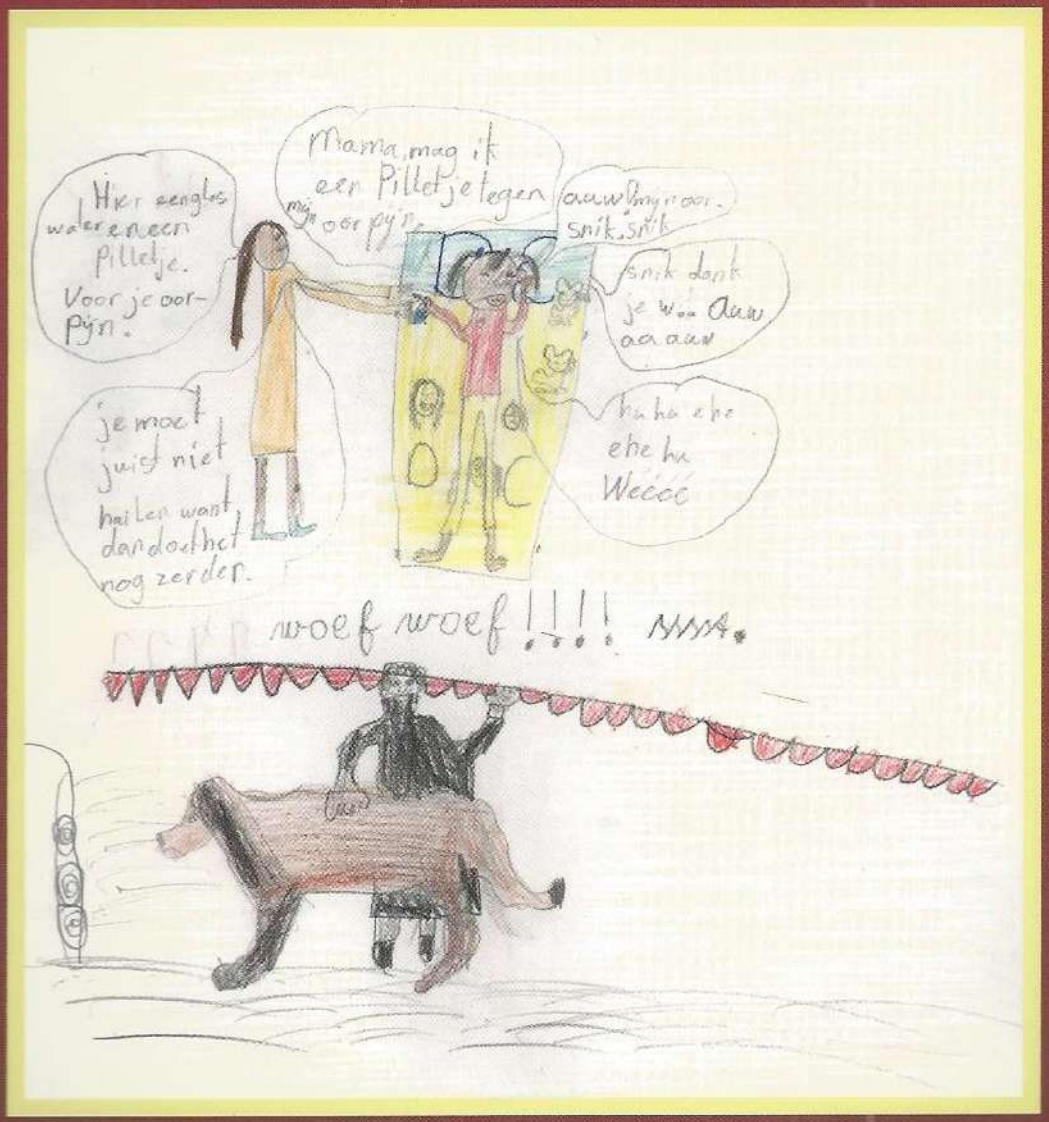
Health-related quality of life in children with recurrent acute otitis media



Carole N.M. Brouwer

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Health-related quality of life in children with recurrent acute otitis media
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Julius Center for Health Sciences and Primary Care
Utrecht, University Medical Center
Thesis Utrecht University - with references - with summary in Dutch

ISBN 90-393-3327-0

Cover
Ontwerp Karin Spijker, Draw & Digit
Tekening Shani-Qwa (9 jaar) en Jenayden Adriaan (7 jaar) © 2003

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Health-related quality of life in children with recurrent acute otitis media

Gezondheidsgerelateerde kwaliteit van leven van kinderen
met recidiverende otitis media acuta

(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. W.H. Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op
dinsdag 15 april 2003 des middags te 16.15 uur

door

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geboren op 12 maart 1974, te Badhoevedorp

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The study presented in this thesis was funded by Care Research Netherlands – Prevention division (ZON, projectnumber 98-2-533) and Praeventiefonds (projectnumber 28-2848.2).

The financial support for the publication of this thesis by the Julius Center for Health Sciences and Primary Care (UMC Utrecht) and Wyeth Pharmaceuticals BV is gratefully acknowledged.

"Oor tegen oor,
ik hoor wat je denkt
denk nog even door
blijf stil bij me zitten
oor tegen oor."

Hans en Monique Hagen

Voor mijn ouders

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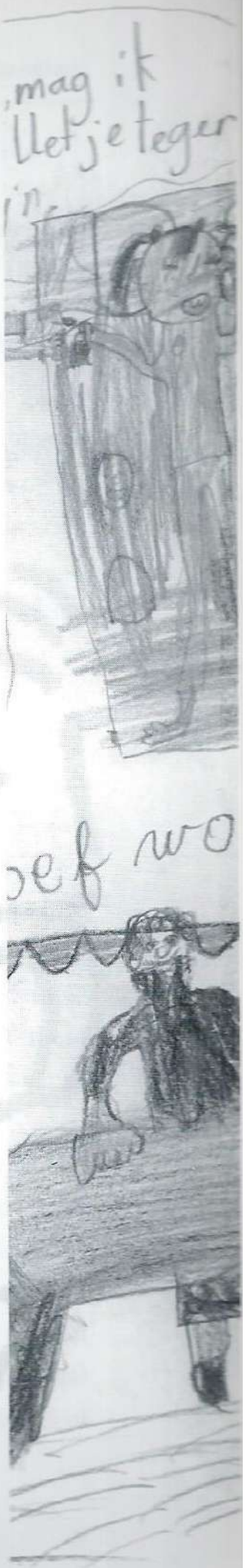
Contents

List of abbreviations

AOM	Acute otitis media
C3PO	Criterion-derived 3-factor Predictive Outcome
Caregiver ES	Caregiver emotional status
95% CI	95% confidence interval
COME	Chronic otitis with effusion
CQOL	Otitis media-related Child Quality Of Life
Ctrl	Control
CV	Construct validity
EIS	Ear Infection Survey
EM	Effect modification
ENT	Ear-, Nose- and Throat
ES	Effect size
FFQ	Family Functioning Questionnaire
FHS	Functional health status
FSQ	Functional Status Questionnaire (=FS II(R))
GIC-PPS	Grommet Insertion in Children – Prospective Parental Survey
GRS	Guyatt's responsiveness statistic
HRQoL	Health-related quality of life
IC	Internal Consistency
ICC	Intraclass correlation coefficient
MCID	Minimally clinical important difference
NRS	Numerical Rating Scale
OM	Otitis media
OM-5	Otitis Media – 5 items (modified version of OM-6)
OM-6	Otitis Media – 6 items
OM-CSI	Otits Media – Clinical Severity Index
OMD	Otitis Media Diary
OME	Otitis media with effusion
OM-FSQ	Otits Media – Functional Status Questionnaire
OMO-22	Otitis Media Outcome –22 items
OPD	Outpatient department
PCC	Pearson's correlation coefficient
Pnc	Pneumococcal
PPSC	Play Performance Scale for Children
QoL	Quality of Life
QoL-3 item	Quality of Life – 3 items questionnaire
RAND	RAND Corporation questionnaire
RAOM	Recurrent acute otitis media
RCT	Randomized controlled trial
Re	Responsiveness
SD	Standard deviation
SE	Standard Error
SEM	Standard error of measurement
SRM	Standardized response mean
TAIQOL	TNO – AZL Infant Quality of Life
TRR	Test-retest reliability
VAS	Visual Analogue Scale
VT	Ventilation tube
WW	Watchfull waiting

Chapter 1

General introduction



"If every day is an awakening, you will never grow old. You will just keep growing."

Gail Sheehy

Acute otitis media (AOM) is a common infection in childhood characterized by earache, fever, and symptoms of acute illness such as irritability, (night) restlessness, feeding difficulties and excessive crying.[1-7] Eighty percent of the afflicted children recover spontaneously with symptomatic relief by adequate prescription of analgesics and decongestants within two to seven days.[8-10] Since antibiotics have only a limited effect on the reduction of pain or fever[2], use of antibiotics during acute episodes is restricted in the Netherlands to children with an increased risk of complications or with progressive general illness or earache, poor fluid intake, or no improvement of symptoms after three days.[3, 11]

At the age of 2 years, 30% to 70% of all children have suffered from at least one episode of AOM[12-15], with a peak incidence during the first year of life[12, 14, 16]. Five to 15% percent experience four or more episodes per year.[13, 17-21] Possible consequences of recurrent AOM on the longer term include conductive hearing loss[22], balance problems and motor dysfunctions[23, 24]. Other adverse events such as disruptions in language[25-27], cognitive and psychosocial development[28, 29] and behavioural problems[30] are still being debated.[25, 31-35]

In particular in this group of children with recurrent AOM, the cyclical nature of recurrent earache, fever and general illness may resemble a chronic disease and impair the child's functioning and quality of life, as well as putting considerable stress on the caregivers and family. For example, many caregivers of these children are concerned about long-term consequences of recurrent AOM such as hearing loss, impaired language development, and learning disabilities.[36-38]

Many studies have addressed the physical and cognitive consequences of AOM and its treatment, such as acute signs and symptoms and potential long-term consequences. Little, however, has been published about the effects of recurrent AOM and its treatments on a child's health-related quality of life (HRQoL) and functional health status (FHS), which include psychological and social consequences of a disease on the child's functioning, besides physical consequences. Although it is obvious that the impact of AOM on the well-being of

a child may be considerable, it was not until 1991 that Facione[39] drew attention to the need of quality of life research in this patient group.

Health-related quality of life and functional health status

Quality of life (QoL) is the level of satisfaction a person imputes to his or her life. QoL is a multidimensional concept; therefore measures of QoL combine perceptions of physical, psychological or emotional and social functioning.[40, 41] The need to incorporate a person's values and preferences regarding his life is what distinguishes quality of life from other measures of well-being.[42-44] *Health*-related quality of life (HRQoL) covers those aspects of QoL in general that are affected by the effects of an illness and its treatment.[40, 41, 45-47]

Another measure of health (often equated with HRQoL) is functional health status, reflecting the (severity of) signs and symptoms and the adequacy of daily functioning across various life-domains in an individual with a certain health condition.[48-51]

How is quality of life measured?

There are generally two types of health-related quality of life instruments: generic and disease-specific HRQoL-questionnaires. Generic questionnaires are applicable to people in different health states and with different medical conditions and cover a wide range of health-related functioning (mental, physical and psychosocial). Consequently, the results derived from generic questionnaires may be comparable between different patient groups.[40, 52, 53] Disease-specific instruments focus on aspects of HRQoL relevant to a specific illness, making them much more likely to detect clinically important and subtle differences in the patient's HRQoL and more responsive to change.[46, 52, 54, 55]

Specific issues in assessing health-related quality of life in children

HRQoL and FHS assessment in children with recurrent AOM will meet difficulties similar to those encountered in HRQoL and FHS assessment in other chronic pediatric conditions. Because a child's vocabulary, language and

perception of health and illness are still developing, measurement of HRQoL from the patient's perspective, which is essential for HRQoL, may be difficult or impossible in young children.[40, 45, 55] In young children reliable self-report measures are therefore not available, while for children aged six years and older some self-report measures on (functional) health status recently have been developed, validated or empirically used for clinical and research purposes.[51, 56-61] Consequently, quality of life measures in young children mainly rely on parental reports or other proxies and therefore restrict assessment to observational consequences of disease expressed in the child's functioning (FHS). The extent to which caregivers are able to judge emotional and cognitive responses in young children is under discussion.[41, 62-65] Such judgment of these responses is however necessary to value their FHS and thereby assess their HRQoL.

Outline of the thesis

In this thesis, health-related quality of life and FHS of children with recurrent AOM will be studied as part of a randomized controlled trial on the effectiveness of pneumococcal vaccination in children with recurrent AOM.

Existing measures of prevention of recurrent AOM through surgery or antibiotic prophylaxis are challenged by a modest effect and emerging antibiotic resistance.[66-70] A meta-analysis of the effect of surgical intervention showed that tympanostomy tube (TT) insertion reduced AOM incidence by a mean of 1.0 episodes per child year, whereas for adenoidectomy in children with prior TT insertion the reduction was 0.32 episodes per child year.[71] Antibiotic prophylaxis resulted in 61% to 64% of children remaining otitis free versus 63% of those receiving placebo.[72]

Since pneumococcus is the most frequent bacterial cause of otitis media[15, 73-75], during the last decade research has been focussed on pneumococcal vaccination. Pneumococcal conjugate vaccination at infant age has been shown to be highly effective in preventing invasive disease.[76-78] In addition, vaccination appeared to reduce AOM incidence, with the largest effect in the prevention of 4 or more episodes per year.[76, 79]

The current trial aimed to assess the effectiveness of vaccination with a pneumococcal conjugate vaccine in children aged 1 to 7 years with recurrent acute otitis media (2 or more AOM episodes per year) in reducing the frequency and severity of AOM episodes and in improving health-related quality of life and functional health status.

The aim of this thesis is to describe the effect of recurrent acute otitis media and vaccination with a pneumococcal conjugate vaccine on health-related quality of life and functional health status of children with recurrent otitis media and on the functioning of their family.

Specific study aims are:

1. To validate instruments for assessment of health-related quality of life and functional health status in children with recurrent acute otitis media.
   A battery of eight instruments selected to assess HRQoL and FHS will be validated. Reliability, expressed as internal consistency and test-retest reliability, and validity, expressed as construct and discriminant validity *(Chapter 3)*, and responsiveness *(Chapter 4)*, will be described.

2. To assess the impact of recurrent acute otitis media on health-related quality of life and functional health status of a child.
   First a systematic review will be given of available literature on HRQoL and FHS assessment in children with recurrent AOM *(Chapter 2)*; subsequently HRQoL and FHS of children in the current study will be assessed and compared with that of other pediatric populations *(Chapter 5)*.

3. To assess the effect of pneumococcal vaccination on health-related quality of life and functional health status of children with recurrent acute otitis media.
   The effect of vaccination with a pneumococcal conjugate vaccine on HRQoL and FHS of a child alongside its clinical effect of frequency of AOM episodes will be described in *Chapter 6*.

4. To assess the impact of recurrent acute otitis media on health-related quality of life and functioning of the caregivers and family.
   The burden of recurrent AOM in a child on its caregiver and siblings will be evaluated in *Chapter 7*.

Finally, implications of the results and recommendations for further research in pediatric HRQoL and FHS assessment will be discussed in *Chapter 8*.
The thesis will be concluded with a summary.

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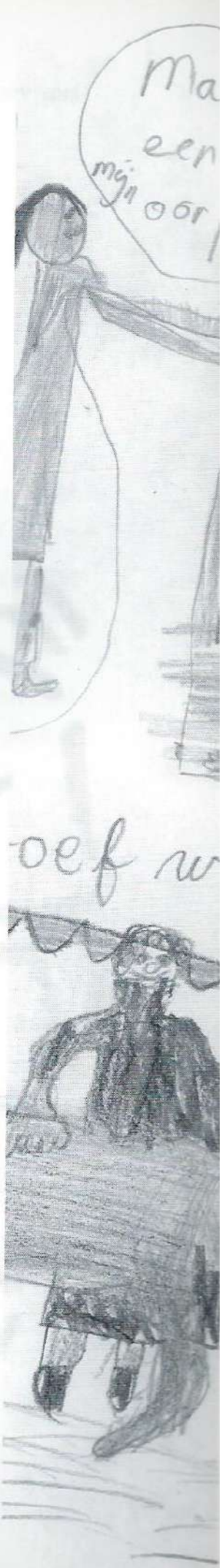
Chapter 2

Health-related quality of life in children with otitis media



Carole N.M. Brouwer, A. Rianne Maillé,
Diederick E. Grobbee, Elisabeth A.M. Sanders,
Anne G.M. Schilder

"Met mijn gedachten ergens anders ben ik altijd overal."

Loesje

Abstract

Background: The growing interest in health-related quality of life (HRQoL) in children with otitis media (OM) has brought the need to investigate currently available HRQoL instruments in OM with respect to their results and their applicability in clinical practice and research. In this review the state of the art regarding HRQoL research and its results in children with OM is presented.

Methods: A search was done on EMBASE (1988 - June 2002) and on NLM Gateway (1966 - July 2002) for studies assessing health-related quality of life or functional health status (FHS) by means of disease specific or generic questionnaires in children aged 0-18 years with chronic or recurrent otitis media with effusion or acute otitis media.

Results: Only 11 of 121 articles retrieved from the EMBASE, NLM Gateway and an additional manual search fulfilled the criteria for inclusion. In these studies more than 50% of children with OM reportedly experience physical suffering (pain, high fever etc), difficulties with hearing or speech, behavioral problems, or emotional distress. Almost all instruments used in children with OM measure functional health status instead of HRQoL. Measures of reliability and validity are lacking for most instruments. Several questionnaires are still being developed.

Conclusions: Recurrent or chronic OM has been reported to substantially affect various domains of FHS and HRQoL of children. Lack of true HRQoL instruments as well as incomplete data on reliability and validity limits the current knowledge of HRQoL in children with OM.

Introduction

Otitis media (OM) is one of the most common disorders in childhood [1-3] and may have a considerable impact on the health-related quality of life (HRQoL, see Table 1[4-18]) of children and their caregivers.[19-21] Up to now, most studies have focussed on the effects of OM and its treatment on hearing, language and psychosocial development[22-29], few have paid attention to the broader scope of health-related quality of life as an outcome measure in OM[30-33]. Growing interest in HRQoL in children in general and those with OM in particular has brought the need for knowledge of currently available HRQoL instruments and their applicability in clinical practice and research.[12, 34-37]

Table 1. Definitions of health-related quality of life, functional health status and instrument types.

