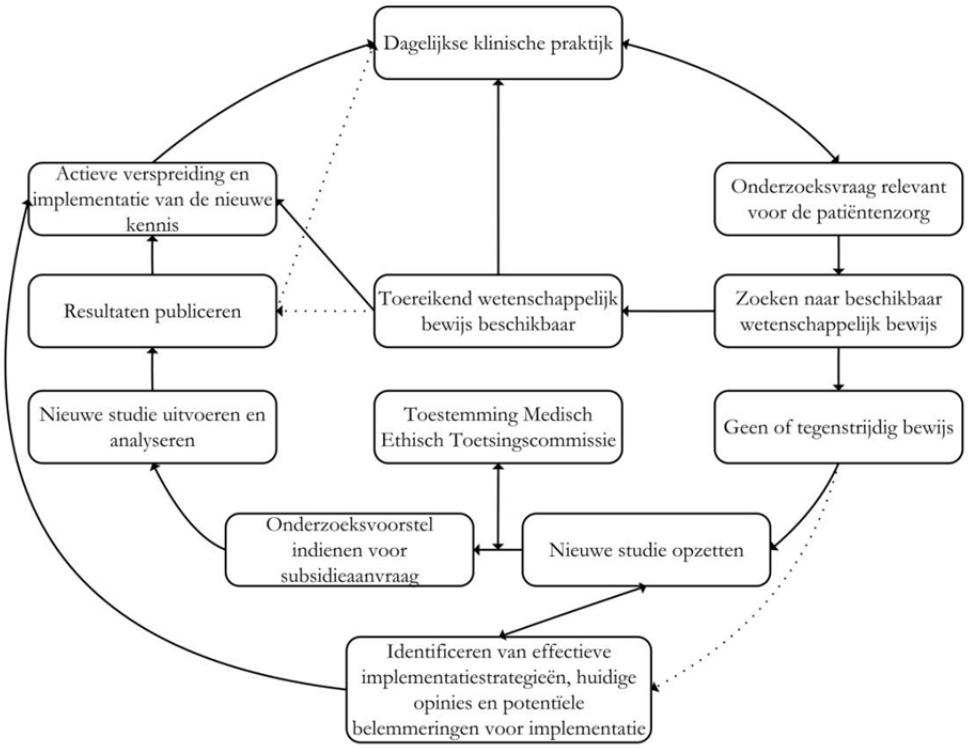
In *chapter 7*, we discussed the striking discrepancy in primary outcome parameters and subgroup analyses between grant applications, trial registries, and publications in more detail. We provided some recommendations to minimize these discrepancies and subsequently maximize the adherence to the intentional research ideas. Researchers could 1) limit of the number of (primary) outcomes, 2) follow publication recommendations, and 3) enable data sharing. Funding agencies could register the study design of their approved grants, and editors could 1) ask for co-submission of the approved grant application and the protocol, and 2) enable authors to report all outcomes (electronically).
The proposed measures will increase research transparency and researchers' awareness of research integrity. With shared effort we should be able to apply higher-quality evidence in daily practice.

Samenvatting

Chapter 8

Het vertalen van kennis verkregen uit klinisch wetenschappelijk onderzoek naar de dagelijkse klinische praktijk gaat niet vanzelf. Factoren die een rol spelen bij de implementatie betreffen de kennis van artsen en beleidsmakers van de resultaten van het uitgevoerde onderzoek, of zij zich kunnen vinden in deze resultaten en of zij vinden dat de deelnemers aan het onderzoek representatief zijn voor hun eigen patiënten. Om de kloof tussen wetenschap en praktijk te overbruggen dienen onderzoekers er zorg voor te dragen dat zij alle stappen van de wetenschappelijke onderzoekscyclus (*Figuur 8.2*) optimaal inzetten.

Figuur 8.2 De wetenschappelijke onderzoekscyclus



In dit proefschrift worden diverse stappen van het klinisch wetenschappelijk onderzoek beschreven voor bovenste luchtweginfecties (BLWI) bij kinderen. We hebben voor dit voorbeeld gekozen omdat het een van de meest voorkomende aandoeningen bij jonge kinderen is, grote nationale en internationale verschillen in

behandelstrategieën kent, de kennis over preventieve en curatieve maatregelen groot is en er nog steeds veel onderzoek naar gedaan wordt.