Health-related quality of life:	level of satisfaction of a person with those aspects of his or her life that are affected by the effects of an illness and its treatment.[4-8] It is a multidimensional concept; measures of HRQoL should incorporate perceptions of physical, psychological or emotional and social functioning.[6,8] Incorporation of a person's valuation of his life distinguishes HRQoL from other measures of well-being.[9-11]
Functional health status:	combination of health status reflecting the (severity of) signs and symptoms of disease, and functional status reflecting the adequacy of an individual's daily functioning across various life-domains.[11-15]
Generic instruments:	are applicable to people in different health states and with different medical conditions. They cover a wide range of health-related functioning (mental, physical, and psychosocial). Consequently, the results of generic questionnaires are comparable across different patient groups.[6,15-17]
Disease-specific instruments:	focus on aspects of HRQoL relevant to a specific illness. Therefore they are much more likely to detect subtle, yet clinically relevant health issues in the patient's HRQoL and are more responsive to change.[5,16-18]

We reviewed existing literature regarding HRQoL research and its results in children with recurrent OM. An overview will be given of the results with regard to the effect of OM on HRQoL and functional health status (FHS, see Table 1) of children assessed with currently available HRQoL instruments. In addition, quality and applicability of these HRQoL instruments in research and clinical practice will be assessed on the basis of their characteristics and contents as well as their psychometrics.

Materials and methods

Search strategy

A search was done on EMBASE for articles dating from 1988 through June 2002 and on NLM Gateway from 1966 through July 2002, using the search terms that are proposed by EMBASE for otitis media ('otitis media' or 'chronic otitis media' or 'mucoid otitis media' or 'secretory otitis media' or 'serous otitis media') or 'acute otitis media' and 'quality of life' or 'health status' or 'functional status'. Search terms were entered as MESH headings as well as text- or keywords. Limitations were age (0-18 years) and language (English, French and Dutch).

Additionally, a manual search of the bibliographies of these selected articles was done. Discussions were conducted with experts in the field. In case of obscurities or missing data, authors were contacted for supplementary information.

Criteria for selecting studies

Studies assessing health-related quality of life (HRQoL) or functional health status (FHS) by means of a disease specific or a generic questionnaire (definitions are given in Table 1) in children aged 0-18 years with chronic or recurrent otitis media with effusion (OME) or acute otitis media (AOM), were considered: only those studies providing actual data through a HRQoL or FHS questionnaire or providing results of development or validation of such a questionnaire, were included.

Review articles without original HRQoL data, articles that did not address HRQoL in OM, studies without presentation of HRQoL data or without the use of either a FHS or HRQoL questionnaire, non-human studies, and studies in adult populations were excluded.

Outcome measures

The studies were systematically assessed according to the following topics:

I. General characteristics of the study: setting; type of patients included; mean age and age-range of the patients; rationale behind the use of the HRQoL instrument in the study.

II. Outcome of the study: effects of OM on HRQoL of a child.

Table 2. Psychometric characteristics of 'quality of life' instruments.

Reliability[35,38]	
Internal consistency:	the homogeneity or coherence of the items of a scale; it examines whether individual items within a (summated) scale contribute consistently to the total score obtained.
Test-retest reliability:	the extent to which an instrument meets the requirement of producing the same score when used in repeated assessments when the condition of the patient and all other relevant circumstances remain constant.
Validity	
Construct validity:	the degree to which an instrument measures the concept it is supposed to measure. As no 'gold standard' exists for quality of life, construct validity of HRQoL instruments is usually assessed by relating the instrument to other, well validated instruments that address the same concept. Construct validity is supported when the correlations between two instruments are as predicted.[14,35,39,40]
Responsiveness:	the ability of the instrument to detect (clinically) important changes in HRQoL. An instrument should be able to detect at least that amount of change that patients experience as important. Responsiveness is essential for outcome measures.[35-37,41]

Reliability and validity provide valuable information on the usefulness, significance and applicability of an instrument.

III. Characteristics of HRQoL instruments: assessment of FHS vs. HRQoL; generic vs. disease specific questionnaires; reporter; scoring; scale; number of items; domains that are addressed (physical symptoms, emotional functioning, social functioning, other domains); psychometric characteristics reflecting reliability and validity (internal consistency, test-retest reliability, construct validity, responsiveness to change, see Table 2[14, 35, 38-41]).

Results

The search resulted in 121 citations. After applying the criteria for inclusion and exclusion, only 9 articles remained for inclusion (Table 3). The manual search and expert discussion yielded 2 extra articles (Haggard & Smith[42], Timmerman et al.[43]).

Table 3. Reasons for exclusion of articles.

	NLM Gateway	EMBASE	Total
Total number of articles retrieved	**84**	**35**	**121**
Reasons for exclusion			
Editorial comment	0	2	2
Review article	6	1	7
OM not subject of study	30	18	48
Pediatric QoL in OM not subject of study	28	6	34
No QoL data presented	2	3	5
No QoL/FHS questionnaire used	3	3	6
Non human study	2	1	3
Adult population	5	0	5
Included			
NLM Gateway & EMBASE search	8	1	9
Manual search of references			2
Total included			**11**

Most articles that were excluded did not assess HRQoL in OM, but rather addressed either functional health status of children in particular populations

Table 4. Results of studies on QoL in children with otitis media.

Study	Instrument	Patients (*n*); condition	Age (range)	Purpose of study**
Asmussen et al. 1996[46] Gupta et al. 1999[44]	EIS	- 65*; rAOM or OME	- 1.5 y (0-3 y)	- validation
Bertin et al. 1996[45]	QoL 3 item	- 219; AOM	- (1-6 y)	- empirical use
Rosenfeld et al. 1997[32]	OM-6	- 186; chronic OME or rAOM	- 3.4 y# (6 mo – 12y)	- validation & empirical use
	NRS – ear related QoL			
Rosenfeld et al. 2000[47]	OM-6	- 248; chronic OME or rAOM	- 1.4 y# (0.5 mo – 9.9 y)	- empirical use
Timmerman et al. 2003[43]	OM-6	- 77; OME	- (1 – 3 y)	- empirical use
Karkanevatos & Lesser 1998[49]	GIC-PPS	- 150; chronic OME	- 4 y# (1 – 6 y)	- empirical use
Alsarraf et al. 1998[33]	OM-SCI	- 51; 25 AOM, 26 well-child controls	- (1 – 3y)	- development & validation
	OMD			- *idem*
	OM-FSQ			- *idem*
	PPSC			- empirical use
Haggard & Smith 2000[31,42]	C3PO	- 1184; 384 OME, 800 well-child controls	- (3.5 y – 7 y)	- development & validation
	CQOL			- development & validation
Rovers et al. 2001[50]	TAIQOL	- 187; chronic OME	- 19.5 mo	- empirical use
	Erickson scales			- empirical use
Richards & Giannoni 2002[48]	OMO-22	- 110; 83 rAOM, 62 chronic OME	- 2.42 y (2 mo – 13 y)	- empirical use

OPD = outpatient department; RCT = randomised controlled trial; mo = months(s); y = year(s); VT = ventilation OM-6 = Otitis Media – 6 items; GIC-PPS = Grommet Insertion in Children – Prospective Parental Survey, Status Questionnaire, PPSC = Play Performance Scale for Children, C3PO = Criterion-derived 3-factor Predictive Quality of Life, OMO-22 = Otitis Media Outcome – 22 items.

Study outcome Child QoL
- > 50% in chronic OM: difficulty sleeping, poor eating, frequent fevers, unusually irritable or fussy; - score on each subscale (physical, mental, social activity) significantly lower in moderate-severe OM than in mild OM
- not available: only assessment of treatment effect
- very much – extreme a problem: physical suffering in 16%, hearing loss 11%, emotional distress 6%, activity limitations 5%, and speech impairment 8%; - median score 7 (out of 10)
- very much – extreme a problem: physical suffering in 37%, emotional distress 24%, activity limitations 12%, hearing loss 9%, and speech impairment 9% - caregiver concern and speech impairment are highest rated problems, followed by physical suffering, hearing loss, and emotional distress, activity limitations rated lowest - year before VT insertion: 76% had episodes of earache, 64% sleeping problems, 49% behaviour problems, 33-62% hearing problems, 37% speech problems, 15% balance problems
- all scores significantly lower in AOM than those in healthy controls ($p<0.001$); - scores 2-4 x lower after recovery from AOM compared to healthy controls
- total score in OME significantly lower than in healthy controls
- score in OME significantly lower than in healthy controls - TAIQOL subscales 'Communication', 'Motor functioning', 'Problem behaviour', and 'Sleeping' most severely affected - parent-child interaction scores slightly poorer than those reported in healthy children
- overall score significantly lower in children with rAOM/chronic OME than those without ear problems ($p = 0.001$); - hearing & vestibular symptoms, speech and social effect most severely affected

tube placement, WW = watchful waiting. EIS = Ear Infection Survey QoL 3 item = Quality of Life – 3 items, OM-CSI = Otitis Media Clinical Severity Index, OMD = Otitis Media Diary, OM-FSQ = Otitis Media Functional Outcome measure for otitis media, CQOL = OM-related Child Quality of Life, TAIQOL – TNO-AZL Infant Quality
* in Asmussen et al.[46], for Gupta et al. [44] the number of subjects is unknown; ** related to questionnaire; # median

where OM was only mentioned as a common condition, or HRQoL in rhinitis or rhinosinusitis for which OM was mentioned as a potential complication, or the functioning of the middle ear after (surgical) treatment for OM.

Characteristics of the studies

The setting of the studies varied, five studies were part of a multi-centre trial[31, 42, 45-47, 50]. All study-populations consisted of children with chronic or recurrent otitis media (Table 4[44, 45]). The definition of chronic and recurrent OM regarding number of OM episodes and duration, however varied considerably. Age of the patients also varied, with the majority of children being younger than 3 years of age at inclusion.

The purpose of the studies ranged from development of a new HRQoL questionnaire for OM to evaluation of effects of treatment of OM on HRQoL or FHS.

Quality of life in otitis media

In the study by Asmussen et al.[46] more than 50% of the caregivers reported physical problems on the part of their child, such as difficulty sleeping, poor eating, irritability or fussiness, as a consequence of OM. Rosenfeld et al.[32, 47] found physical suffering (e.g. ear pain or discomfort, high fever, poor balance), hearing loss and emotional distress to be prominent in children with OM, especially in those admitted for ventilation tube (VT) insertion. Children with rAOM and chronic OME referred for VT placement in a trial by Richards & Giannoni[48] scored significantly poorer on an ear-related questionnaire (OM-22) than children without a significant history of ear problems. Hearing and vestibular symptoms, speech and social effect were most severely affected.

Children suffering from an episode of acute otitis media scored significantly worse than healthy children did on the total scores of all clinical and functional measures in the study by Alsarraf et al.[33]. Those who had recovered from AOM continued to score 2 to 4 times worse on these measurements compared to healthy controls during 6 to 12 weeks of follow-up.

In children admitted for bilateral VT insertion for OME, Karkanevatos & Lesser[49] found that the majority suffered from disturbed sleep. Behavioral problems at school or nursery, as well as difficulties with hearing, speech, and to a less extent, balance, were also common. Rovers et al.[50] described similar results in children with persistent bilateral OME. Besides, in their study, the parent-child interaction scores in the children with persistent OME were slightly poorer than had been reported in children without disease.

Characteristics of HRQoL instruments

In 11 studies, 14 different instruments were used to measure HRQoL (Table 5). Except for the TAIQOL, all questionnaires address FHS and not HRQoL as such. The TAIQOL is the only true generic HRQoL questionnaire used in these studies, as it includes valuation by a caregiver of the FHS of a child when experiencing signs or symptoms of a disease. Unfortunately, normscores are not available yet. The VAS-global ear-related QoL and the CQOL are 1-item global scales of HRQoL.

Both disease specific and generic questionnaires have been applied in the reviewed studies, however only Alsarraf et al.[33] combined both types of questionnaires in one study. Twelve instruments are completed by caregivers, the OM-CSI is a physician-completed instrument, the Erickson scales require an observer. The number of items per instrument ranged from 1 to 64 items (mean 15.2). One questionnaire (QoL 3 items) focuses solely on physical functioning or symptoms related to OM. Six questionnaires (EIS, OM-6, GIC-PPS, OM-FSQ, TAIQOL, OMO-22) include items from all 3 areas of functioning (physical, emotional, social). Three questionnaires (EIS, OM-6 and C3PO) address the child's functioning as well as that of the caregiver or family (Table 5). The VAS global ear-related QoL and CQOL are visual analogue scales, the other questionnaires use Likert scales.

Table 5. Characteristics of QoL instruments used in assessment of QoL in children

	Type	Score	Items	Topics (nr of items)
				Physical
EIS[44,46]	FHS ds	NA	64	- physical health
QoL 3 item[45]	FHS ds	Total	3	- appetite, sleep, playing, activity
OM-6[32,43,47]	FHS ds	Subdomain (6) Total	6	- physical suffering, hearing loss, speech impairment
NRS ear-related QOL[32]	HRQoL ds	Global 1 item	1	
GIC-PPS[49]	FHS ds	Item	17	- earache, balance, general health, hearing,speech/language
OM-CSI[33]	FHS ds	Total	10	- fever at home, earpain, temperature, tympanic membrane examination
OMD[33]	FHS ds	Total	3	- *Idem* to OM-CSI
OM-FSQ[33]	FHS ds	Total	14	- eating well, sick & tired, sleeping (2)
			3	- episodes of OM, pain, sleep loss
PPSC[33]	FHS gen	Global 1 item	1	
C3PO[31,42]	FHS ds	Subdomain (3) Total	27	- hearing difficulty, ear-related symptoms, URTI-related symptoms, balance, non-specific health
CQOL[31,42]	HRQoL ds	Global 1 item	1	
TAIQOL[50,51]	HRQoL gen	Subdomain (9) Total	46	- lung-, stomach-, skin-problems, sleeping, appetite, motor functioning, communication*
Erickson scales[50]	FHS gen	Subdomain (2)	10	
OMO-22[48]	FHS ds	Item Subdomain Total	22	- ear discomfort (2), ear drainage, fever, balance, difficulty hearing (4), receptive language, speech (4)

HRQoL = health-related quality of life; FHS = functional health status; ds = disease specific; gen = generic; construct validity; Re = responsiveness; NA = not available. ' Cronbach's alpha: ± = moderate,

with otitis media.

Emotional	Social	Other	IC*	TRR (R)	CV (R)	Re
- emotional health (child)	- social activity (child)	- emotional health (family), social activity (family)	±/+	NA	+	NA
			NA	NA	NA	NA
- emotional distress	- activity limitations	- caregiver concerns	+	+	+	+**
		- global rating child HRQoL	NA	NA	NA	NA
- behaviour at school/nursery	- social skills		NA	NA	NA	NA
- irritability			+	NA	+	+**
			+	NA	+	+**
- contented, moody, lively, irritable, seeming difficult, crying	- communicating, occupying oneself, responsive (2)		+	NA	+	+**
		- overall quality & vigor of play behaviour	NA	NA	+	+**
	- behaviour	- parental quality of life	NA	NA	NA	NA
		- global rating of child HRQoL	NA	±	NA	NA
- positive mood, anxiety, liveliness, problem behaviour	- social functioning		±/+	NA	+	NA
		- mother-child interaction during structured play	NA	NA	NA	NA
- irritability, frustration, sadness, restlessness, poor appetite	- playing, sleeping, friends/family, school/ daycare attendance		+	NA	NA	NA

* = items about speech & language capacity. IC = internal consistency; TRR = test-retest reliability; CV = + = good IC; (R) correlation coefficient: ± = moderate, + = strong; **: + = responsive

Psychometric characteristics of the instruments: validity and reliability

The psychometric properties of the questionnaires used in the studies are presented in Table 5. The internal consistency (IC, Cronbach's alpha) of the questionnaires was generally good[33, 43, 44, 48, 51]. Except for the OM-6[32, 47] and the CQOL[31, 42], no adequate data on test-retest reliability (TRR), reflecting the stability of the scores, were available. The TRR of the OM-6 and CQOL was appropriate.

Construct validity (CV) was assessed for seven questionnaires.[32, 33, 43, 44, 47, 51] In all of them CV was qualified as appropriate, because a sufficient number of predicted correlations was confirmed.

Responsiveness, the ability to detect (clinically) meaningful changes, was assessed in only two studies[32, 33]. Rosenfeld et al.[32] used the standardized response mean (dividing instrument change scores by their standard deviation) which may have been flattered by the fact that parents were not blind to the intervention. Alsarraf et al.[33] used an unusual statistical test for the assessment of responsiveness: the ANOVA test of trends. Responsiveness was reported to be good for the OM-6 and the PPSC, OM-CSI, OM-FSQ and OMD.

Because the C3PO is still under development, psychometrics are not yet available. Up to this moment, the QoL 3 item and the GIC-PPS have not been validated.

Discussion

Various studies aimed to assess health-related quality of life in children with OM in recent years. Due to the heterogeneity of these studies regarding population and instruments used, pooling of the results in a meta-analysis proved impossible; instead, a systematic review was conducted.

Except for the TAIQOL, so-called HRQoL questionnaires used in children with OM thus far mainly address symptoms and functioning of the child and thus in fact measure FHS. They focus on physical and behavioural consequences; only a

few address emotional or social symptoms and functioning in OM. Questions exploring feelings or perceptions of children themselves towards their health status, essential to HRQoL assessment, are also lacking.

The impact of AOM on the domain of physical functioning appeared to be similar between the studies in this review, with the majority of children with AOM reported experiencing physical suffering (pain, high fever etc), difficulty with hearing or speech, behavioural problems or emotional distress. In OME, hearing-, behavioural-, and balance-problems were prominent. These results correspond largely with previous epidemiological and diagnostic studies of physical symptoms in AOM [52-55] and OME [22-25, 27, 28, 56-58] and thus support the notion that FHS instruments in OM used in the reviewed studies apparently mainly assess the severity of signs and symptoms and their impact on physical functioning.

In HRQoL studies in children with OM, similar problems are faced as in studies on HRQoL in children with other medical conditions[9, 14, 59]. As children have limited cognitive and language abilities, studies often rely on (observable) measures that are assumed to be related to HRQoL, but actually reflect functional health status, or rely on caregivers as proxies. There is considerable discussion about the appropriateness of the use of caregivers to assess HRQoL in children[8, 60-64]. It appears that caregivers may be more able to judge the child's HRQoL in terms of physical functioning, rather than less observable functioning such as emotional or social functioning.[65] Besides, one may wonder whether HRQoL of a child as judged by caregivers is not merely a reflection of caregiver worries and emotional stress, which appears to be considerable.[19, 20] None of the studies, however, explored possible relations between caregiver reports of HRQoL in their children and level of caregiver worries or disruption.

Most instruments are also limited in their use, because of lack of evidence for reliability and validity. Responsiveness, an essential requirement for an instrument[66, 67], has been assessed and reported for only 5 instruments in 2 studies[32, 33]. Some studies[33, 48] used small sample sizes to assess psychometrics of

their instruments. Although there is no consensus yet about what constitutes adequate sample sizes, small numbers impair the reliability and validity of a study.[68, 69] Only one study[33] combined disease specific as well as a generic questionnaire to allow for comparisons between populations and identification of specific areas of problems for certain patient groups.[6, 70] The psychometrics of the OM-6 have been assessed the most extensively and appear to be appropriate. Several questionnaires are still in development. Except for internal consistency and construct validity, which generally were good, our knowledge about the psychometric characteristics of the FHS and HRQoL instruments is therefore quite limited.