In *hoofdstuk 2* presenteren wij de resultaten van een literatuurstudie waarin we gezocht hebben naar de meest efficiënte strategieën om professionals de resultaten van klinisch wetenschappelijk onderzoek bij kinderen met bovenste luchtweginfecties in de praktijk toe te laten passen. (*Figuur 8.2*: "Zoeken naar beschikbaar wetenschappelijk bewijs") In het onderzoek konden de resultaten van 10 studies worden meegenomen, waarvan de meesten zich richtten op het voorschrijven van antibiotica bij acute middenoorontstekingen (acute otitis media, AOM). In de studies zijn diverse strategieën onderzocht; computerondersteuning, nascholingsbijeenkomsten, informatiemateriaal, het gezamenlijk ontwikkelen van richtlijnen, trainingsvideo's en checklijsten, of combinaties hiervan. Het bleek dat alle onderzochte methoden leidden tot een effectieve gedragsverandering bij de professionals. Gecombineerde implementatiestrategieën (bijvoorbeeld een trainingsvideo in combinatie met informatiemateriaal) en strategieën waarbij gebruik gemaakt wordt van computerondersteuning blijken het beste te werken. Gegevens over de kosten van de onderzochte methoden waren helaas niet beschikbaar waardoor over de kosteneffectiviteit geen uitspraak gedaan kon worden.

In *hoofdstuk 3* presenteren wij de resultaten van een tweede literatuurstudie. Wij onderzochten de kosteneffectiviteit van pneumokokkenvaccinaties ter preventie van AOM. (*Figuur 8.2*: "Zoeken naar beschikbaar wetenschappelijk bewijs") In ons onderzoek konden wij de resultaten van 21 studies vergelijken. De resultaten laten zien dat de kosten per voorkomen AOM episode sterk variëren tussen de diverse gepubliceerde studies (€ 168 - € 4.214 per voorkomen episode). De kosteneffectiviteit hangt sterk af van een aantal factoren, zoals de veronderstelde incidentie, de kosten per episode en het aantal episodes dat door het vaccin wordt voorkomen. Om de kosteneffectiviteit van huidige en toekomstige vaccins tegen AOM op een betrouwbare manier met elkaar te vergelijken, zijn dus uniforme methoden nodig voor het schatten van de incidentie van AOM en de directe en indirecte kosten per episode.

In *hoofdstuk 4* worden de resultaten beschreven van de NOA studie (Nederlands Onderzoek Adenotomie). In deze studie onderzochten we of kinderen met recidiverende bovenste luchtweginfecties baat hebben bij het knippen van de

neusamandel (adenotomie). (*Figuur 8.2*: "Nieuwe studie opzetten") Aan het onderzoek deden 111 kinderen mee in de leeftijd van 1-6 jaar die volgens de dagelijkse praktijk in aanmerking kwamen voor adenotomie vanwege recidiverende bovenste luchtweginfecties. Zij werden door middel van loting verdeeld (gerandomiseerd) over twee groepen; bij één groep werd de neusamandel binnen 6 weken geknipt, bij de kinderen in de andere groep werd afgewacht. De kinderen werden 2 jaar lang gevolgd. De ouders van de kinderen hielden tijdens deze 2 jaar een dagboek bij waarin bovenste luchtwegklachten werden genoteerd, evenals het verzuim van kinderdagverblijf of school, doktersbezoeken, medicatiegebruik en andere kosten vanwege bovenste luchtweginfecties. Met een speciale oorthermometer maten de ouders dagelijks de temperatuur bij hun kind. De belangrijkste uitkomstmaat was het aantal bovenste luchtweginfecties per persoonsjaar gedurende de totale follow-up. Andere uitkomstmaten waren het aantal dagen met een bovenste luchtweginfectie, dagen met koorts, episoden met middenoorklachten en koorts, dagen verzuim van kinderdagverblijf of school, prevalentie van bovenste luchtweginfecties, gezondheidsgerelateerde kwaliteit van leven en de gemaakte kosten. De klinische resultaten worden beschreven in *hoofdstuk 4.1*. De kinderen in de adenotomie-groep hadden 7,91 bovenste luchtweginfecties per persoonsjaar en degenen in de afwachtend-beleidgroep 7,84 (verschil: 0,07; 95% betrouwbaarheidsinterval: -0,70 tot 0,85). De prevalentie van bovenste luchtweginfecties nam in beide groepen in gelijke mate af gedurende de twee jaar dat de kinderen gevolgd werden. Ook vonden we geen relevante verschillen tussen beide groepen voor wat betreft het aantal dagen met een bovenste luchtweginfectie, middenoorklachten met koorts, verzuim van kinderdagverblijf of school en gezondheidsgerelateerde kwaliteit van leven. Kinderen in de adenotomie-groep hadden meer dagen koorts (20,00 per persoonsjaar) dan degenen in de afwachtend-beleidgroep (16,49) (verschil 3,51; 95% betrouwbaarheidsinterval 2,33 tot 4,69.) Tijdens het onderzoek werden 10 kinderen (19%) uit de adenotomie-groep nogmaals geopereerd en werd bij 23 kinderen (40%) uit de afwachtend-beleidgroep alsnog een chirurgische interventie uitgevoerd. Sensitiviteitsanalyses waarbij de cross-overs uit de analyse werden gelaten, of werden geanalyseerd in de adenotomie-groep veranderden de resultaten niet. Twee kinderen hadden een complicatie die samenhing met de operatie. De kosten van beide strategieën worden beschreven in *hoofdstuk 4.2*. Tijdens de twee jaar dat de kinderen gevolgd werden, waren de kosten per kind in de adenotomie-groep € 1,385, en in de afwachtend-beleidgroep € 844. De kosten in de adenotomie-groep waren dus ruim

anderhalf keer zo hoog als die in de afwachtend-beleidgroep. Adenotomie lijkt dus geen klinisch relevant voordeel te bieden ten opzichte van een afwachtend beleid, maar brengt wel hogere kosten met zich mee.

In *hoofdstuk 5* laten wij aan de hand van 79 door ZonMw gesubsidieerde projecten zien wat er gebeurt in de periode tussen het verstrekken van een subsidie voor het onderzoek en de uiteindelijke publicatie van de resultaten in de wetenschappelijke tijdschriften. (*Figuur 8.2*: "Onderzoeksvoorstel indienen voor subsidieaanvraag" en "Resultaten publiceren"). In *hoofdstuk 5.1* hebben wij de primaire uitkomsten die genoemd werden in het onderzoeksvoorstel waarvoor de subsidie verkregen was vergeleken met de primaire uitkomsten in de internationale online beschikbare trialregistraties en de uiteindelijke publicaties. We vonden 68% overeenstemming tussen de primaire uitkomsten in de online beschikbare trialregistraties en het onderzoeksvoorstel, en 37% overeenstemming tussen de publicaties en het onderzoeksvoorstel. In meer dan een derde van de projecten werd (één van) de primaire uitkomst(en) niet gerapporteerd in de publicatie. Over het algemeen werd geen verklaring gegeven voor de discrepantie tussen het onderzoeksvoorstel en de gerapporteerde uitkomsten. In wetenschappelijke tijdschriften met een hogere Impact Factor (IF; de betere tijdschriften) was de overeenkomst tussen de onderzoeksvoorstellen en de publicatie groter dan in de tijdschriften met een lagere IF. De kans dat een statistisch significante uitkomst gerapporteerd werd in het wetenschappelijke artikel was bijna 3 keer groter dan de kans dat een niet significante uitkomst werd vermeld. In *hoofdstuk 5.2* onderzochten wij dezelfde projecten, maar dan voor subgroepanalyses. 62% van de onderzoeksvoorstellen en 67% van de wetenschappelijke publicaties rapporteerden subgroepanalyses. In slechts 25% van de projecten was er overeenstemming tussen de subgroepen die genoemd werden in het onderzoeksvoorstel en de publicaties. Van alle subgroepanalyses die genoemd werden in de onderzoeksvoorstellen werd 31% uiteindelijk gerapporteerd. Van de gerapporteerde subgroepen was 76% gebaseerd op een post-hoc bevinding; deze subgroepen werden dus niet genoemd in het onderzoeksvoorstel, maar zijn later aan het onderzoek toegevoegd. Net als bij de primaire uitkomsten, werd ook bij de subgroepanalyses zelden een verklaring gegeven voor de discrepanties tussen het onderzoeksvoorstel en de publicatie.
Voor primaire uitkomsten en voor subgroepanalyses vonden wij grote discrepanties tussen onderzoeksvoorstellen en de publicaties waarin de resultaten van de studies

beschreven worden. De discrepanties waren vaak te herleiden tot het wel of niet statistisch significant zijn van de resultaten.