In conclusion, the impact of OM on quality of life in children has been reported to be substantial. However, up to now widely different instruments have been used and most of them actually measure FHS instead of HRQoL in children with recurrent OM. Furthermore, adequate data on reliability and validity are lacking for most of the instruments. As a result, our knowledge of HRQoL in children with recurrent or chronic OM is still limited. We recommend the OM-6, based on its content validity and psychometric characteristics, as the most appropriate instrument currently available for FHS assessment in a research setting in children with OM. Although the TAIQOL appears promising, currently there is no instrument available for valid HRQoL assessment in children with otitis media.

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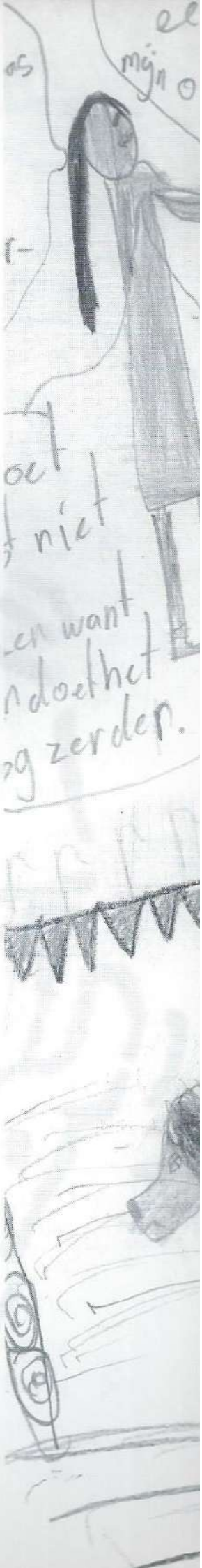
Chapter 3

Validity of health-related quality of life and functional health status instruments in children with recurrent acute otitis media:

I. Reliability, construct-, and discriminant validity



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"Wonderbaar als de sterren is de geest van de mens die hun loop gadeslaat."

Ds. Martin Luther King Jr.

Abstract

Background: Five to fifteen percent of all children suffer from recurrent acute infections of the middle ear. The repetitive episodes of infection cause considerable distress to the child and its family. Assessment of this burden of disease through measures of functional health status (FHS) and health-related quality of life (HRQoL) has become an important element of evidence-based medicine in acute otitis media (AOM). However, until now few of these instruments have been sufficiently validated; moreover, none of the existing validation studies have compared generic against disease-specific questionnaires on measures of reliability and validity. This study evaluates reliability, construct validity, and discriminant validity of both generic and disease-specific questionnaires in the assessment of FHS and HRQoL in 1 to 7 year-old Dutch children with recurrent acute otitis media (rAOM).

Methods: Quality of life was assessed in children with recurrent acute otitis media (rAOM; 2 or more episodes of AOM in the year prior to enrolment) participating in a placebo controlled trial on the effectiveness of pneumococcal vaccination. Caregivers completed a battery of questionnaires assessing general FHS (RAND, FSQ Generic, FSQ Specific), general HRQoL (TAIQOL), disease-specific FHS (OM-6), disease-specific HRQoL (NRS Child), and family functioning (FFQ, NRS Caregiver) during clinic visits at baseline and at 7, 14, and 26 months follow-up. For each instrument, floor and ceiling effects were estimated as well as internal consistency (item-total correlations, Cronbach's α), test-retest reliability (Pearson's r, ICC), construct validity, and discriminant validity.

Results: Internal consistency and test-retest reliability were excellent (Cronbach's α 0.80-0.90, ICC 0.81-0.93) for most instruments, while the TAIQOL subscales had borderline to good reliability coefficients (Cronbach's α 0.72-0.90, ICC 0.76-0.90). Construct validity was demonstrated by moderate to strong correlations between the questionnaires and between items covering physical impact. Construct validity was further supported by moderate to strong

correlations of global assessments of FHS (RAND) as well as of OM-specific HRQoL (NRS Child and NRS Caregiver) with the number of physician visits for upper respiratory tract infections (r = 0.41-0.48), and by moderate to strong correlations between disease-specific instruments and the number of AOM episodes in the preceding year (r = 0.39-0.49). Discriminant validity for children with few versus frequent AOM episodes per year was good for the RAND, FSQ Generic, FSQ Specific, OM-6 and FFQ ($p \leq 0.004$) but poor for the OM-related subscales of the TAIQOL (p = 0.10-0.97) and both numerical rating scales (p = 0.22 and 0.48).

Conclusions: Generic as well as disease-specific questionnaires demonstrated similar and high reliability, construct- and discriminant validity for assessment of FHS in children with recurrent AOM. Numerical rating scales and TAIQOL subscales demonstrated poor discriminant validity in this study.

Introduction

Acute otitis media (AOM) is a common childhood infection with a peak incidence during the second half of the first year. Five to fifteen percent of all children, depending on their age, suffer from recurrent acute infections of the middle ear (4 or more per year).[1-6] Repetitive episodes of pain, fever and general illness during acute ear infections[7-10] as well as worries about potential long-term sequelae such as hearing loss and disturbed language development[11-17] may all compromise the quality of life of the child and its family[18-20].

Assessment of this burden of disease through measures of functional health status (FHS) and health-related quality of life (HRQoL) has become an essential element of evidence-based medicine in otitis media (OM). Both generic and disease-specific instruments have been used to assess the impact of OM in children.[18, 21-23] However, until now few of these instruments have been sufficiently validated.[24] Besides, none of the existing validation studies compared the reliability and validity of FHS and HRQoL assessment between generic and disease-specific questionnaires in children with recurrent OM.

Reliability and validity are essential features of instruments and depend partly on the population in which they are used. Therefore, they have to be reassessed for every newly translated version and for every population that differs from the original population. Moreover, repeated validation of instruments demonstrates their strengths and weaknesses and consequently their value and applicability as an outcome measure in clinical practice and research.[25, 26]

This paper describes the reliability, construct and discriminant validity of both generic and disease-specific questionnaires assessing FHS and HRQoL in 1 to 7 year-old Dutch children with recurrent acute otitis media (rAOM). The purpose is to indicate which instruments are most useful for FHS and HRQoL assessment in children with recurrent acute otitis media.

Methods

Setting and procedure

Quality of life was assessed in children with recurrent acute otitis media participating in a double-blind placebo controlled randomized trial (RCT) on the effectiveness of pneumococcal vaccination. The trial was conducted at the pediatric outpatient departments of a general hospital (Spaarne Hospital Haarlem) and a tertiary care hospital (University Medical Center Utrecht). Children were recruited for this trial through referral by general practitioners, pediatricians, or otolaryngologists, or by self-referral from April 1998 to February 2001.

Inclusion criteria were age 12 to 84 months and a history of recurrent acute otitis media defined as having had at least 2 episodes of physician diagnosed AOM in the preceding year. Exclusion criteria were: known immunodeficiency other than IgA or IgG2 subclass deficiency; cystic fibrosis; immotile cilia syndrome; cleft palate; chromosomal abnormalities such as Down syndrome, or severe adverse events upon vaccination in the past. Table 1 summarises the population characteristics.

At each follow-up visit, data were collected regarding the number of episodes of AOM, upper respiratory tract infections, and pneumonia as well as medical treatment and ear-, nose-, and throat surgery in the preceding six months. Caregivers completed questionnaires assessing HRQoL and FHS of their child and family during clinic visits at baseline and at 7, 14, and 26 months follow-up.

Informed consent was obtained from the caregivers of all children before participation.

The ethics committees of both participating hospitals approved the protocol.

Table 1. Characteristics of study population at inclusion.

	mean or % (n=383)	SD or 95% CI
age *(months)*	34	(19.7)
male gender	62%	(57 – 67)
In the year prior to inclusion		
number of AOM episodes/year	5.0	(2.7)
2-3	37%	(32 – 42)
4-5	31%	(26 – 36)
6 or more	32%	(27 – 37)
impaired hearing	35%	(30 – 40)
language or speech problems	22%	(18 – 26)
History of		
chronic airway problems or atopic symptoms **	51%	(46 – 56)
adenoidectomy	47%	(42 – 52)
tympanostomy tubes	51%	(46 – 56)
other ear-, nose-, and throat surgeries	2%	(0.6 – 3)
antibiotic prophylaxis	15%	(11 – 19)
ever had speech-therapy	9%	(6 – 12)

** asthma, wheezing, hayfever, or eczema

Instruments

Three generic questionnaires and one disease-specific questionnaire were used to assess FHS of the children in the study. One generic questionnaire assessed the child's HRQoL. Two numerical rating scales were used: one to obtain a global rating of HRQoL of the child and one to obtain a global rating of HRQoL of the caregiver, respectively. Family functioning was assessed using a newly composed questionnaire. Questionnaires were completed by the caregivers during the clinic visits. In case of obscurities or questions, the caregiver was assisted by one of the two research physicians (C.N.M. and R.H.V.).

Appendix 1 summarises the characteristics of the questionnaires. For all questionnaires, higher scores indicate a better HRQoL or FHS.

Generic instruments

The RAND and the Functional Status Questionnaire (FSQ), both assessing general functional health status, were translated and validated for Dutch children by Post et al.[27-29] (Appendix 1, p. 179). The 7 items of the RAND, originally selected from a child FHS instrument developed at the RAND Corporation[30], assess general health perceptions of caregivers regarding their child, i.e., current health, susceptibility to illness, and prior health.

The FSQ consists of two parts: one measuring general functional limitations (FSQ Generic, FSQ-G) and the other measuring illness-specific functional limitations (FSQ Specific, FSQ-S). The FSQ-S only rates functional loss that is attributable to any illness.[30] Functional limitations in the FSQ are mainly expressed as behavioural problems. The RAND and FSQ have been applied to various pediatric populations[27-29, 31-38], including children with AOM.[21]

During the course of the study, a new Dutch instrument on generic HRQoL became available: the TNO-AZL Infant Quality of Life (TAIQOL)[38, 39]. Beginning in July 1999 this questionnaire was added to the previously selected set of instruments. The TAIQOL is the only Dutch instrument providing a generic HRQoL profile for children aged 1 to 5 years. Although the TAIQOL has been developed for children aged up to 5 years, we also used the questionnaire in children aged six up to seven years, as no appropriate alternative was available.

Disease-specific instruments

To measure disease-specific FHS, the Otitis Media-6 (OM-6)[18, 22] was translated into Dutch according to principles of backward-forward translation.[40-43] This six-item questionnaire covers both acute and long-term functional effects of OM in children (see Appendix 2, p.181).

To assess the impact of recurrent OM in children on their caregivers and

siblings a family functioning questionnaire (FFQ) was created. The FFQ is composed of six questions covering effects of the child's recurrent OM on caregiver and family activities and two questions assessing these effects on emotional behaviour of the other siblings (see Appendix 3, p.182).

Finally, two numerical rating scales (NRS) (0-100) were used, reflecting global judgements of the caregiver of their own (NRS Caregiver) and their child's HRQoL (NRS Child) due to the child's episodes of OM. The NRS Child[18] was translated into Dutch according to the same principles of backward-forward translation that have been applied to translation of the OM-6. The newly created NRS Caregiver was modelled upon the NRS Child and added to the previously selected set of instruments beginning in July 1999.

Floor and ceiling effects

Floor and ceiling effects were estimated for the baseline-assessment of each instrument. They were expressed as percentage of respondents that had minimum and maximum scores, respectively. Additionally, the percentage of respondents in each quartile of the possible score range were calculated, reflecting the distribution of the scores.

Reliability

Internal consistency was assessed by calculating item-total correlations using the formula provided by Nunnally[44] and by calculating Cronbach's alpha for each questionnaire or subscale. Inter-item correlations of questionnaires were assessed to reveal 'hidden' subscales that may erroneously yield a high overall Cronbach's alpha. The lower limit for item-total correlations was set at 0.20, whereas Cronbach's alpha should be above 0.70[45].

To assess test-retest reliability, a subset of caregivers (n=160) was given a second set of the same questionnaires (test 2) to complete at home within 2 weeks after completing the first set of questionnaires during the outpatient visit at 14 months follow-up (test 1). Test-retest reliability was examined by calculating the

Pearson's correlation coefficients as well as the intraclass correlation coefficients (ICC) between the two sets of questionnaires. A reliability of 0.80 was considered the required minimum.[45, 46]

Construct validity

To demonstrate construct validity, à priori predictions were made about the strength of correlations between questionnaires as well as between related items or subscales. The number of correct predictions was expressed as a percentage of all predictions made. The higher this percentage and the stronger the predicted convergent correlations, the stronger construct validity was supported. Correlation between FSQ Generic and NRS Caregiver was predicted to be weak since they assess two very different constructs. Moderate-to-strong correlations ($r>0.40$) were predicted between RAND and NRS Caregiver. Moderate-to-strong correlations were also expected between OM-6 and FSQ Specific, NRS Child, NRS Caregiver and FFQ, as all assess OM-related HRQoL or FHS. The correlation between FSQ Generic and FSQ Specific was expected to be strong. The remaining correlations among the instruments were expected to be moderate.

The same procedure was followed for correlations between certain items or subscales. Items covering similar subjects were predicted to have at least moderate-to-strong correlations.

Finally, correlations between questionnaire scores and number of physician visits for upper respiratory tract infections in the preceding 6 months and between questionnaire scores and number of AOM episodes were calculated.

Since distributions of instrument scores were skewed, correlations were assessed using Spearman's rho. A correlation of 0.10-0.30 was defined as weak, 0.30-0.50 as moderate, and 0.50 or more as strong.[47]

Discriminant validity

Discriminant validity was assessed by dichotomizing the study participants in children with 2-3 versus 4 or more episodes of OM per year. Based on clinical and

immunological data, children with 4 or more AOM episodes per year are considered as 'otitis prone'[2, 4, 48-51], reflecting a sub-group with an increased rate of upper respiratory tract infections, ear-, nose-, and throat surgery and medical consumption.[52, 53] It was assumed that this group would perform significantly poorer than children with 2-3 OM-episodes per year on all questionnaires and the otitis media-related subscales of the TAIQOL (independent sample Mann-Whitney tests). The following TAIQOL subscales were considered otitis media related: 'Sleeping', 'Appetite', 'Problem behaviour', 'Positive mood' and 'Liveliness'.

Data of all children at baseline were used for the reliability and validity assessment.

Results

Floor and ceiling effects

Generally, the instruments demonstrate no floor-effects (Table 2). The FSQ Specific, the OM-related TAIQOL subscale 'Appetite', the OM-6, and FFQ showed moderate ceiling effects. Two OM-related TAIQOL subscales, 'Positive mood' and 'Liveliness', showed large ceiling effects.

Table 2. Floor and ceiling effects of instruments: percentage of respondents with minimum and maximum scores, and percentage of respondents for each quartile score range.

	Minimum (%)	Maximum (%)	1st quartile (%)	2nd quartile (%)	3rd quartile (%)	4th quartile (%)
Generic						
RAND	0	0	10	31	45	14
FSQ Generic	0	2	1	7	45	47
FSQ Specific	0	21	1	5	34	61
TAIQOL						
Sleeping	2	12	6	37	32	25
Appetite	0	22	3	22	31	45
Positive mood	0	80	0	9	14	86
Liveliness	0.6	81	1	0	13	87
Problem behaviour	1	4	8	21	40	32
Disease-specific						
OM-6	0	14	6	30	26	38
NRS Child	2	3	10	44	42	5
FFQ	0.5	27	1	7	28	64
NRS Caregiver	0	0	2	29	57	12

Internal consistency

Item-total correlations generally were moderate to high for all questionnaires (Table 3). For the FSQ Generic and FSQ Specific, only the 'Communicated what he/she wanted' item had poor correlations with the overall score. Two of four items of the TAIQOL subscale 'Motor functioning' correlated poorly with the total subscale score.

Cronbach alpha coefficients were high for all questionnaires. The Cronbach alpha coefficients of TAIQOL subscales were adequate to high (range 0.72-0.90). Although for the FFQ and three TAIQOL subscales Cronbach's alpha coefficients reached 0.90, no 'hidden' subscales were revealed by calculation of inter-item correlations.

Table 3. Internal consistency and test-retest reliability.

	Internal consistency		Test-retest reliability	
	Item-total correlation	Cronbach's alpha	Pearson's $r^{\#}$	ICC
Generic				
RAND	0.43 – 0.72	0.81	0.90	0.89
FSQ Generic	0.15* - 0.58	0.80	0.92	0.92
FSQ Specific	0.26 – 0.73	0.86	0.89	0.89
TAIQOL				
Sleeping	0.74 – 0.81	0.90	0.83	0.83
Appetite	0.73 – 0.75	0.86	0.81	0.82
Lungs	0.53 – 0.76	0.81	0.90	0.90
Stomach	0.55 – 0.64	0.76	0.85	0.86
Skin	0.51 – 0.61	0.72	0.80	0.79
Motor functioning	0.21 – 0.44	0.90	0.86	0.86
Social functioning	0.50 - 0.72	0.77	0.79	0.82
Problem behaviour	0.57 – 0.72	0.86	0.85	0.85
Communication	0.40 – 0.63	0.88	0.82	0.82
Anxiety	0.47 – 0.69	0.76	0.78	0.78
Positive mood	0.75 – 0.86	0.90	0.81	0.81
Liveliness	0.76 – 0.77	0.88	0.76	0.76
Disease-specific				
OM-6	0.30 – 0.80	0.85	0.89	0.89
NRS Child			0.84	0.83
FFQ	0.49 – 0.81	0.90	0.94	0.93
NRS Caregiver			0.82	0.81

$^{\#}$ = all correlations were significant at the 0.01 level

* = one item, all other items $r \geq 0.32$

Test-retest reliability

Of the caregivers, 160 were requested to complete the second set of questionnaires, 126 (79%) completed the questionnaire, and 113 returned sets (71%) were completed within 2 weeks. Seven children with AOM at the time of the clinic visit were excluded, resulting in 106 sets for analysis. The Pearson

correlation coefficients (PCC) and ICC's were largely in agreement (Table 3). Correlations were moderate to high for the RAND, FSQ Generic and Specific, OM-6, FFQ and both numerical rating scales (0.81-0.94). For the TAIQOL, the PCC's and ICC's were in the borderline range for the subscales 'Anxiety' and 'Liveliness' (0.76 to 0.78) and moderate to high for the other subscales (0.79-0.90).

Construct validity

Table 4a reflects the predicted and calculated correlations between the instruments. Of 21 correlations, 14 (67%) were predicted correctly. False predictions were mainly made about correlations of the NRS Child and NRS Caregiver with the other instruments, which were generally expected to be at least moderate, but were found to be weak. The RAND, FSQ Generic, FSQ Specific, OM-6, and FFQ showed considerably strong correlations, which was in agreement with our predictions

Table 4a. Construct validity on the instrument level.*

	RAND	FSQ Generic	FSQ Specific	OM-6	NRS Child	FFQ	NRS Caregiver
RAND	1.00	**0.52** ***mod-str***	**0.49** ***mod***	**0.34** ***mod***	**0.33** ***mod***	**0.43** ***mod***	**0.49** ***mod-str***
FSQ Generic		1.00	**0.80** ***str***	**0.37** ***mod***	0.25 *mod*	**0.43** ***mod***	**0.24** ***wk***
FSQ Specific			1.00	**0.49** ***mod-str***	0.26 *mod*	**0.52** ***mod***	0.24 *mod*
OM-6				1.00	0.23 *mod-str*	**0.74** ***mod-str***	0.28 *mod-str*
NRS Child					1.00	0.22 *wk-mod*	**0.47** ***mod***
FFQ						1.00	0.39 *str*
NRS Caregiver							1.00

* Spearman correlation coefficients & *predicted strength of correlations*, appropriately predicted correlations are bold-printed.

wk = weak; wk-mod = weak to moderate; mod = moderate; mod-str = moderate to strong; str = strong

On the item-level and subscale-level, twelve of 16 (75%) correlations were correctly predicted to be at least moderate (Table 4b). Weak correlations (Spearman's rho 0.17 - 0.29) were found between items covering emotional aspects. The TAIQOL subscales assessing physical functioning demonstrated moderate correlations with questionnaire-items assessing similar topics (Spearman's rho 0.39 - 0.48).

Table 4b. Construct validity – correlations (Spearman's rho) on the item and TAIQOL subscale level.

Pairs of items or subscales					Spearman's rho
RAND	Worries caregiver by child's health	-	OM-6	Worries of caregiver by AOM	**0.40**
RAND	Pain or distress child	-	OM-6	Pain/discomfort by AOM	**0.44**
		-	OM-6	Upset by AOM	**0.44**
FSQ-G	Eating well	-	TAIQOL	Appetite	**0.41**
FSQ-G	Sleeping well	-	TAIQOL	Sleeping	**0.39**
FSQ-G	Content and cheerful	-	TAIQOL	Positive mood	**0.41**
FSQ-G	Acting moody	-	TAIQOL	Positive mood	0.24
FSQ-G	Feeling sick and tired	-	TAIQOL	Liveliness	0.17*
FSQ-G	Lively and energetic	-	TAIQOL	Liveliness	**0.38**
FSQ-G	Unusually irritable	-	OM-6	Upset by AOM	0.29
FSQ-G	Sleeping through the night	-	TAIQOL	Sleeping	**0.48**
FSQ-G	Unusually difficult	-	OM-6	Upset by AOM	0.24
OM-6	Speech difficulties	-	TAIQOL	Communication	**0.47**
OM-6	Worries of caregiver by AOM	-	FFQ	Disturbed sleep caregiver	**0.60**
		-	FFQ	Change of daily activities	**0.58**
		-	FFQ	Tense, irritable caregiver	**0.60**

* Correlation significant at 0.05 level, all other correlations significant at 0.01 level.

Appropriately predicted correlations are bold-printed.

Moderate to strong correlations were found for the global assessments of FHS (RAND) and of OM specific HRQoL (NRS Child and NRS Caregiver) with the

number of physician visits for upper respiratory tract infections, a more global clinical indicator of illness. The disease-specific instruments, i.e., OM-6, NRS Child, FFQ and NRS Caregiver, showed moderate to strong correlations with the number of AOM episodes in the preceding 6 months (Table 4c).

Table 4c. Construct validity – correlations (Spearmans'rho) between instrument scores and physician visits for URTI* and number of AOM* epsiodes.

	Nr of physician visits for URTI	Nr of AOM epsiodes
Generic		
RAND	- 0.48	- 0.31
FSQ Generic	- 0.20	- 0.07#
FSQ Specific	- 0.27	-0.12##
Disease-specific		
OM-6	-0.32	-0.41
NRS Child	- 0.41	-0.49
FFQ	- 0.29	- 0.39
NRS caregiver	- 0.41	- 0.40

* URTI: upper respiratory tract infection; AOM: acute otitis media

All correlations p < 0.001, except for # (p=0.16) and ## (p=0.02).

Discriminant validity

The RAND, FSQ Generic, FSQ Specific, OM-6 and FFQ were able to discriminate between children with moderately serious recurrent AOM (2-3 episodes per year) and "otitis-prone" children with serious recurrent AOM (4 or more episodes per year) (Table 5). As expected, on these questionnaires scores of "otitis-prone" children were significantly lower than those of children with 2-3 AOM episodes per year. However, the two numerical rating scales (NRS Child and NRS Caregiver) and the OM-related subscales of the TAIQOL did not discriminate between these two groups.

Table 5. Discriminant validity (Mann-Whitney test) for children with 2-3 versus 4 or more AOM episodes in the preceding year.

	2-3 AOM episodes	≥ 4 AOM episodes	Mann-Whitney p-value
Generic			
RAND	21.1	19.6	0.004
FSQ Generic	76.5	72.2	0.002
FSQ Specific	83.9	78.4	0.001
TAIQOL			
Sleeping	66.2	60.7	0.10
Appetite	74.7	73.2	0.44
Liveliness	93.2	91.3	0.81
Positive mood	92.0	92.5	0.97
Problem behaviour	64.8	60.9	0.24
Communication	83.8	84.5	0.69
Disease-specific			
OM-6	18.9	17.0	< 0.001
NRS Child	5.2	5.4	0.48
FFQ	84.9	78.5	< 0.001
NRS Caregiver	6.6	6.2	0.22

Discussion

In this study, we assessed the reliability, construct-, and discriminant validity of four generic questionnaires (RAND, FSQ Generic, FSQ Specific, TAIQOL), two disease-specific questionnaires (OM-6 and FFQ) and two disease-specific numerical rating scales (NRS Child and NRS Caregiver) in a randomized controlled trial on the effectiveness of pneumococcal vaccination in children with recurrent acute otitis media. Internal consistency and test-retest reliability was excellent for most questionnaires and good for most TAIQOL subscales. Construct validity was demonstrated by moderate to strong correlations between

the questionnaires and between items covering physical impact, which were in agreement with our predictions. However, correlations with both numerical rating scales and with items of emotional functioning were surprisingly low. In further support of construct validity, global assessments of FHS (RAND) and of OM-specific HRQoL (NRS Child and NRS Caregiver), and assessment of OM-specific FHS (OM-6 and FFQ) correlated at least moderately with relevant clinical indicators.

Discriminant validity was good for the RAND, FSQ Generic, FSQ Specific, OM-6 and FFQ but poor for the OM-related subscales of the TAIQOL and both numerical ratings scales. Generic (RAND and FSQ) and disease-specific (OM-6 and FFQ) questionnaires demonstrated similar and adequate construct validity and discriminant validity.

Internal consistency of the RAND, FSQ Generic, FSQ Specific, TAIQOL and OM-6 in this study, as expressed by Cronbach's alpha, was comparable with results of previous studies using these instruments.[18, 21, 27, 28, 38] For the FSQ Generic, FSQ Specific, and OM-6, another estimate of reliability, the test-retest reliability, was also consistent with previously reported results.[18, 27, 28] The consistency of these results across different pediatric populations supports the reliability of these instruments.

Heterogeneity of methods limits the comparability of data on validity of instruments in this study with those from previous studies. Regarding discriminant validity, subscales of the TAIQOL that were considered OM-related in this study showed to differentiate between children with recurrent AOM and healthy children (Chapter 5).[54] However, they were not sensitive to differences in HRQoL between children who differ in severity of rAOM. Likewise, Fekkes et al.[38] found that the subscales 'Problem behaviour', 'Positive mood', and 'Liveliness' discriminated neither between healthy and preterm children nor between healthy and chronically ill children.

Adequate discriminant validity between children with asthma and healthy children has been demonstrated for the Dutch versions of the RAND, FSQ Generic and FSQ Specific by Post et al.[27, 28] In this study, the generic questionnaires also demonstrated sensitivity to differences between children with different AOM frequency, which may be a more subtle difference.

The FFQ and NRS Caregiver were newly composed instruments. The FFQ demonstrated excellent reliability and validity. The strong correlation with the OM-6 supports its complementary usefulness in HRQoL and FHS assessment in children with rAOM. The NRS Caregiver, however, yielded the same kind of poor results as did the NRS Child for construct and discriminant validity and needs further exploration.

The poor performance of both numerical rating scales on construct validity and discriminant validity may be explained by their global assessment of HRQoL. Global judgement of HRQoL or 'well-being' may be too crude to reflect subtle differences in FHS or HRQoL.[55, 56] On the other hand, comments of the caregivers indicated that some of them may have misunderstood the instructions to judge their child's and their own HRQoL as *related to* the recurrent AOM episodes, instead interpreting the instructions as to judge their child's and their own HRQoL *during* AOM episodes. If misapprehension had been a major cause of poor construct validity, results are expected to improve by learning effects during follow-up assessments. Both numerical rating scales indeed had adequate construct validity at subsequent test moments.

Several issues need to be considered with regard to this study. First, because we did not include psychological or social assessment instruments, construct and discriminant validity of the emotional and social items of the HRQoL and FHS questionnaires may not have been sufficiently assessed. The rationale to restrict the total number of questionnaires to five was to limit the burden on caregivers and to increase compliance.

Second, the FFQ and NRS Caregiver are both instruments that assess the impact of rAOM in a child on the caregivers and family. Although family life and caregiver-child relationship are considered important aspects of a child's HRQoL[57-59], it remains to be discussed to what extent they should be integrated in the assessment of a child's HRQoL and FHS.[60]

Third, there is discussion about the reliability of caregivers as proxies in the assessment of FHS or HRQoL in children. Loonen et al.[61, 62], for example, state that analysing test-retest reliability requires assessment by the patient himself. However, as pre-school children are not capable of judging their FHS nor HRQoL, caregivers are considered the best informants[63-65] and were surveyed as proxies in this study. The influence of caregivers on the assessment of FHS and HRQoL in children needs further study.

Finally, since indices of validity and reliability are not fixed characteristics of FHS and HRQoL instruments but rather are influenced by study design, intervention, and especially study population, the results of this study should only be generalized to pediatric populations with moderately serious to serious recurrent ear-infections.

Although the instruments in this study are used to assess HRQoL and FHS in groups, some meet reliability standards for assessment in individuals. The minimally required reliability coefficient of 0.90 for individual assessment[45, 66] was met by the FFQ for both internal consistency and test-retest reliability, while the RAND, FSQ Generic, and four TAIQOL subscales (Sleeping, Lungs, Motor functioning, and Positive mood) met this minimum coefficient for one of these two reliability measures.

Generic questionnaires are generally expected to be less sensitive to differences in FHS or HRQoL than disease-specific questionnaires.[25, 67-69] However, in this study disease-specific questionnaires performed only marginally better than generic questionnaires on the discriminant validity test. For the FSQ Generic and FSQ

Specific, sensitivity to differences in FHS could be explained by their content, as they include many physical and emotional items that may be affected by rAOM.

In conclusion, generic (RAND, FSQ Generic and FSQ Specific) as well as disease-specific (OM-6, FFQ) questionnaires demonstrated similar and high reliability and construct- and discriminant validity for assessment of FHS in children with recurrent AOM. The Family Functioning Questionnaire (FFQ) in particular is potentially suitable for individual assessment. However, numerical rating scales as used in this study seem less adequate for assessment of HRQoL in this population. The TAIQOL, the only true HRQoL questionnaire, unexpectedly showed poor discriminant validity and will need revision before use in clinical outcome studies in children with otitis media.

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Chapter 4

Validity of health-related quality of life and functional health status instruments in children with recurrent acute otitis media:

II. Responsiveness

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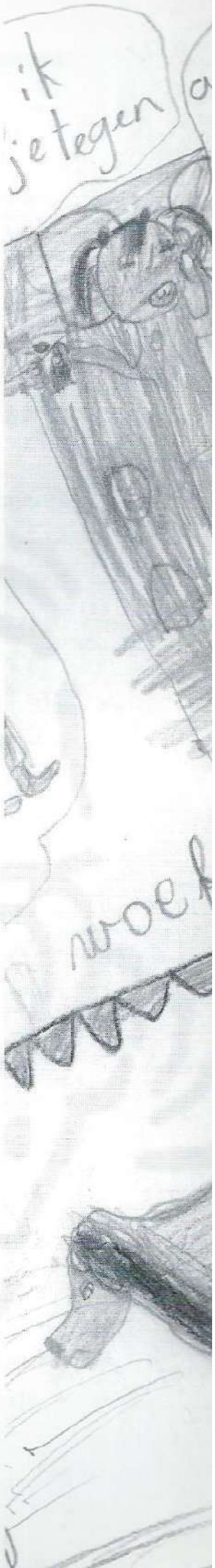

"If you would hit the mark you must aim a little above it."

Henry Wadsworth Longfellow

Abstract

Background: meaningful evaluation of treatment effects on health-related quality of life (HRQoL) and functional health status (FHS) requires instruments that are responsive, that is, are able to detect clinically important change. Recently developed guidelines recommend the use of multiple strategies as well as head to head comparison between generic and disease-specific instruments in the assessment of responsiveness.

Purpose: To assess responsiveness as part of the validation of instruments assessing HRQoL and FHS in children with recurrent acute otitis media.

Methods: Generic HRQoL (TAIQOL), disease-specific HRQoL (NRS Child and NRS Caregiver), generic FHS (RAND, FSQ Specific and FSQ Generic) and disease-specific FHS (OM-6 and FFQ) were assessed in 383 children aged 1 to 7 years with recurrent acute otitis media (rAOM) participating in a trial on the effectiveness of pneumococcal vaccination. Assessment of responsiveness involved 2 steps:

- Assessment of sensitivity to change by a paired t-test and calculation of effect size;
- Assigning meaning to change by applying distribution-based (MCID based on a change of 1-SEM or 0.3 ES) and anchor-based (using AOM frequency and AOM severity as clinical anchors) methods to estimate minimally clinical important change or difference (MCID).

All methods were implemented over two intervals: 0 to 7 months and 7 to 14 months follow-up.

Results: Sensitivity to change: except for the TAIQOL subscales, change-scores were significant ($p \leq 0.003$) for generic and disease-specific instruments. Effect sizes were somewhat higher for disease-specific compared to generic instruments (0.55-0.95 versus 0.29-0.60). The TAIQOL subscales showed very poor sensitivity to change and were excluded from further analyses.

Interpretation of change: distribution-based methods yielded similar estimates of MCID for generic and disease-specific instruments: 5-9 points on a 0-100 scale.

Anchor-based methods resulted in a larger range of estimates of MCID: 3-29 points on a 0-100 scale for AOM frequency and 2-17 points for AOM severity. Combining distribution-based and anchor-based methods resulted in similar ranges for the MCID for generic (2-10 points on a 0-100 scale) and disease-specific instruments (3-15 points, excluding the NRS Child, which had much larger estimates for the MCID).

Conclusions: Both generic and disease-specific instruments used in this study show adequate responsiveness to be used in clinical studies on children with recurrent otitis media. The TAIQOL subscales, however, displayed very poor sensitivity to change, making them inadequate for the assessment of change in this population.

Introduction

Assessment of health-related quality of life (HRQoL) and functional health status (FHS) has increasingly become a part of clinical trials on the effectiveness of treatment in pediatric chronic conditions. Meaningful evaluation of treatment effects on HRQoL and FHS requires instruments that not only are reliable but also are responsive to changes in HRQoL and FHS.[1, 2] In this study responsiveness is defined as the ability to detect clinically important change over time and therefore involves both assessment of sensitivity to change and the assignment of meaning to that change.[3, 4]

Various strategies have been used to assess responsiveness of instruments. Since none of these is without limitations, the use of multiple strategies, categorized into distribution-based and anchor-based methods, is most suitable in assessing responsiveness of HRQoL and FHS instruments.[5] Distribution-based methods express the amount of change over the amount of random variance of an instrument.[5, 6] Anchor-based methods enhance interpretability of changes in instrument scores by linking meaning and clinical relevance to change-scores.[5, 7]

Health-related quality of life has been assessed by generic and disease-specific instruments. Generic instruments cover a wide spectrum of quality of life concepts and various health states and populations, while disease-specific instruments assess health-related issues specific to particular conditions and populations. As a consequence, generic instruments may not detect small but clinically important changes which can be found by more sensitive disease-specific instruments.[1, 8] However, there have been few head-to-head comparisons between generic and disease-specific HRQL measurement instruments in the setting of randomized controlled trials (RCTs).[2]

In this study, responsiveness of HRQoL and FHS instruments will be assessed in a randomized controlled trial on the effectiveness of pneumococcal vaccination in children with recurrent acute otitis media, a condition of repetitive middle ear

infections causing pain and general illness. Reliability, construct- and discriminant validity have been described in a separate article.[9] Assessment of the responsiveness of both generic and disease-specific HRQoL and FHS instruments using distribution-based as well as anchor-based methods will result in recommendations regarding applicability of these instruments in clinical studies in children with recurrent acute otitis media.

Methods

Setting and procedure

HRQoL and FHS were assessed in 383 children with recurrent acute otitis media participating in a double-blind RCT on the effectiveness of pneumococcal vaccination versus control hepatitis vaccination. The study was conducted at the pediatric outpatient departments of a general hospital (Spaarne Hospital Haarlem) and a tertiary care hospital (University Medical Center Utrecht). Inclusion criteria were age 12 to 84 months and a history of recurrent acute otitis media defined as having had at least 2 episodes of physician diagnosed acute otitis media in the year prior to study entry. Exclusion criteria were conditions with a known increased risk for acute otitis media such as known immunodeficiency other than IgA or IgG2 subclass deficiency, cystic fibrosis, immotile cilia syndrome, cleft palate, chromosomal abnormalities like Down syndrome or severe adverse events upon vaccination in the past. Table 1 summarises the population characteristics.

During clinic visits at inclusion and at 7 and 14 months follow-up, data on episodes of physician diagnosed acute otitis media were documented and several questionnaires assessing HRQoL and FHS of their child and of the family were completed by caregivers. A research physician assisted the caregiver in case of obscurities or questions. Informed consent was obtained from caregivers of all children before study entry. Medical ethics committees of both participating hospitals approved the protocol.