In *hoofdstuk 6* beschrijven wij de resultaten van een individuele patiënten data meta-analyse, waarin de gegevens van 576 kinderen uit drie eerdere onderzoeken werden samengevoegd. (*Figuur 8.2*: "Zoeken naar beschikbaar wetenschappelijk bewijs") Doel van dit onderzoek was om te kijken of er subgroepen van kinderen met vocht achter het trommelvlies (otitis media met effussie, OME) zijn, die meer of juist minder baat hebben van adenotomie met of zonder trommelvliesbuisjes. De kinderen varieerden in leeftijd van 0 tot 9 jaar. De primaire uitkomst was het gehoorverlies na 12 maanden. Secundaire uitkomsten waren het gehoorverlies na 6, 18 en 24 maanden. Na 12 maanden was het gehoor bij kinderen die een adenotomie ondergingen in combinatie met het plaatsen van (een) trommelvliesbuisje(s) 3.2 dB (95% betrouwbaarheids-interval 0.7 – 5.6) beter dan bij kinderen met een afwachtend beleid, en 3.5 dB (95% betrouwbaarheidsinterval 1.7 – 5.2) beter dan bij kinderen die alleen (een) trommelvliesbuisje(s) kregen. De verschillen tussen de groepen waren ook significant na 6, 18 en 24 maanden. Voor de primaire uitkomst (gehoorverlies na 12 maanden) werden geen subgroepen van kinderen gevonden die meer of minder baat hadden bij adenotomie met buisjes.

In *hoofdstuk 7* geven wij een nadere beschouwing op de meest opvallende bevinding uit dit proefschrift; de discrepantie tussen onderzoeksvoorstellen en wetenschappelijke publicaties voor wat betreft primaire uitkomsten en subgroepanalyses. Om dergelijke discrepanties in de toekomst te voorkomen, wat ons inziens vanuit ethisch perspectief wenselijk is, presenteren wij in dit hoofdstuk enkele aanbevelingen die bij kunnen dragen aan het verkleinen van de discrepantie. Zo adviseren wij onderzoekers om 1) het aantal (primaire) uitkomsten te beperken tot de klinisch meest relevante, 2) publicatierichtlijnen te volgen en 3) het delen van hun data met andere onderzoekers mogelijk te maken. Subsidiegevers kunnen de door hen gehonoreerde onderzoeksvoorstellen online registeren, en redacteuren van wetenschappelijke tijdschriften zouden onderzoekers 1) moeten vragen om hun onderzoeksvoorstel mee te sturen met het artikel dat zij aanbieden ter publicatie en 2) de mogelijkheid moeten geven om al hun uitkomsten te rapporteren (elektronisch).
Alleen middels gezamenlijke inspanningen is het mogelijk om hoogwaardige wetenschappelijke kennis in de dagelijkse praktijk te incorporeren.

Chapter 8

Dankwoord

Chapter 8

Als laatste geschreven, als eerste gelezen: het dankwoord van een proefschrift.
Na jaren bezig geweest te zijn met mijn onderzoeken en het schrijven van wetenschappelijke artikelen volgt hieronder een heel andere tekst. Misschien wel de belangrijkste uit het hele proefschrift. Wellicht ook de moeilijkste, want hoe krijg je goed op papier wat je eigenlijk wilt zeggen. Dat is in de wetenschappelijke artikelen al een hele kunst, maar wanneer het om persoonlijke zaken gaat is het een nog grotere uitdaging.

Als eerste wil ik mijn promotoren en co-promotor bedanken die mij de kans gegeven hebben om de 's' van de 'drs.' af te halen.

Prof. dr. A.W. Hoes, geachte promotor, beste Arno, ik heb grote bewondering voor het feit dat je, ondanks je drukke agenda, altijd wist waar ik mee bezig was. Mocht het je een keer niet gelukt zijn om alle stukken voor een bespreking te lezen, dan deed je dat ter plekke en was ook dan in staat om de kritieke punten uit de stukken te halen. Menigmaal heb je, zoals je dat zelf pas zo mooi omschreef 'consensus tussen de dames' weten te bereiken. Ik ben blij met jouw inbreng en kritische noten. Door jouw kennis en kunde werd ik aan het denken gezet en zijn de artikelen in dit proefschrift geworden zoals ze zijn.