Table 1. Characteristics of study population at inclusion.

	mean or % (*n=383*)	SD or 95% CI
age *(months)*	34	(19.7)
male gender	62%	(57 – 67)
In the year prior to inclusion		
number of AOM episodes/year	5.0	(2.7)
2-3	37%	(32 – 42)
4-5	31%	(26 – 36)
6 or more	32%	(27 – 37)
impaired hearing	35%	(30 – 40)
language or speech problems	22%	(18 – 26)
History of		
chronic airway problems or atopic symptoms *	51%	(46 – 56)
adenoidectomy	47%	(42 – 52)
tympanostomy tubes	51%	(46 – 56)
other ear-, nose-, and throat surgeries	2%	(0.6 – 3)
antibiotic prophylaxis	15%	(11 – 19)
ever had speech-therapy	9%	(6 – 12)

* asthma, wheezing, hayfever, or eczema

Instruments

Four generic questionnaires (RAND, FSQ Generic, FSQ Specific, and TAIQOL) and one disease-specific questionnaire (OM-6) were used to assess HRQoL and FHS of the children in the study. Additionally, two numerical rating scales (NRS Child and NRS Caregiver) were used to obtain a global rating of HRQoL in the child and in the caregiver, respectively. Finally, a newly composed questionnaire (FFQ) was used to assess family functioning.[9] Appendix 1, p.179, summarises the characteristics of the questionnaires. From the TAIQOL only those subscales assumed to be sensitive to the consequences of acute otitis media were used: 'Sleeping', 'Appetite', 'Liveliness', 'Problem behaviour', and 'Positive mood'. For all questionnaires higher scores indicate a better HRQoL or FHS. To enhance comparability, all scores were linearly transformed into 0-100 scales.

Responsiveness

Since pneumococcal vaccination showed no clinical effectiveness as compared to the control vaccine[10], the intervention could not be used as an external criterion of change. Instead, data of both vaccine groups were pooled for the assessment of responsiveness. Based on clinical experience of pediatricians and pediatric otolaryngologists, a reduction of 2 or more episodes of acute otitis media per child per year was set as the external criterion for 'changed' subjects while no reduction or a reduction of 1 episode identified 'unchanged' subjects. Responsiveness was evaluated for two intervals; from study entry to 7 months follow-up and from 7 to 14 months follow-up. The two intervals differed considerably regarding the reduction of acute otitis media incidence during the interval-periods: during the first 7 months follow-up the mean incidence per child decreased with 3.1 episodes per year, whereas during 7-14 months follow-up the mean decrease in AOM incidence was 0.6 episodes per year (see also Chapter 6).[11]

The first step in the assessment of responsiveness was to explore the ability of instruments to detect change at all, i.e., its sensitivity to change. The second step was to determine meaning and clinical relevance of the change-score.

Sensitivity to change

Sensitivity to change was assessed by calculating statistical significance of change-scores using a paired t-test as well as by calculating effect sizes for changed subjects. Guyatt's responsiveness statistic[12] was used as a measure of effect size (ES, for mathematical formulas see: Appendix 4, p.182). This statistic is a quantitative descriptor of the magnitude of change that actually took place in the studied population, that is, the observed or actual change-score that occurred in changed subjects relative to the random change or random error in unchanged subjects. According to the benchmarks of Cohen[13], an ES of 0.2 represents a small change, 0.5 a moderate change and 0.8 or higher represents a large change.

In accordance with recent recommendations[5, 14-16], both distribution- and anchor-based interpretability of responsiveness are given.

Interpretation of change - distribution-based methods

Distribution-based methods consisted of calculation of the minimally clinically important difference (MCID) according to ES benchmarks (ES-MCID) and according to standard error of measurement (SEM-MCID). The MCID gives an interpretation of the magnitude of change, as it is the smallest difference in a instrument or domain score that patients perceive as beneficial.[17] The ES-MCID and SEM-MCID reflect the smallest change needed to be substantially larger than the random variability in the study population based on the calculated SD of the unchanged subjects. A change on a questionnaire corresponding with an effect size (in this study Guyatt's Responsiveness Statistic) of 0.3 to 0.5 has been found to be consistent with other estimates of the MCID.[7, 18, 19] In this study an effect size of 0.3 is used as benchmark. Similarly, a SEM change of 1 is considered to correspond with the MCID of an instrument.[16, 20-22] Both methods of identifying a MCID were applied to the questionnaires in this study.

Interpretation of change - anchor-based methods

Anchor-based methods require an independent standard, the anchor, that in itself is easily interpretable and that is at least moderately correlated with the instrument being assessed. Changes in questionnaire scores were compared with change in two clinically relevant anchors: the acute otitis media frequency (incidence of acute otitis media episodes per child) and the acute otitis media severity assessed with a Dutch version of the OM-Functional Status Questionnaire specific (OM-FSQ specific[23]).

Frequency of recurrent acute otitis media was expressed as the number of episodes per child per year. Paediatricians and paediatric otolaryngologists considered a change of 2 episodes per year as a small or minimally clinical important change, whereas a change of 4 episodes per year was considered moderate to large.

The OM-FSQ specific consists of 3 questions assessing clinical acute otitis media severity (see Appendix 5, p.183). In our population, the OM-FSQ specific demonstrated high internal consistency (Cronbach's α 0.88) and good test-retest reliability (ICC 0.94). The OM-FSQ specific correlated moderately with the RAND (Spearman's rho 0.36), FSQ Generic (0.37), TAIQOL subscale 'Sleeping' (0.31), and NRS Caregiver, and strongly with the FSQ Specific (0.52), OM-6 (0.73) and FFQ (0.61). In the study of Alsarraf et al.[23], the OM-FSQ specific score was ± 62 on a scale of 0-100 during an episode of acute otitis media, increasing to 92 at 6 weeks and 90 at 12 weeks after an episode of acute otitis media (higher scores reflecting less severe ear-symptoms). Therefore, we considered a score change of 10-20 on a 0-100 scale in the current population as a small change in acute otitis media severity, a score change of 30-50 as a moderate to large change.

Results

According to our external criterion of change (a reduction of 2 or more episodes of acute otitis media per year), 270 children were classified as 'changed' for the first interval (0 to 7 months follow-up) and 126 children for the second interval (7 to 14 months).

Responsiveness

Sensitivity to change

Sensitivity to change, expressed as significance of change and effect size, is presented in Table 2. Except for the TAIQOL subscales, generic as well as disease-specific instruments yielded significant change-scores for changed subjects during both follow-up periods. Of the TAIQOL subscales, only 'Sleeping' showed consistent and significant change.

Table 2. Sensitivity to change – mean change-scores, paired t-test and effect size (Guyatt's responsiveness statistic) for changed subjects.

	Mean change-score				Effect size – GRS	
	0 – 7 mo#		7 – 14 mo		0 – 7 mo	7 – 14 mo
	n = 270*	*p-value*	*n* = 126**	*p-value*	*n* = 270*	*n* = 126**
Generic						
RAND	10.2	*< 0.001*	7.7	*< 0.001*	0.60	0.54
FSQ Generic	7.0	*< 0.001*	4.9	*0.001*	0.37	0.29
FSQ Specific	9.1	*< 0.001*	6.0	*< 0.001*	0.37	0.32
TAIQOL						
Sleeping	9.9	*< 0.001*	7.1	*0.03*	0.37	0.36
Appetite	6.8	*0.001*	0.0	*1.0*	0.28	0.00
Problem behaviour	0.4	*0.80*	- 2.8	*0.33*	0.02	0.13
Positive mood	1.5	*0.30*	3.9	*0.11*	0.06	0.25
Liveliness	2.3	*0.19*	1.6	*0.51*	0.22	0.11
Communication	2.9	*0.12*	1.7	*0.32*	0.16	0.11
Disease-specific						
OM-6	16.6	*< 0.001*	11.5	*< 0.001*	0.60	0.73
NRS Child	28.3	*< 0.001*	14.2	*< 0.001*	0.91	0.64
FFQ	13.6	*< 0.001*	8.0	*< 0.001*	0.55	0.60
NRS Caregiver	19.2	*0.003*	9.1	*0.003*	0.95	0.57

GRS = Guyatt's responsiveness statistic

mo = months

* *n* = 114 for TAIQOL subscales and NRS Caregiver

** *n* = 51 for TAIQOL subscales and NRS Caregiver

The ES for the generic FHS questionnaires ranged from small to moderate (0.29 to 0.60). For the generic TAIQOL subscales, the ESs were low, ranging from almost zero for the subscales 'Appetite', 'Problem behaviour' and 'Positive mood' to small for 'Sleeping', and 'Liveliness' (0.22 to 0.37). For the disease-specific instruments, ESs were moderate to large (0.55 to 0.95).

ESs for the questionnaires were similar for the first (0 - 7 months) and second interval (7 - 14 months), although for the second interval absolute change-scores were smaller. The ESs for the two numerical rating scales were however strikingly lower during the second interval as compared to the first interval.

Because of its poor sensitivity to change, the TAIQOL was excluded from further analyses on the interpretation of change.

Interpretation - distribution-based methods

Minimally clinical important differences (MCIDs) calculated with distribution-based methods are presented in Table 3. During the first interval, ES-MCIDs using 0.3 ES as benchmark were somewhat smaller for generic instruments (5.0 - 7.4 on a 0-100 scale) than those for disease-specific instruments (6.1 - 9.4). During the second interval, however, ES-MCIDs for generic and disease-specific instruments were comparable (4.0 - 6.7), indicating that for both types of instruments similar change-scores are needed to be clinically relevant.

Table 3. Responsiveness – distribution-based indices: MCID.

	ES – MCID*		SEM – MCID**	
	0 – 7 mo#	7 – 14 mo	0 – 7 mo	7 – 14 mo
Generic				
RAND	5.0	4.3	5.3	4.5
FSQ Generic	5.7	5.1	5.4	4.8
FSQ Specific	7.4	5.6	7.8	5.9
Disease-specific				
OM-6	8.3	4.7	8.8	5.0
NRS Child	9.4	6.7	12.5	8.9
FFQ	7.4	4.0	6.1	3.3
NRS Caregiver	6.1	4.8	8.3	6.6

* MCID using 0.3 ES as benchmark; ** MCID using 1-SEM as benchmark

mo = months

Except for the two numerical rating scales, the SEM-MCIDs were comparable with the ES-MCIDs for both generic and disease-specific questionnaires. Assuming that the estimated MCIDs using either a 0.3 ES benchmark or a 1-SEM, are correct, a range can be given for the MCID of generic as well as disease-specific questionnaires. In this study the distribution-based MCID corresponds

Table 4. Responsiveness – anchor based responsiveness indices: AOM frequency.

Change in AOM frequency (episodes/year)	Change – score generic instruments					
	RAND		FSQ Generic		FSQ Specific	
	0 – 7 mo#	7 – 14 mo	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo
0 to 1	6 (17)*	1 (14)	5 (19)	3 (17)	6 (25)	2 (19)
(none)	*68*	*154*	*67*	*154*	*67*	*154*
2	10 (16)	6 (16)	7 (15)	3 (16)	9 (18)	5 (16)
(small)	*73*	*77*	*71*	*74*	*72*	*75*
4	12 (17)	11 (15)	6 (16)	9 (18)	10 (19)	10 (19)
(moderate – large)	*51*	*29*	*50*	*30*	*50*	*30*

Table 5. Responsiveness – anchor based responsiveness indices: AOM severity.

OM-FSQ change-score	Change – score generic instruments					
	RAND		FSQ Generic		FSQ Specific	
	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo
0 to 10	1 (16)*	6 (14)	4 (17)	1 (13)	8 (17)	-5 (14)
(none)	*9*	*11*	*7*	*11*	*8*	*11*
20	10 (14)	6 (7)	6 (15)	2 (19)	8 (7)	5 (9)
(small)	*11*	*9*	*11*	*9*	*11*	*9*
40	17 (16)	7 (15)	10 (13)	8 (20)	14 (18)	7 (18)
(moderate – large)	*39*	*17*	*39*	*15*	*39*	*16*

mo = months * mean (SD)
number

with a change of 5 - 9 points on a 0-100 scale.

Interpretation - anchor-based methods

When changes in acute otitis media *frequency* (incidence of acute otitis media per child) were compared to magnitude of change-scores on the HRQoL and FHS questionnaires, a *small* change in acute otitis media frequency corresponded with 3 - 10 points change on a 0-100 scale for the generic instruments (Table 4). For

(Table 4 continued)

Change – score specific instruments							
OM-6		**NRS Child**		**FFQ**		**NRS Caregiver**	
0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo
10 (28)*	1 (16)	10 (31)	0 (22)	8 (25)	0 (13)	15 (20)	1 (16)
68	*156*	*69*	*154*	*68*	*152*	*24*	*63*
13 (20)	8 (19)	29 (26)	11 (26)	13 (18)	6 (16)	15 (17)	5 (19)
70	*77*	*72*	*77*	*69*	*76*	*29*	*34*
19 (22)	14 (26)	28 (22)	18 (25)	14 (16)	8 (19)	21 (24)	19 (24)
51	*31*	*50*	*31*	*47*	*30*	*23*	*7*

(Table 5 continued)

Change – score specific instruments							
OM-6		**NRS Child**		**FFQ**		**NRS Caregiver**	
0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo	0 – 7 mo	7 – 14 mo
6 (13)*	0 (11)	19 (24)	5 (8)	5 (9)	-3 (12)	13 (19)	3 (9)
9	*11*	*9*	*11*	*9*	*10*	*9*	*11*
8 (7)	4 (8)	16 (30)	17 (30)	4 (12)	6 (9)	8 (11)	8 (20)
11	*9*	*11*	*9*	*11*	*9*	*11*	*9*
22 (21)	24 (18)	32 (23)	13 (18)	19 (19)	19 (18)	22 (16)	19 (17)
38	*17*	*39*	*16*	*35*	*15*	*39*	*16*

disease-specific questionnaires, a small change in acute otitis media frequency corresponded with 5 - 29 points change on a 0-100 scale.

Change-scores on the questionnaires were compared in a similar manner to change in acute otitis media *severity* (Table 5). A *small* improvement in acute otitis media severity corresponded with change-scores ranging from 2 - 10 points

on a 0-100 scale for the generic questionnaires and with change-scores from 4 - 17 points for the disease-specific instruments.

It should be noted that the larger change-scores for disease-specific instruments are mainly caused by the results of the NRS Child.

Change-scores corresponding with *moderate to large* changes in acute otitis media frequency and severity are also presented in Table 4 and 5. Comparing small change with moderate to large change shows that, overall, the larger the change in acute otitis media severity or frequency, the larger the magnitude of the change-score on the questionnaires. However, this trend was not so evident for the FSQ Generic, NRS Child and NRS Caregiver. Changes on the questionnaires per unit change in acute otitis media severity or frequency were generally larger during the first follow-up period than during the second follow-up period.

Comparing the results of the anchor-based methods with those of the distribution-based methods (Table 6), small anchor-based change-scores were somewhat larger than the MCIDs found with the distribution-based methods during the first follow-up period but not during the second follow-up period.

Table 6. Comparing distribution-based with anchor-based responsiveness: MCID.

	SEM - MCID		ES - MCID		AOM severity		AOM frequency		mean
	0 – 7#	7 - 14	0 – 7	7 – 14	0 – 7	7 – 14	0 – 7	7 – 4	(range)
Generic									
RAND	5	5	5	4	10	6	10	6	6 (4-10)
FSQ Generic	5	5	6	5	6	2	7	3	5 (2-7)
FSQ Specific	8	6	7	6	8	5	9	5	7 (5-9)
Disease-specific									
OM-6	9	5	8	5	8	4	13	8	8 (4-13)
NRS Child	13	9	9	7	16	17	29	11	14 (7-29)
FFQ	6	3	7	4	4	6	13	6	6 (3-13)
NRS Caregiver	8	7	6	5	8	8	15	5	8 (5-15)

months

Generic questionnaires (RAND, FSQ Generic, and FSQ Specific), disease-specific questionnaires (OM-6 and FFQ) and the NRS Caregiver yielded similar estimates of the MCID for both methods (distribution and anchor-based) as well as for both follow-up periods. Averaging these distribution-based and anchor-based estimates of MCID yields a point-estimate MCID for generic questionnaires of 6.0 (range 2-10) and for disease-specific questionnaires of 7.3 (range 3-15) on a 0-100 scale (excluding the NRS Child, for it had much larger estimates for the MCID).

Discussion

In this study, the responsiveness of generic as well as disease-specific instruments has been assessed in children with recurrent acute otitis media. Generic as well as disease-specific instruments proved to be sensitive to change in incidence of acute otitis media. Effect sizes showed small to moderate responsiveness for generic instruments and moderate to large responsiveness for disease-specific instruments. However, most subscales of the TAIQOL, the only true HRQoL instrument, proved insensitive to change and were therefore excluded from further analysis. MCIDs for generic questionnaires and disease-specific questionnaires were similar; however, the sensitivity to change of some generic instruments (FSQ Generic and Specific) seemed to be somewhat poorer. MCIDs found with anchor-based methods were similar or somewhat larger than the MCIDs found with distribution-based methods.

Although HRQoL and FHS are increasingly integrated in outcome assessment for intervention in pediatric diseases, responsiveness has been assessed for only a few instruments.[24-28] Similarly, although data on reliability and cross-sectional validity of the instruments used in this study have been published previously, little attention has been given to their responsiveness. For the Dutch versions of the RAND and FSQ, Post et al.[29-31] gave only a rough estimate of sensitivity to change by comparing median scores at two test moments for unchanged and

changed patients. Rosenfeld et al.[32] estimated sensitivity to change for the OM-6 using standardized response means (SRM) of change-scores after tympanostomy tube placement. Their effect size estimates (SRM) were much larger (1.1 to 1.7) than the effect size estimates found in this study. This may be explained by the use of different identifiers of change: in our study a clinical indicator was used to identify subjects that had changed, i.e., a reduction of 2 or more acute otitis media episodes per child per year, while Rosenfeld et al.[32] used an intervention with expected effectiveness, for which parents were not blinded, as indicator.

There are several issues that need to be considered with regard to the current results. First, AOM frequency at enrolment was based on caregiver report, whereas during the trial only physician-diagnosed AOM episodes were counted. The number of acute otitis media episodes in the year prior to inclusion is likely to have been overestimated[33], leading to the underestimation of HRQoL change-scores. However, if such a caregiver recall-bias regarding AOM frequency was in fact present, it obviously may also have influenced caregivers' reflection on subjective measures such as HRQoL and FHS. Consequently, the assessment of responsiveness may have been biased in any direction. This limitation has however been overcome by comparing responsiveness for two intervals (0 to 7 months vs 7 to 14 months), whereby for the second interval all AOM episodes were physician diagnosed; consequently, AOM frequency was not affected by recall-bias.

Second, since the distributions of change-scores for the FFQ were skewed, it would have been more appropriate to use non-parametric tests for this instrument.[34] Although the Wilcoxon matched pairs test gave the same significance ($p<0.001$) as the paired t-test, the effect size is smaller when using a non-parametric instead of parametric effect size (0.31 versus 0.55). Therefore the FFQ appears to be less responsive when using non parametric tests, which is probably in part a consequence of its ceiling effects on baseline (64% scored in the highest quartile of the total score range).