Prof. dr. A.G.M. Schilder, geachte promotor, beste Anne, jouw gedrevenheid in het kinder-KNO-onderzoek werkt aanstekelijk. Daarnaast ben je in staat om niet alleen oog te hebben voor het werk, maar ook voor de persoon erachter. Dat waardeer ik enorm. Door jouw manier van werken "het kan altijd beter", vond ik het vaak spannend om stukken naar je op te sturen. Die kwamen namelijk meestal behoorlijk rood terug, maar wel vaak met de opmerking 'Het wordt prachtig!' of 'Mooi!'. Dat laatste moest ik dan zelf op zo'n moment nog wel in gaan zien, maar het was waar; het zijn mooie stukken geworden!

Dr. M.M. Rovers, geachte co-promotor, beste Maroeska, in het rijtje promotor 1, promotor 2, co-promotor noem ik je als laatste, maar eigenlijk had je bovenaan moeten staan. Zonder jou had ik het nooit gered. Jouw deur stond altijd open, zowel in Utrecht als in Nijmegen. Ik waardeer je om meer dan ik kan zeggen. Je hebt me de afgelopen jaren op meerdere gebieden op het juiste moment de juiste spiegel voorgehouden. Ik heb veel van je geleerd en hoop dat je nog heel lang promovendi

blijft begeleiden, zodat zij allemaal profijt kunnen hebben van jouw laagdrempelige en vriendelijke aanpak. Onze reis naar Madrid zal ik nooit vergeten!

Arno, Anne en Maroeska, ik had me geen betere begeleiding kunnen wensen, heel hartelijk bedankt daarvoor!

De leden van de beoordelingscommissie, te weten Prof. dr. H.A. Smit, Prof. dr. ir. G.A. Zielhuis, Prof. dr. K.J. Kvaerner en Prof. dr. R.J.P.M. Scholten wil ik bedanken voor het kritisch beoordelen van het manuscript; thank you for your willingness to assess the quality of this thesis

Twee hoofdstukken uit mijn proefschrift zijn gewijd aan de resultaten van de NOA studie. Allereerst wil ik uiteraard de 111 jonge tot zeer jonge deelnemers bedanken die het goed vonden dat zij, ten behoeve van het onderzoek, twee jaar lang elke avond een thermometer in hun oor kregen. Ook de onderzoeken van dokter Maaike hebben jullie zonder al te veel commentaar doorstaan, zelfs wanneer zij bloed moest prikken of met een camera in jullie neus wilde kijken. Velen van jullie hebben, hoe klein jullie soms ook waren, jullie ouders helpen herinneren aan het temperaturen ('oortje piep?'). De ouders wil ik bedanken voor het twee jaar lang bijhouden van het dagboekje. Ik weet niet of ik het zelf gekund zou hebben!
Maaike, bedankt voor het includeren en controleren van onze deelnemers. Ik ben eigenlijk wel benieuwd hoeveel kilometer je daarvoor door heel Nederland hebt moeten rijden. Veel succes bij het afronden van je eigen promotie en je opleiding tot KNO-arts.
Nelly, wat hadden we moeten doen zonder jou? Het maken van afspraken voor de huisbezoeken bij alle deelnemers, waarbij ook nog rekening gehouden moest met schooltijden en werkende ouders, is zeker geen makkelijke opgave. In het begin van het onderzoek kwamen daar ook nog eens de maandelijkse telefonische controles bij en de administratie die gepaard gaat met zo'n groot onderzoek. Ondanks dat je werk, zeker aan het eind van NOA, ook fysiek veel van je vroeg, was je altijd benieuwd hoe het met mij ging. Nelly, bedankt voor alles!
Nicole, bedankt voor alle tijd die jij in het datamanagement hebt gestoken. Zonder jou was het een stuk moeilijker geweest om de analyses uit te kunnen voeren. Ardine, bedankt voor je adviezen voor de economische evaluatie. Rolf, heel fijn dat je mij wilde helpen om de adjusted RD's uit R te toveren!