Third, since pneumococcal vaccination proved to be clinically ineffective[10], treatment could not be used as an external criterion for change. Instead, a change of 2 or more acute otitis media episodes per year was used as criterion to identify changed from unchanged subjects. Although clinical criteria have been suggested as adequate alternatives[5], the choice for any external criterion is somewhat arbitrary. The poor responsiveness of the TAIQOL subscales 'Behavioural problems', 'Positive mood' and 'Liveliness', for example, may indicate that change in the incidence of acute otitis media episodes is less suitable as external criterion for change in emotional and behavioural functioning. However, considering the overall poor responsiveness of the TAIQOL subscales, it seems more obvious that poor responsiveness in itself also applies for these three subscales.

Fourth, by applying and comparing multiple methods as well as two evaluation periods, we have been able to demonstrate consistency in responsiveness and to give ranges for minimally clinical important changes. Similar estimates of these MCID ranges were found previously by Norman et al.[35] As there is no 'golden standard' for the assessment of responsiveness in HRQoL measurement, giving score-ranges instead of point-estimates seems more appropriate. Point estimates may wrongly pose as being accurate and precise.

Although various methods have been developed to assess responsiveness, their applicability in various populations and conditions remains to be evaluated. Calculation of effect size, for example, has been considered infeasible for assessment of responsiveness when changes in health status are small.[20] However, although changes in HRQoL and FHS were smaller during the second than during the first follow-up period, no substantial differences in ESs, with the exception of the numerical rating scales, were found in this study.

Several studies have supported the link between 1-SEM and MCID for HRQoL instruments.[16, 18, 21, 22] In this study the SEM largely corresponded with a MCID that was estimated using 0.3 ES as a benchmark, which is in further support of the 1-SEM as an indicator of MCID. However, it should be realized that 1-SEM as well as the ES are both statistical indicators, which relate change to random

(error) variance. Interestingly, the anchor-based methods yielded similar estimates for the MCIDs.

Some investigators have expressed their concern about the responsiveness of generic instruments, and their usefulness as measures of outcome in randomized trials.[2] Although some authors indeed found generic measures to be less responsive to treatment effects than specific instruments[36-39], others have found comparable responsiveness[28, 40, 41]. In this study, the smaller effect sizes for the FSQ Generic and FSQ Specific may indicate that responsiveness of generic instruments is somewhat poorer than that of disease-specific instruments. In addition, sensitivity to change was poor for most of the examined TAIQOL subscales.

In conclusion, although sensitivity to change was larger for disease-specific instruments, both generic (RAND, FSQ Generic, FSQ Specific) and disease-specific (OM-6, NRS Child, FFQ, NRS Caregiver) instruments showed adequate responsiveness to justify use in clinical studies of children with recurrent acute otitis media. Estimates of the minimally clinical important difference were comparable for generic and disease-specific questionnaires. The TAIQOL, the only true generic HRQoL questionnaire, unfortunately showed a poor sensitivity to change, questioning its usefulness in assessing effects of treatment on HRQoL in children with recurrent acute otitis media.

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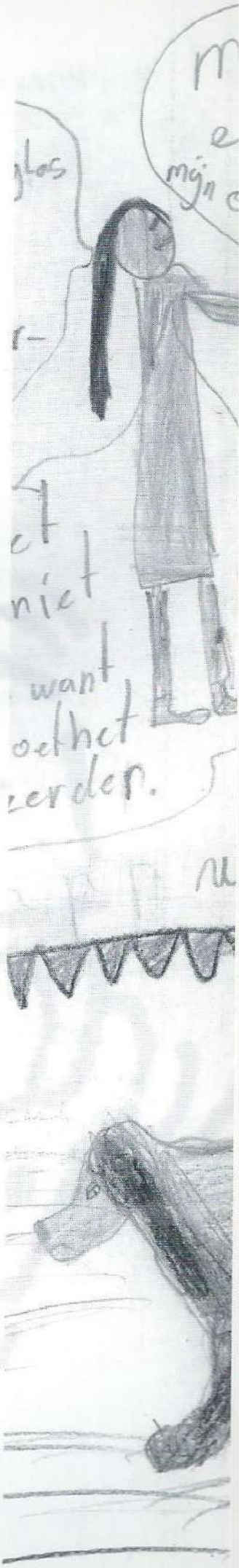
Chapter 5

Health-related quality of life in children with recurrent acute otitis media



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"Science can only ascertain what is, but not what should be, and outside of its domain value judgements of all kinds remain necessary."

Albert Einstein

Abstract

Objective: Knowledge about health-related quality of life (HRQoL) in children with recurrent otitis media (OM) is limited. Most studies thus far have focused on functional health status (FHS) instead of HRQoL, and most instruments have been insufficiently validated. This study aims to assess both FHS and HRQoL of children with recurrent OM, using both generic and disease-specific questionnaires that have been validated for this particular population.

Methods: Caregivers of 384 Dutch children aged 1 to 7 years with at least 2 episodes of acute otitis media (AOM) in the preceding year completed instruments assessing generic FHS (RAND and FSQ), generic HRQoL (TAIQOL), disease-specific FHS (OM-6), and disease-specific HRQoL (NRS - Child). Age-adjusted total and subscale scores were compared to those of reference populations. Reference populations consisted of children from the general population, children with mild to moderately severe asthma, children with mild to moderately severe chronic illness and children with chronic OM with effusion (OME) or recurrent AOM.

Results: Scores of the study population were low for subscales assessing physical problems, emotional distress, problem behaviour and parental concern. For all generic questionnaires, the study population had poorer scores than healthy children. They also had lower scores for most subscales of the TAIQOL compared to children with mild to moderately severe chronic illness. Results of the study population were similar to those of children with asthma and U.S. children with chronic OME or recurrent AOM.

Conclusion: Recurrent AOM has a considerable impact on both FHS and HRQoL of children and causes great concern to caregivers.

Introduction

Health-related quality of life (HRQoL) in recurrent or chronic OM has increasingly become the subject of study in recent years. Initially, studies on the impact of OM on children's health focused on symptoms of acute illness in OM and on the effects of OM and its treatment on hearing, language, cognition and psychosocial development.[1-13] These conventional clinical indices, however, were found to correlate poorly with patients' feelings and functioning in daily life.[14-17] More sensitive and comprehensive outcome measures such as HRQoL, reflecting the experiences of children and their family with respect to the impact of the child's illness on daily life, were seen to be needed.[18-24]

Studies performed so far of the quality of life in OM patients indicate that besides well-known physical problems, recurrent OM may cause emotional distress and behavioral problems in children. Understandably, recurrent OM may also have a negative influence on caregivers and family life.[25-30]

However, in most studies performed so far, instruments have focused on functional health status (FHS), reflecting the level of a child's functioning across various life-domains. Essential characteristics of HRQoL, such as subjective valuation of the child's functioning, are lacking when assessing FHS. More importantly, most studies lack adequate data on reliability and validity of the instruments used.[31] Studies of HRQoL in children with recurrent acute otitis media (rAOM) addressing these needs are therefore wanted.

This paper describes the results of a quantitative assessment of both HRQoL and FHS in children with rAOM. Generic as well as disease-specific questionnaires, validated for this particular patient group [32, 33], have been used. Instrument scores of the children in our trial are compared with norm-scores and existing data for HRQoL or FHS in various pediatric populations.

Methods

Design, setting and patients

This study has been conducted at the pediatric outpatient departments of a general hospital (Spaarne Hospital Haarlem) and a tertiary care hospital (University Medical Center Utrecht). Quality of life was assessed in children with rAOM participating in a prospective, double blind RCT on the effectiveness of pneumococcal vaccination. From April 1998 to February 2001, children with rAOM were recruited for this trial through referral by General Practitioners, pediatricians, or otolaryngologists or by self-referral. Inclusion criteria were: age 1 to 7 years and a history of recurrent acute otitis media defined as having had at least 2 physician-diagnosed episodes of AOM in the preceding year. Exclusion criteria were conditions with a known increased risk for acute otitis media such as immunodeficiency other than IgA or IgG2 subclass deficiency; cystic fibrosis; immotile cilia syndrome; cleft palate; chromosomal abnormalities like Down syndrome, or severe adverse events upon vaccination in the past.

Upon enrollment, demographic data and clinical indices of the severity of OM were recorded. Caregivers completed several questionnaires assessing HRQoL and FHS of their child. Informed consent was obtained from the parents or caregivers of all children before participation.

The Medical Ethics Committees of both participating hospitals approved the study protocol.

Outcome measures

Functional health status and HRQoL were assessed by a combination of generic and disease-specific instruments for the purpose of increasing both comprehensiveness and sensitivity of the assessment.[34] While generic instruments allow for comparisons with other populations (children with other health conditions), disease instruments may identify specific areas of problems within this particular patient group.[24, 35-37] Questionnaires were completed by the caregivers during the clinic visit. In case of obscurities or questions, the parent or

caregiver was assisted by one of the three research physicians. Appendix 1, p.179, summarises the characteristics of the questionnaires. For all questionnaires, higher scores indicate a better HRQoL or FHS.

Generic instruments

The RAND and the Functional Status Questionnaire (FSQ), both assessing general functional health status, have been translated and validated for Dutch children by Post et al.[38, 39]. The 7 items of the RAND, originally selected from a child FHS instrument developed at the RAND Corporation[40], assess general health perceptions of caregivers regarding their child, i.e. current health, susceptibility, and prior health.

The FSQ is a modification of the short (14-items) version of the FS II(R). The FSQ consists of two parts: one measuring general functional limitations (FSQ-G) and the other measuring illness-specific functional limitations, i.e. functional loss attributable to illness (FSQ-S).[40] Functional limitations in the FSQ are mainly expressed as behavioral problems.

During the study, a new Dutch instrument on generic HRQoL became available: the TNO-AZL Infant Quality of Life (TAIQOL).[41, 42] The TAIQOL is the only Dutch instrument providing a generic HRQoL profile in pre-school children. From July 1999 on, this questionnaire has been added to the previously selected set of instruments (n=169).

Disease-specific instruments

To measure disease-specific FHS, the Otitis Media-6 (OM-6) was translated into Dutch according to principles of backward-forward translation.[43-46] The OM-6 is a validated questionnaire, covering both acute (pain, irritability) and long-term (language impairment) consequences of OM in children.[25, 29] Since the OM-6 had only been validated as an evaluative survey, discriminant validity has additionally been assessed for the current population; we found the OM-6 able to discriminate between children who differed in AOM incidence.[32]

Finally, a Child QoL numerical rating scale (0-10) was translated according to the same principles of backward-forward translation. This is a global judgement by the caregiver of the child's HRQoL related to recurrent OM.[25]

Reference populations

Data collected in previous studies using the same questionnaires that were used in the present study, served as references. Authors were contacted to obtain the original databases. Data of the following five reference populations were available:

Children from the general population

1. A cross-sectional population sample of consecutively included children visiting well-baby clinics and community health care centres in a particular region (Utrecht area) in the Netherlands (mean age 3.0 year, 49% male);[39, 47]
2. Another cross-sectional sample of children without chronic illness visiting six well-baby clinics and community health care centres in a particular region in the Netherlands (mean age 2.5 year, 55% male);[42]

Children with asthma

A cross-sectional sample of asthmatic children (mean age 4.2 year, 66% male), registered in electronic patient-databases of General Practitioners in a particular region (Utrecht area) in the Netherlands;[39, 47]

Children with chronic illnesses

A subselection of the children visiting well-baby clinics and community health care centres mentioned above[42], consisting of children with a mild to moderately severe chronic illness during the preceding year (mean age 2.7 year, 60% male): allergy (n=33), chronic bronchitis (n=16), asthma (n=13), hearing impairment (n=12), disease of the eye (n=10), growth impairment (n=4), chronic intestinal problems (n=4), heart condition (n=2), spinal problem (n=1);

Children with recurrent AOM or chronic otitis media with effusion

An U.S. population consisting of children referred by pediatricians and General Practitioners because of chronic otitis media with effusion (middle ear effusion in one or both ears for at least 3 months; 74% of children), recurrent AOM (at least 3 episodes of AOM in the past 12 months; 46% of children) or both (20% of children) (mean age 3.2 year, 63% male).[25, 29]

Data analysis

Mean total scores or sub-scores on the HRQoL and FHS questionnaires were calculated according to the instructions of the original authors. To create comparable scores, all total scores and sub-scores were converted into a 0-100 scale. Simple linear regression was used to assess the influence of gender and age on the HRQoL and FHS scores for the RAND, FSQ, TAIQOL, OM-6 and NRS Child. Since simple linear regression analysis showed that age affected FHS and HRQoL scores, it was included in a multiple linear regression model to compare scores on the RAND, FSQ, TAIQOL, OM-6 and NRS Child between the present study group and reference populations. Mean total and subscale scores were then adjusted for age, using the regression coefficients.

To compare the scores of the present study population with those of the reference population on ordinal subscales of the OM-6 while correcting for the influence of age, logistic regression analysis was applied. The 4 point Likert scale was dichotomised into 'low QoL' (score 1 & 2) versus 'high QoL' (score 3 & 4). Since dichotomization leads to loss of information, ordinal regression analysis (logit) was applied to check whether dichotomization had led to important differences in results. Ordinal regression analysis allows modelling of the dependence of a polytomous ordinal response on a set of independent variables or covariates. As both methods yielded similar results, logistic regression analysis was accepted. Significance level was set at 0.01.

For all analyses the statistical package of Statistical Product and Service Solutions (SPSS) version 10.1 was used.

Results

Patients

Table 1 summarises the patient characteristics at inclusion. A total of 384 children were included of which 62% was male. The mean age of the children was 34 (SD=20) months. In the year before inclusion, 142 children had had 2 or 3 episodes of AOM, and 242 children had had 4 or more episodes of AOM. The mean number of AOM episodes was 5.0 (± 2.7 SD), while 61% had undergone ear-, nose-, and throat (ENT) surgery.

Table 1. Characteristics of study population.

	% or mean (*n*=384)	(95% CI or SD)
age *(months)*	34	(20)
male gender	62%	(57 - 67)
age when 1st AOM *(months)*	11	(9)
birthweight < 1500 gram	0.8 %	(0 - 1.7)
number of siblings	1.1	(0.9)
education > highschool* - father	40%	(35 - 45)
education > highschool* - mother	39%	(34 - 44)
In the year prior to inclusion		
number of AOM episodes/year	5.0	(2.7)
impaired hearing	35%	(30 - 40)
language or speech problems	22%	(18 - 26)
History of		
chronic airway problems or atopic symptoms**	51%	(46 - 56)
adenoidectomy	47%	(42 - 52)
tonsillectomy	11%	(8 - 14)
tympanostomy tubes	51%	(46 - 56)
other ENT surgery	2%	(0.6 - 3)
speech-therapy	9%	(6 - 12)

* Minimum educational level was highschool

** Asthma, wheezing, hayfever, or eczema

Table 2. Mean HRQoL and FHS total and domain scores – adjusted for age.

	Study population Recurrent AOM		Reference populations Children from a general population			Children with chronic illnesses -			Population type
	Standardized score	*n*	Standardized score *	*n*	*p-value***	Standardized score	*n*	*p-value***	
Generic									
RAND	***63.1***	***384***	***80.8***	***117***	< 0.001	***66.9***	***64***	0.09	children with asthma[38 45]
FSQ generic	***73.8***	***384***	***88.9***	***117***	< 0.001	***76.2***	***64***	0.32	idem
FSQ specific	***80.5***	***384***	***94.8***	***117***	< 0.001	***83.5***	***64***	0.20	idem
TAIQOL		***169***		***255***			***82***		children with chronic
Sleeping	62.1	169	83.6	255	< 0.001	78.6	82	< 0.001	illness, such as asthma,
Appetite	73.7	169	86.0	255	< 0.001	80.8	82	0.007	bronchitis, allergy,
Lungs	84.3	169	97.0	255	< 0.001	82.8	82	0.61	hearing impairment,
Stomach	80.7	169	92.6	255	< 0.001	89.3	82	0.002	eye disease, intestinal
Skin	87.2	169	92.8	255	< 0.001	88.4	82	0.59	problems[40]
Motor functioning	94.0	123	99.1	212	< 0.001	98.5	74	0.007	
Social functioning	85.1	123	91.4	212	< 0.001	90.8	74	0.07	
Problem behaviour	62.5	169	67.8	255	< 0.001	67.5	82	0.05	
Communication	84.2	123	91.8	212	< 0.001	91.6	74	0.006	
Anxiety	71.8	169	79.0	255	< 0.001	75.9	82	0.13	
Positive mood	92.5	169	98.7	255	< 0.001	98.8	82	0.001	
Liveliness	92.0	169	97.9	255	< 0.001	98.3	82	0.002	
Disease-specific									
OM-6	***64.7***	***384***				***65.2***	***169***	0.80	recurrent AOM or OME
Physical suffering	53.7	383				52.3	169	0.74	(scheduled for VT
Hearing loss	68.0	381				66.3	169	0.68	placement)[29]
Speech impairment	80.3	380				75.7	169	0.08	
Emotional distress	60.7	384				66.0	169	0.05	
Activity limitations	67.7	384				83.3	169	0.001	
Caregiver concerns	57.7	383				45.0	169	0.01#	
NRS Child	***53.2***	***383***				***66.3***	***169***	< 0.001	

* scoring 0 – 100; ** compared to present study population; # $p < 0.001$ with ordinal regression

Health-related quality-of-life in recurrent AOM

Scores on the questionnaires assessing FHS ranged from 63.1 (RAND) to 80.5 (FSQ specific) on a 0-100 scale (Table 2). For the TAIQOL, the only true HRQoL questionnaire, the lowest scores were found on the subscales 'Sleeping' (62.1), 'Problem behaviour' (62.5 out of 100), 'Anxiety' (71.8) and 'Appetite' (73.7). 'Motor functioning' (94.0) was relatively unaffected.

For the disease-specific OM-6 questionnaire, the lowest scores were found on the subscales 'Physical suffering' (53.7), 'Caregiver concerns' (57.7) and 'Emotional distress' (60.7).

Health-related quality of life in recurrent AOM versus general population

Children with recurrent AOM had considerably lower scores than healthy children on all questionnaires (Table 2). For the TAIQOL, the largest differences between children with rAOM and children from a general population were found on the subscales 'Sleeping', 'Lungs' (difficulty breathing, bronchitis, dyspnea or other lungproblems) and 'Appetite'. All differences were statistically significant and showed the same trend.