Een ander onderzoek dat een prominente plaats in dit proefschrift inneemt, is het onderzoek dat ik uitgevoerd heb aan de hand van de dossiers van ZonMw. De eerste contacten zijn gelegd via Elsbeth Steenland en Viviënne Lahaut. Tijdens het project heeft Trudy van der Burg ervoor gezorgd dat de dossiers op de juiste tijd op de juiste plek waren. Bedankt daarvoor. Karen van Liere-Visser wil ik bedanken voor haar bereidheid om mee te denken en voor haar kritische blik op de artikelen die naar aanleiding van dit onderzoek geschreven zijn.

Prof. dr. E.A.M. Sanders, beste Lieke, bedankt voor je bijdrage aan het review over de kosteneffectiviteit van pneumokokkenvaccinaties ter preventie van acute otitis media. Ook wil ik je bedanken voor het door jou in mij gestelde vertrouwen nu je mij hebt aangesteld als epi-begeleider van het onderzoek in het WKZ. Ik hoop dat wij nog lang samen mogen blijven werken!

I would like to thank Prof. N. Black, Prof. G.G. Browning, Prof. M. Haggard, and dr. A.R. Maw for providing the data of their trials on the effectiveness of adenoidectomy in children with otitis media with effusion. We will continue this project including the data provided by dr. M.L. Casselbrant, dr. P. Koivunen, dr. J.J. Manoukian and dr. P. Mattila. I thank you all for your willingness to share your data with me. Martin Burton, I am looking forward to collaborating with you on the remaining parts of the IPD meta analysis.

Beste Monique, bedankt voor je gezelligheid, het samenwerken in de PV (wat is Sinterklaas toch een leuk feest!), je bereidheid om te helpen met wat dan ook, de mogelijkheden die je ziet om ogenschijnlijk onmogelijke agenda's te combineren en vooral bedankt voor de mooie lay-out van mijn proefschrift!
Beste Henk en Coby, jullie wil ik bedanken voor het feit dat jullie in oplossingen en mogelijkheden denken.

Annette, Charles, Corine, Ewoud, Geert-Jan, Ilse, Irene, Jaap, Judith, Lennie, Madeleine, Margriet, Marieke, Nienke, Roderick en Rolf, met jullie heb ik kortere of langere tijd een kamer gedeeld. We deelden echter niet alleen onze werkplek, maar ook de hoogte en diepte punten die horen bij het leven in het algemeen, en bij een promotietraject in het bijzonder. Bedankt voor de tijd die we hadden met en voor elkaar!

Mijn stagiaires Marie-José en Pieter wil ik uiteraard ook bedanken. Er staan drie mooie artikelen in dit proefschrift waarvoor jullie de basis (of meer) hebben gelegd. We hebben veel van elkaar geleerd. Jullie over onderzoek doen en ik over hoe je het beste een stagiair kunt begeleiden.

Sander, in oktober vroeg Arno mij of ik jou wilde begeleiden als co-promotor. Hoe bijzonder is het om nog niet gepromoveerd te zijn, maar al wel een eigen promovendus 'te hebben'? Ik vind het in elk geval een eer. Jouw enthousiasme inspireert mij, en ik hoop dat we de komende jaren tot mooie resultaten zullen komen. Ik kan alleen maar wensen dat ik je daarbij, samen met Arno en Anne, op dezelfde manier kan begeleiden als dat Arno, Anne en Maroeska dat bij mij hebben gedaan.

Saskia, Harmieke, Margit en Koert, ik vond het fijn om een deel van de MSc Epidemiology samen met jullie te doen. Ik denk met veel plezier terug aan het samenwerken tijdens de practica en aan de lunches die wij ook na afloop van de opleiding nog regelmatig hebben gehad. Wanneer plannen we weer een lunch?
Harmieke, wat leuk dat wij elkaar nu in een andere rol weer tegenkomen. Saskia, puur toeval (jij zocht iets op de website van de zwemvereniging en kwam daar mijn naam tegen) heeft ertoe geleid dat wij elkaar beter hebben leren kennen. Ik vind het fijn om met je te praten en om van de zijlijn mee te mogen genieten van de zwemsuccessen van Yara.