Health-related quality of life in recurrent AOM versus other chronic illnesses

Compared to asthmatic children, scores of the present study population were lower for the RAND, FSQ generic, and FSQ specific, though none of these differences were statistically significant. Compared to children with other chronic illnesses, scores of the present study population were lower on all subscales of the TAIQOL except for the subscale 'Lungs'. The differences were largest for the subscales 'Sleeping' (62.1 vs. 78.6), 'Stomach' (gastro-intestinal problems, 80.7 vs. 89.3), 'Communication' (84.2 vs. 91.6) and 'Appetite' (73.4 vs. 80.8). For the 'Lungs', 'Skin', 'Social functioning', 'Problem behaviour', and 'Anxiety' subscales, the differences were not significant. (Table 2)

Health-related quality of life in recurrent AOM and chronic otitis media with effusion

Scores for the OM-6 of the present study population were very similar to those of a U.S. group with recurrent AOM and chronic otitis media with effusion (OME) (Table 2). Considerable differences were only found for the subscales 'Activity limitations' and 'Caregiver concerns'; 67.7 vs. 83.3 and 57.7 vs. 45.0 for the present Dutch study population and the U.S. population, respectively.

The present study population had significantly lower scores on the numerical rating scale of OM-related quality-of-life than the U.S. population (53.2 vs. 66.3).

Discussion

In this study we set out to quantify the impact of recurrent OM on FHS and HRQoL, which appears to be considerable. The burden is most evident in the global parental judgement of FHS (RAND) and HRQoL (numerical rating scale) of the child and in reported physical symptoms, emotional distress, problem behaviour and caregivers' concern (subscales of the TAIQOL and OM-6). Caregivers of the children in the present study population with recurrent AOM not only judge their child's FHS and HRQoL markedly lower than caregivers of children of a general population, but also lower than those of children with mild to moderately severe chronic illnesses. HRQoL and FHS of the present study population were similar to those of children with mild to moderately severe asthma and U.S. children with chronic OME or rAOM.

To appreciate these results, some issues should be considered. In the first place, although we intended to focus on HRQoL, the majority of our questionnaires actually assess FHS. At the beginning of the study, no questionnaire for HRQoL assessment was available in the Dutch language for this age group. Instead of initiating the resource-intensive process of cross-cultural translation of a HRQoL questionnaire, we decided to profit from the advantages of available FHS

questionnaires as suggested by Streiner & Norman.[48] Both the RAND and FSQ had been validated in age-groups that covered our population, they had been applied to a general pediatric population and most importantly, they address items related to HRQoL. As no Dutch OM-specific questionnaire was available, the OM-6 and a numerical rating scale on OM specific HRQoL were translated into Dutch. A Dutch HRQoL questionnaire (TAIQOL) was added to the set of questionnaires as soon as it became available.

Second, considering the heterogeneity of the background of the study population and reference populations, care should be taken in drawing conclusions from differences in FHS and HRQoL between populations. However, except for the population with chronic OME or rAOM, all reference populations were Dutch. Furthermore, we adjusted FHS and HRQoL scores for age differences between the populations, which often is the most important confounder.

Third, the questionnaires were completed by caregivers as proxies for the child. The ability of caregivers to rate their child's FHS and HRQoL adequately has been widely discussed.[49-51] In a condition such as rAOM with a high prevalence of caregiver concern[25, 52], one may reasonably wonder to what extent this concern has influenced their proxy rating of the child's HRQoL and FHS. However, the age range of the children in the study population precluded self-reported FHS or HRQoL.[53-55]

Fourth, participation in a trial on recurrent OM may have triggered caregivers to be more alert on issues of FHS and HRQoL in OM.

Fifth, it is important to realise that the present study population consisted of children with relatively severe recurrent AOM: the majority had had more than 4 episodes of AOM in the preceding year. Besides, several subgroups in which the prevalence of severe rAOM is likely to be high, such as children with Down syndrome or cleft palate, were excluded. Consequently, results can only be generalised directly to a population of children similar to the current study population.

Finally, the broad scope of FHS and HRQoL precludes any questionnaire from covering every aspect. One way to overcome this problem is by combining several questionnaires. A disadvantage of this strategy is, however, that the concepts of FHS and HRQoL underlying the questionnaires differ and therefore results may not always be comparable. The results on the questionnaires in this study therefore should be viewed as complementary rather than similar.

This study is unique in assessing both FHS and HRQoL in children with rAOM using both generic and disease-specific questionnaires. Importantly, all questionnaires have been validated for this particular population[32, 33] and interpretation of the FHS and HRQoL scores of children with rAOM is greatly facilitated by comparing results with several reference populations.

Comparing rAOM with other health conditions, it is apparent that recurrent AOM has a larger impact on FHS and HRQoL of children than until recently may have been understood. In addition, results of the current study population are comparable to those of children with OM in previous studies.[25, 26, 56] Although not all differences on the questionnaires and subscales were significant, they generally showed the same trend.

The similar impact of asthma and rAOM on FHS and HRQoL may be explained by their nature; both are closely related to upper airway infections and are to some extent unpredictable in their occurrence. The poorer scores for the present study population on 'Activity limitations' (OM-6 item) compared to the U.S. group of children with recurrent AOM or chronic OME might be explained by a high percentage of chronic OME in the latter population. Chronic OME may have less impact than recurrent AOM on daily activities of the child such as playing. On the other hand, the poorer scores of the U.S. group on 'Caregiver concerns' compared to the Dutch group might well reflect a cultural difference in how health and illness are experienced.

In conclusion, results of the present study among a group of 384 children with recurrent acute otitis media, show a considerable impact of recurrent OM on FHS and HRQoL of the children as well as on their caregivers' concerns. The impact is similar to that of chronic OME and/or recurrent AOM in U.S. children or of asthma in Dutch children.

Acknowledgements

We would like to thank Marcel Post, Minne Fekkes and Richard Rosenfeld for generously providing their databases for inclusion in the current analyses and Herma Kiezenbrink for her loyal support of the clinical assessments.

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Chapter 6

Effect of pneumococcal vaccination on quality of life in children with recurrent acute otitis media: a randomized controlled trial

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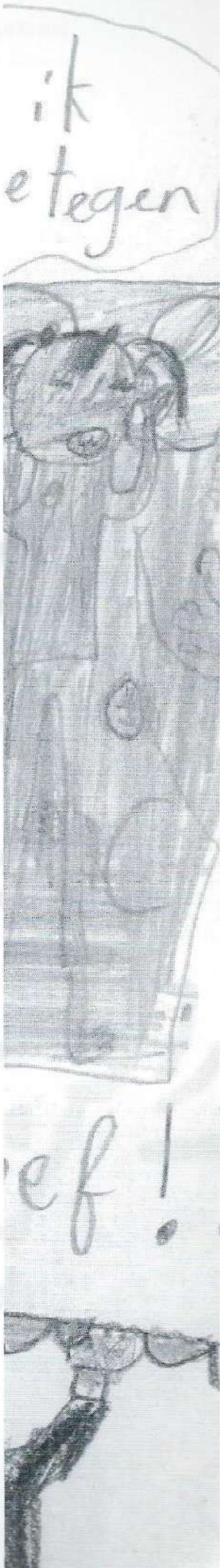

"Probeer opnieuw. Faal opnieuw. Faal beter."

Samuel Becket

Abstract

Background: Limited effectiveness of current treatment strategies for recurrent acute otitis media (rAOM) and increasing antibiotic resistance have diverted attention to prevention of AOM by vaccination. Pneumococcal vaccination for AOM appears to have only modest clinical effectiveness, though effectiveness seems higher for children with *recurrent* AOM. So far, the effect of vaccination on health-related quality of life (HRQoL) or functional health status (FHS) in children with rAOM has not yet been studied.

Methods: In a double blind randomized controlled trial, 383 children aged 1 to 7 years with rAOM were vaccinated with either heptavalent pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine (pneumococcal group, n=190), or with hepatitis A or B vaccines (control group, n=193). Parents completed validated Dutch versions of 8 HRQoL and FHS instruments assessing generic FHS (RAND, FSQ Specific and FSQ Generic), OM-specific FHS (OM-6), OM-specific child HRQoL (NRS Child), family functioning (FFQ), and OM-specific caregiver HRQoL (NRS Caregiver). Scores were compared at baseline, 14 months and 26 months follow-up.

Results: No substantial differences in HRQoL or FHS were found between the pneumococcal and the control group at baseline, 14 months or 26 months follow-up. AOM frequency decreased in both groups with a considerable and comparable improvement in HRQoL and FHS.

Conclusion: Pneumococcal vaccination has no beneficial effect compared to control vaccination on either health-related quality of life or functional health status in children aged 1 to 7 years with recurrent acute otitis media.

Introduction

Acute otitis media (AOM) is one of the most common infectious diseases in childhood[1-4] with a considerable impact on daily functioning and health-related quality of life (HRQoL) of the affected child and its family[5-9]. As the benefit of both medical treatment and surgery has proved limited[10-15] and with resistance against common antibiotics still on the increase[16-19], there is much interest in developing alternative methods to *prevent* AOM[20-25]. Since pneumococcus is the most frequent bacterial cause of otitis media[4, 26-28], research over the past decade has focussed on pneumococcal vaccination[29, 30]. Pneumococcal conjugate vaccination in infancy has been shown to be (highly) effective in preventing invasive disease.[31-33] Regarding AOM, the clinical effectiveness appears to be modest, i.e. 6-7%. A larger effect has been found in the prevention of recurrent AOM episodes with up to 12% reduction of 4 or more AOM episodes per year.[31, 34, 35] Children at risk for recurrent acute otitis media (rAOM) are assumed to benefit most through priming of their deficient immune response by pneumococcal conjugate vaccination.[31, 35-37]

Since previous studies mainly addressed the *clinical* effectiveness of pneumococcal vaccination regarding AOM, little is known about the benefit of vaccination for functional health status (FHS) and HRQoL. Assessment of such outcome is important, especially as recurrent AOM may be considered a chronic illness, regarding which HRQoL and FHS are assumed to be particularly relevant as outcome measures.[38-40]

In 1998 we started a randomised controlled trial on the effects of pneumococcal versus control vaccination in children aged 1 to 7 years who had suffered from recurrent episodes of acute otitis media. In this paper we will focus on the effects of pneumococcal vaccination versus control vaccination on functional health status and health-related quality of life.

Methods

Patients

The current study is part of a double-blind randomised controlled trial (RCT) studying the effect of pneumococcal vaccination on FHS and HRQoL of children with rAOM alongside its clinical effectiveness. The trial was carried out at the pediatric outpatient departments of a general hospital (Spaarne Hospital Haarlem) and an academic hospital (University Medical Center Utrecht) from April 1998 to December 2001. Children were referred by general practitioners, pediatricians and otolaryngologists or were enrolled on the caregiver's own initiative.

Inclusion criteria were: age 1 to 7 years and a history of recurrent acute otitis media defined as having had at least 2 physician-diagnosed episodes of AOM in the preceding year. Exclusion criteria were conditions with a known increased risk for acute otitis media such as immunodeficiency other than IgA or IgG2 subclass deficiency; cystic fibrosis; immotile cilia syndrome; cleft palate; chromosomal abnormalities such as Down syndrome, or severe adverse reaction to previous vaccinations. Informed consent was obtained from the caregivers of all children before participation in the trial. The Medical Ethics Committees of both participating hospitals approved the study protocol.

Intervention and follow-up

After inclusion in the trial, children were randomly assigned to vaccination with either a 7-valent pneumococcal conjugate vaccine (Prevnar®) followed 6 months later by a 23-valent polysaccharide vaccine (Pneumune®) (= pneumococcal vaccine group), or with a control vaccine (hepatitis A vaccine, Havrix = AE Junior® in children aged 12-24 months or recombinant hepatitis B vaccine, Engerix-B = AE Junior® in children aged 24-84 months) (= control vaccine group) (Figure 1). Randomisation was balanced over age (12-24 months vs. 24-84 months) and number of AOM episodes in the year prior to enrolment (2-3 vs. 4 or more episodes).

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In 1998 we started a randomised controlled trial on the effects of pneumococcal versus control vaccination in children aged 1 to 7 years who had suffered from recurrent episodes of acute otitis media. In this paper we will focus on the effects of pneumococcal vaccination versus control vaccination on functional health status and health-related quality of life.

To limit the number of comparisons, the RAND (generic questionnaire) and the OM-6 (disease-specific questionnaire) were considered as primary outcome measures, based on their face validity, reliability and responsiveness.[5, 42-46] Consequently, the other questionnaires were considered secondary outcome measures.

As questionnaire scores generally were skewed, Mann Whitney tests were used to assess differences in FHS and HRQoL scores between the pneumococcal and control vaccine group at baseline, and 14 months and 26 months follow-up.

A multivariate analysis of variance (MANOVA) was performed to detect a treatment effect for all questionnaires combined; for this analysis we modelled the scores at 14 and 26 months follow-up.

Finally, the following variables were considered as possible effect modifiers: age at inclusion (12-24 months vs. 24-84 months), number of AOM episodes in the year prior to enrolment (2-3 vs. 4 or more episodes), number of upper respiratory tract infections other than AOM in the preceding year (< 6 vs. 6 or more episodes), symptoms of hearing-impairment (yes/no) or language difficulties in the preceding year (yes/no), previous ENT-surgery (yes/no), history of antimicrobial prophylaxis (yes/no), atopy (yes/no), number of siblings, and educational level of the caregivers (high school or higher, yes/no). The variables were tested by linear regression models to find potential modifiers of effect of the intervention on HRQoL or FHS outcome at 14 months follow-up.

Questionnaire scores that are displayed in the graphs (figure 2a and 2b) were transformed into 0-100 scales to enhance comparability.

Results

Population characteristics

At baseline, demographic and clinical characteristics between the pneumococcal and control vaccine group were similar (Table 1), as were the mean baseline scores on the measures of FHS and HRQoL (Table 2).

Table 1. Characteristics of study population at inclusion.

	Pneumococcal vaccinees		Control vaccinees	
	(n = 190)	*SD or 95% CI*	*(n = 193)*	*SD or 95% CI*
age *(months)*	32.8	19.3	34.8	20.1
male gender	62.1%	(55.2 – 69.0)	61.7%	(54.8 - 68.6)
age when 1st AOM *(months)*	11.2	9.4	10.8	8.4
number of siblings	1.05	0.8	1.11	0.9
caregiver's education ≥ highschool*	54.4%	(47.1 – 61.3)	52.6%	(45.6 – 59.6)
In the year prior to inclusion				
mean number of AOM episodes/year	5.0	2.8	4.9	2.6
≥ 6 episodes of URTI/year**	38.4%	(31.5 – 45.3)	36.8%	(30.0 – 43.6)
pneumonia	10.0%	(5.7 – 14.3)	16.6%	(11.4 – 21.8)
hearing difficulties	36.3%	(29.5 – 43.1)	33.2%	(26.6 – 39.8)
speech or language difficulties	25.3%	(19.1 – 31.5)	19.2%	(13.6 – 24.8)
History of				
chronic airway problems or atopy***	49.5%	(42.4 – 56.6)	51.8%	(44.8 – 58.8)
adenoidectomy ± tonsillectomy	47.4%	(40.3 – 54.5)	46.4%	(39.4 – 53.4)
tympanostomy tubes	52.6%	(45.5 – 59.7)	48.9%	(41.8 – 56.0)
antimicrobial prophylaxis	15.8%	(10.6 – 21.0)	14.5%	(9.5 – 19.5)
speech-therapy	7.4%	(3.6 – 11.1)	10.4%	(6.1 – 14.7)

* Minimum educational level was highschool for at least one of the caregivers.

** URTI = upper respiratory tract infection

*** asthma, wheezing, hayfever, or eczema

Clinical effectiveness of pneumococcal vaccination

After 14 and 26 months follow-up, no differences between the pneumococcal vaccine group and control vaccine group were observed with respect to reduction of AOM episodes and associated use of analgesics or antibiotics. Furthermore, the number of children receiving tympanostomy tubes was comparable in both groups.[41]

Effectiveness of pneumococcal vaccination on HRQoL and FHS

After 14 months follow-up, the RAND showed no significant difference between the pneumococcal and control vaccine group (23.5 vs. 23.8, p=0.45). A small but statistically significant difference was found on the OM-6 in favour of the control vaccine group (21.3 vs. 22.3, p=0.002, respectively). Subsequent comparison of scores on the secondary generic and disease-specific HRQoL and FHS instruments showed no significant differences between both intervention groups. After 26 months follow-up, HRQoL and FHS scores between the pneumococcal and control vaccine group did not differ at all (Table 2, Figures 2a & 2b).

Table 2. Differences in mean scores between pneumococcal and control vaccine group on health-related quality of life and functional health status instruments, and in AOM frequency at 0, 14 and 26 months follow-up (Mann-Whitney test).