In mijn schaarse vrije tijd waren jullie er, Bjorn, Chantalle, Chia-Nien, David, Elise, Nicole, Thijs, Tim, Tom, Tristan, Willemijn en ouders! Ik vind het een voorrecht dat ik jullie heb mogen leren kennen en ben blij dat ik een aantal stappen met jullie heb meegelopen op jullie weg naar het hoogst haalbare. Jullie waren mijn ontspanning door inspanning. Ik geniet nu vanaf de zijlijn mee van jullie regionale, nationale en zelfs internationale successen. Ga zo door, ik ben trots op jullie!

Na het noemen van 'onze' zwemmers is de link naar jou snel gemaakt. Marjolein, lieve Marjo, we hebben elkaar leren kennen via het zwemmen. Eerst was jij een van de coaches en ik een van de zwemmers. Later mochten wij samen het hierboven genoemde groepje zwemmers coachen. We bleken echter meer gemeen te hebben dan onze liefde voor het zwemmen en coachen. Ik vind het fijn dat jij vandaag, als mijn

paranimf, letterlijk achter mij staat. En Marjo, dit boek is om te houden ... niet om door te geven ;-)

Lieve oma, ik vind het bijzonder dat u mijn promotie mee mag maken! Uw oprechte belangstelling voor uw kinderen, kleinkinderen en achterkleinkinderen maakt u tot een heel fijn mens. De afgelopen jaren zijn zeker niet makkelijk geweest voor u. Er waren en zijn helaas altijd wel ergens zorgen en die gaan u niet in uw koude kleren zitten. Helaas kan niemand die zorgen helemaal wegnemen. Maar dit jaar staan er vooral ook mooie dingen 'op het programma'. Dit proefschrift is er één van. Lieve oma, ik hou van u!

Ludo, lieve broer, we hebben de deur nooit bij elkaar platgelopen, en we bellen ook niet overdreven vaak. Maar als het nodig is kan ik altijd bij jou en Suzanne terecht. We hebben veel belangrijke momenten in onze levens samen meegemaakt. Ik kijk er naar uit om nog veel momenten met jullie mee te maken, en dan vooral leuke momenten! Lieve Ludo, bedankt dat jij vandaag mijn paranimf wilt zijn.

Jonathan, zo klein, zo mooi, zo lief! Ik ben er trots op jouw tante te mogen zijn. We gaan veel leuke dingen doen samen!

Lieve papa en mama, jullie staan vooraan in mijn proefschrift en dat is niet voor niets! Jullie eindeloze en rotsvaste vertrouwen in mijn mogelijkheden, ook op de momenten dat ik dat zelf soms niet had, heeft mij heel ver gebracht. Waar ook ter wereld, ik weet dat jullie achter mij staan. Het is de laatste jaren zeker niet gemakkelijk geweest, maar ook hier komen we weer sterker uit. Weet dat ik nog altijd niet zonder jullie kan. Ik hou onbeschrijfelijk veel van jullie en ik ben zeer dankbaar dat ik jullie dochter ben.

Nieuwegein, 1 maart 2012

Chapter 8

Curriculum vitae

8

Chapter 8

Chantal Wilma Bianca Boonacker was born on March 23, 1977 in Nieuwegein. In 1998 after obtaining her VWO diploma at SG De Monnikskap in Nijmegen, she studied Biomedical Health Sciences at the Radboud University in Nijmegen. In 2007 she obtained her Master of Science degree with a specialization in Health Technology Assessment. She combined her study and part of her PhD-work with a career as an elite Paralympic athlete in swimming. She successfully participated in three Paralympic Games (Sydney 2000, Athens 2004, Beijing 2008) and several European and World Championships. She won two Paralympic bronze medals (100 meter backstroke Athens 2004 and Beijing 2008), three medals on World and four on European Championships. During her career she set many Dutch, European and World records, some still standing. She retired after the Beijing Paralympic Games. In January 2008 she started the work described in this thesis at the Julius Center of Health Sciences and Primary care (supervised by Prof. dr. AW Hoes, Prof. dr. AGM Schilder and dr. MM Rovers). She obtained her Master of Science degree in Clinical Epidemiology at the Utrecht University in 2010, and her Certificate of university teaching qualification in 2012.
Currently she is working as a post-doctoral researcher at the Julius Center of Health Sciences and Primary Care.

Chapter 8