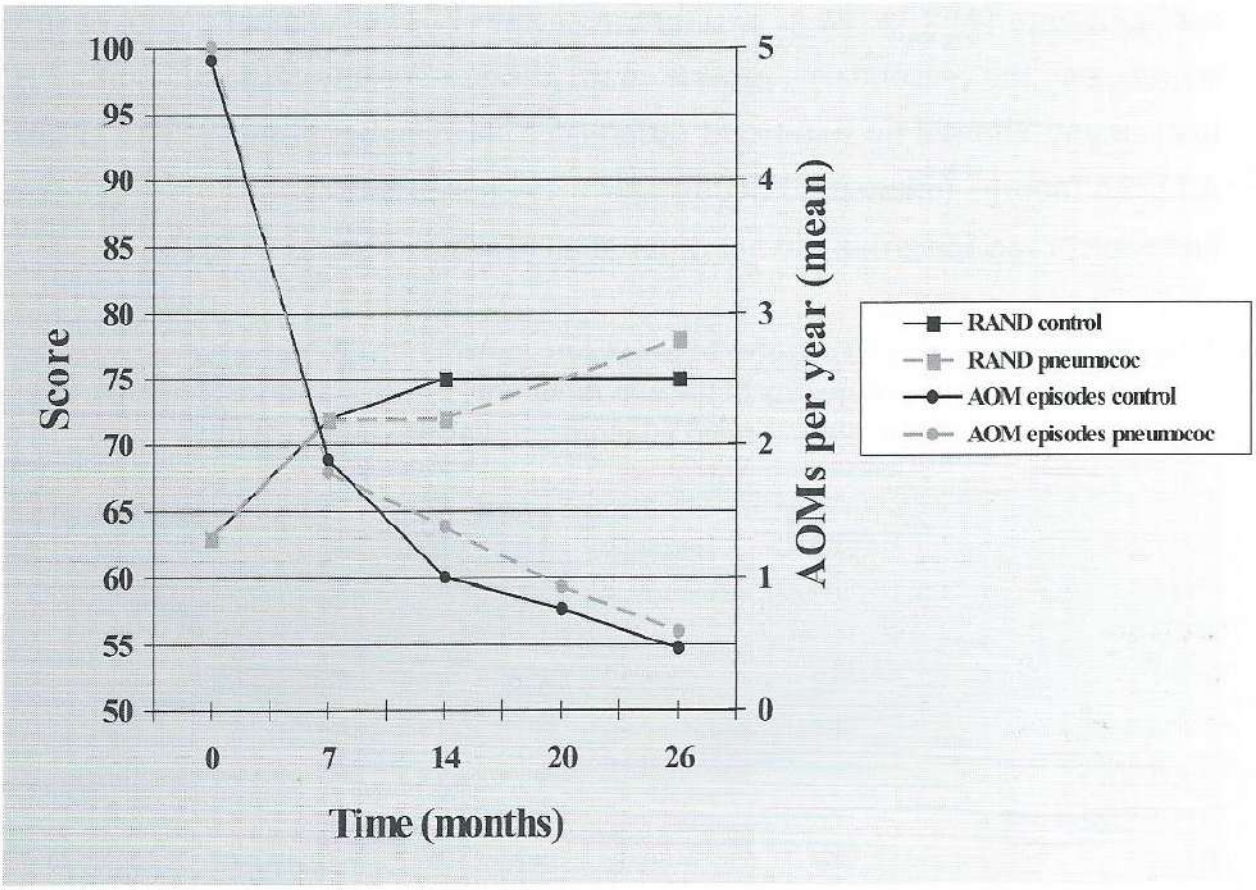
	0 months		sig.	**14 months**		sign.	**26 months**		sign.
	Pnc*	Ctrl*	*(p-value)*	Pnc	Ctrl	*(p-value)*	Pnc	Cntrl	*(p-value)*
Generic									
RAND	20.2	20.1	*0.63*	23.5	23.8	*0.45*	25.0	24.3	*0.34*
FSQ Generic	73.9	73.7	*0.85*	81.6	83.6	*0.10*	87.2	86.1	*0.59*
FSQ Specific	80.9	79.9	*0.57*	90.0	91.5	*0.16*	92.9	91.3	*0.42*
Disease-specific									
OM-6	17.6	17.5	*0.93*	21.3	22.3	*0.002*	22.1	22.2	*0.41*
NRS Child	5.3	5.4	*0.94*	7.9	8.2	*0.14*	8.3	8.4	*0.50*
FFQ	25.2	25.4	*0.87*	31.3	31.3	*0.78*	32.1	31.9	*0.81*
NRS Caregiver	6.1	6.6	*0.20*	8.3	8.3	*0.88*	7.9	8.3	*0.45*
AOM episodes/childyear	5.0	4.9		1.4	1.0		0.6	0.5	

* Pnc = pneumococcal vaccinees; Ctrl = control vaccinees

The MANOVA on all questionnaires combined showed a marginal significant difference at the expense of pneumococcal vaccination at 14 months follow-up (p=0.04 with the Hotelling-Lawley Trace test). At 26 months follow-up no association was found between the scores on all questionnaires combined and type of vaccination (p= 0.89).

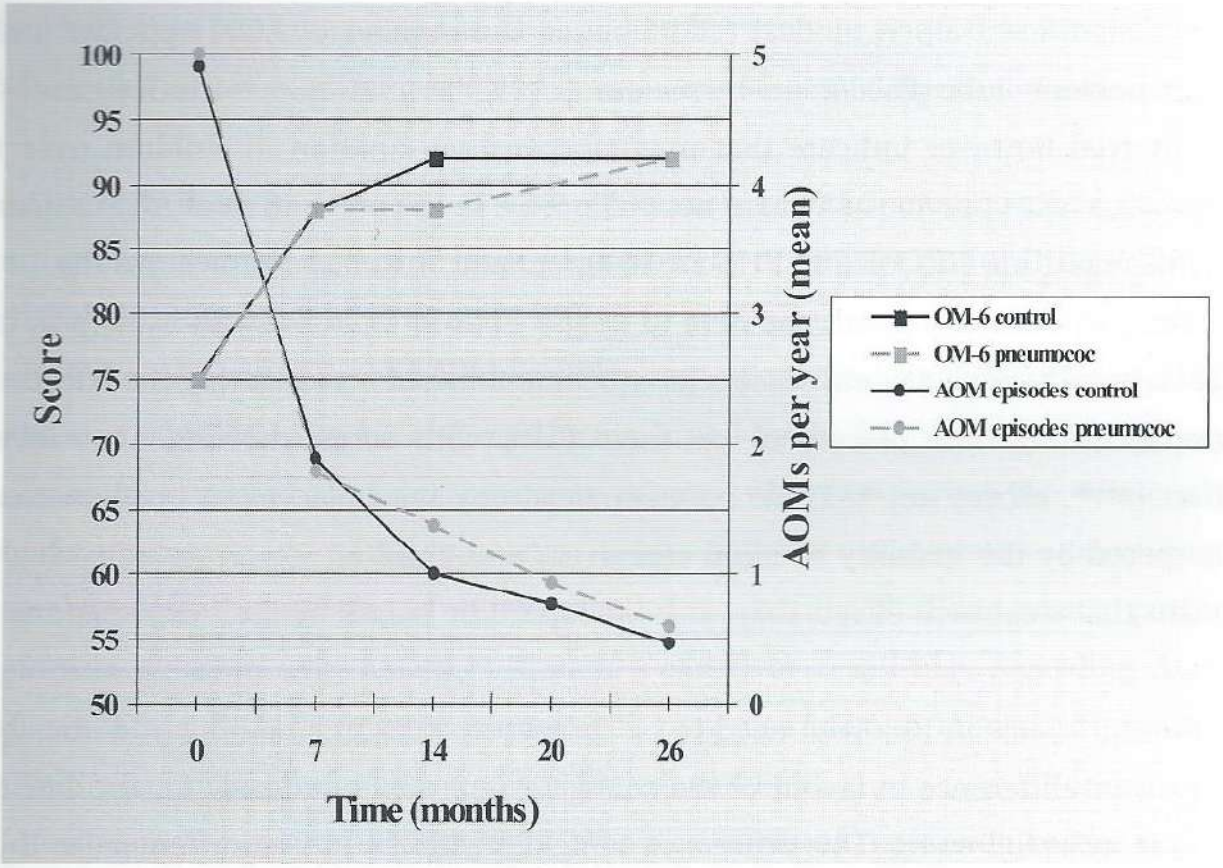
None of the possible effect modifiers showed a significant interaction effect, neither at 14 nor at 26 months follow-up.

Figure 2a. RAND scores and AOM frequency in pneumococcal vs. control vaccinees.



Figures 2a & 2b show considerable improvements in FHS and HRQoL in both the pneumococcal and control vaccine group simultaneous with a decrease in AOM incidence (from 5.0 to 0.60 and from 4.9 to 0.47 AOM episodes in Pnc vs. Ctrl group, respectively).

Figure 2b. OM-6 scores and AOM frequency in pneumococcal vs. control vaccinees.



Discussion

In this double-blind randomised controlled trial on the effect of pneumococcal vaccination on health-related quality of life (HRQoL) and functional health status (FHS) in children with a history of recurrent acute otitis media, no substantial difference between the two intervention groups could be found. Neither could sub-groups be identified that benefited either more or less from pneumococcal vaccination. Functional health status and health-related quality of life improved substantially in both the pneumococcal and control vaccine group.

This study is the first to assess the effect of pneumococcal vaccination on HRQoL and FHS of older children with rAOM. Previous clinical trials in infants have shown significant albeit modest reductions in the number of AOM episodes and tympanostomy tube placements by pneumococcal vaccination.[31, 34] Clinical results of our trial however indicate that pneumococcal vaccination in children over 1 year of age with previous rAOM is not efficacious in the prevention of AOM.[41] Our results regarding HRQoL and FHS are in agreement with these clinical results.

The current study is not the first to assess FHS in children with otitis media (OM). In particular, several studies have been published investigating the effect of tympanostomy tube placement on their FHS, with some showing a positive effect[5, 46-48], others not[49]. Trials on tympanostomy tube placement are however hampered by the inability to blind caregivers and children for treatment, which means that treatment effects may, at least in part, be biased by their expectations.

Several issues in this trial need to be discussed. First, a small but statistically significant difference in favour of the control group was found only for the OM-6 at 14 months follow-up. This difference coincides with the largest difference in the incidence of AOM episodes between both intervention groups. The OM-6 is a disease-specific questionnaire and may accordingly be most sensitive to real changes in otitis media-related FHS. However, the clinical relevance of the difference in AOM frequency at 14 months follow-up might be questioned since there seems to be no reasonable explanation for it and because it did not persist to follow-up.

Second, the influence of various patient characteristics on treatment outcome was evaluated to identify subgroups that might benefit more from pneumococcal vaccination than others. No such effect modifiers could however be identified. Although this could be due to a lack of power, it is unlikely that relevant effect modifiers are present since no overall beneficial effect of pneumococcal vaccination was observed. Therefore, for one subgroup of children to have benefited more from pneumococcal vaccination, another should have deteriorated.

Finally, during the trial, 8 (4.2%) children of the pneumococcal vaccine group and 13 (6.7%) of the control vaccine group were lost to follow-up. One child switched from the control to the pneumococcal vaccine group. It is unlikely that these small numbers of dropouts and crossovers influenced the trial results.

Although there are no overall differences between the pneumococcal vaccine and control vaccine group in HRQoL and FHS after vaccination, there was a striking improvement of FHS and HRQoL in both intervention groups, especially during the first 7 months of follow-up. This improvement coincides with a marked reduction of AOM episodes and may be explained by the fact that AOM frequency at enrolment was based on caregiver report, whereas during the trial only physician-diagnosed AOM episodes were counted. Caregivers may have overestimated the number of AOM episodes, something that has been reported before in children with rAOM.[50] If such a caregiver recall-bias regarding AOM incidence was in fact present, it obviously may also have influenced caregivers' reflection on subjective measures like HRQoL and FHS.

Furthermore, the reduction might be an example of regression to the mean. The children we studied, with relatively serious rAOM - i.e., at the extreme end of AOM-frequency distribution - are more likely to improve by chance alone.

The reduction in AOM frequency may also partly result from the natural course of rAOM. Similar but spontaneous reductions in AOM incidence in children with rAOM have been described previously.[2]

Finally, there is growing evidence that medical as well as HRQoL outcomes may improve substantially by trial participation in itself, which is assumed to be related to the expectation of future benefit, better clinical follow-up and other aspects of management of the condition.[51-54]

In conclusion, pneumococcal vaccination in children aged 1 to 7 years with previous recurrent episodes of acute otitis media does not improve their health-related quality of life or functional health status compared to control vaccination.

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Chapter 7

Does caregiver well being influence their rating of child health-related quality of life?

A study in children with recurrent acute otitis media

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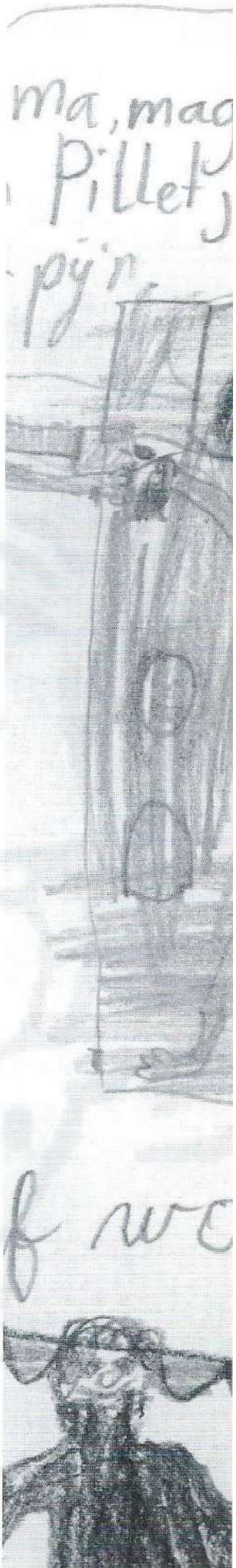


"Liefde is de meest subtiele kracht in de wereld."

Mahatma M.K. Gandhi

Abstract

Background: Health-related quality of life and functional health status have been increasingly recognized as important outcome measures in pediatrics. Chronic conditions in a child may not only have a considerable impact on the child's well-being, but also on family-life and caregiver well-being. In addition, perceptions of caregivers of their child's functioning are influenced by various factors, such as their own quality of life and emotional status. Both issues appear to be interrelated and may influence the judgement of caregivers of their child's health-related quality of life (HRQoL) and functional health status (FHS).

Objective: To establish the impact of recurrent acute otitis media (rAOM) on family life, especially on the main caregiver. To explore how caregiver HRQoL and emotional status influence their rating of HRQoL of children with rAOM.

Methods: Caregivers of 383 children with rAOM aged 1 to 7 years completed questionnaires on the impact of the child's rAOM on their own HRQoL (NRS Caregiver), and on family functioning (FFQ), as well as questionnaires on FHS (OM-6), and HRQoL (NRS Child) of their child.

The influence of caregiver HRQoL and emotional status on the relation between AOM frequency and their rating of child HRQoL were examined by multiple regression modeling.

Results: Twenty percent of caregivers reported 'lack of sleep' as a frequent problem of rAOM in their child, and 10% frequently felt 'agitated, nervous or irritable'. Family functioning was 81 on a 0-100 scale and was judged poorer in children with 4 or more AOM episodes per year compared to children with 2-3 AOM episodes. Family functioning and caregiver HRQoL improved alongside a reduction of AOM frequency during follow-up. In children with equal AOM incidence, caregivers with poorer HRQoL or emotional status rated their child's HRQoL lower than caregivers with better HRQoL or emotional status.

Conclusions: Recurrent AOM in a child negatively affects caregiver functioning and family life. This impact on caregiver HRQoL and emotional status appears to

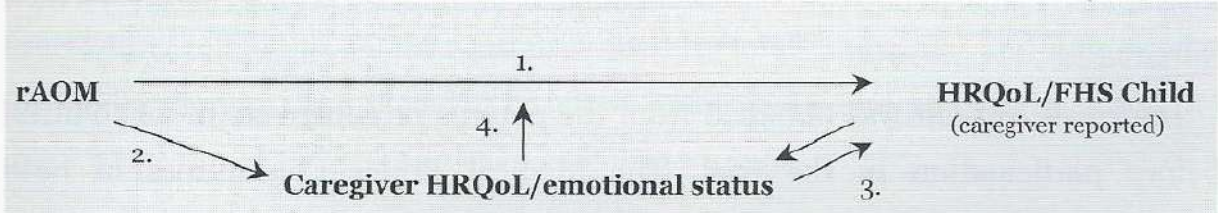
influence the association between AOM frequency and child HRQoL and FHS. Studies on HRQoL in children should therefore include assessment of caregiver psychological adjustment and HRQoL.

Introduction

Acute otitis media (AOM) is a common infection in childhood. Up to 15% of all children suffer from recurrent infections of the middle ear, resembling a chronic illness. Such chronic illness in a child may have a considerable impact on well-being of both the child and its caregiver. It also may affect family-life by disruption of daily family activities, over-attention to the child in question, and limited emotional availability and awareness of caregivers regarding the other siblings.[1-5] While intuitively obvious, few, mainly 'qualitative' studies are available on the impact of AOM on caregivers and family. They indicate that recurrent acute otitis media (rAOM) is indeed a stressful condition not only for the child, but also for its caregivers. Frequently mentioned sources of distress are sleeping problems or unusual irritability or fussiness in the child, anxiety about its suffering, disruption of daily life, and concerns about possible negative sequelae of rAOM, such as hearing impairment and delayed development.[6,7]

In young children, who are unable to judge their own health-related quality of life (HRQoL) due to their limited cognitive and language abilities, caregivers are considered the best proxies.[8,9] Their rating of child HRQoL, however, is

Figure 1. Relationships between AOM frequency, caregiver HRQoL & emotional status, and child HRQoL & FHS.



1. effect of rAOM on child HRQoL (direct)
2. effect of rAOM on caregiver; (lack of) sleep, daily activities etc.
3. effect of child HRQoL/FHS on caregiver HRQoL/emotions and vice versa
4. effect of caregiver HRQoL/emotional status on their judgement of child HRQoL/FHS (effect modification)

influenced by factors such as the caregiver's psychological condition, impact of the child's condition on family life, and caregiver - healthcare relationship.[10-12] Caregiver judgement of child HRQoL therefore appears to be interrelated with their own HRQoL (Figure 1), and these caregiver factors may thus affect the assessment of HRQoL in young children.

Aim of the present study is to examine the complex interactions between caregiver HRQoL and child HRQoL[a] in rAOM. For this purpose we will first describe the impact of rAOM in children on HRQoL of the caregiver and family functioning. Second, we will study the influence of caregiver HRQoL and emotional status on their judgement of child HRQoL.

Methods

Patients

The current study was performed as an extension of a double-blind randomised controlled trial (RCT) into the effect of pneumococcal vaccinations on FHS and HRQoL of children with rAOM alongside its clinical effectiveness. The trial was carried out at the pediatric outpatient departments of a general hospital (Spaarne Hospital Haarlem) and an academic hospital (University Medical Center Utrecht) from April 1998 to December 2001. Children were referred by Primary Care Physicians, Pediatricians and Otolaryngologists or enrolled on the caregiver's own initiative.

Informed consent was obtained from the parents or caregivers of all children before participation in the trial. The Medical Ethics Committees of both participating hospitals approved the study protocol.

[a] To enhance legibility 'health-related quality of life' in this article also refers to 'functional health status'

Intervention and follow-up

After inclusion in the trial, children were randomly assigned to vaccination with either a pneumococcal conjugate vaccine followed by a polysaccharide vaccine 6 months later, or with hepatitis control vaccines. Children were seen at the outpatient department at inclusion, and at 7, 14, and 26 months follow-up. At each visit, data on physician diagnosed AOM episodes (based on predefined criteria) and other upper respiratory tract infections as well as data on medical and surgical treatment for AOM were collected.[13]

Instruments

At inclusion and during follow-up visits, caregivers completed a questionnaire assessing disease-specific functional health status (FHS) of their child (OM-6[14, 15]) and a questionnaire addressing family functioning related to the child's rAOM (FFQ, see Appendix 3, p.182). Global health-related quality of life of the child and of the caregiver related to the child's ear-infections were assessed by two numerical rating scales (NRS Child[14, 15] and NRS Caregiver). Characteristics of these instruments are given in Appendix 1, p.179. For all instruments higher scores reflect better HRQoL or less problems. The instruments have been demonstrated to be reliable and valid.[16, 17]

Analysis

Health-related quality of life of the caregiver as well as caregiver and family functioning related to rAOM were described by total-, subscale- and item-scores for the instruments completed at baseline, and at 7, 14, and 26 months of follow-up.

The influence of HRQoL of the caregiver on their judgement of the HRQoL of their child was assessed at 7 months follow-up through the use of multiple regression models. Separate multiple regression analyses were conducted with two measures of the child's HRQoL (NRS Child and OM-5[b]) as dependent variables, and AOM frequency and caregiver HRQoL (NRS Caregiver) or AOM frequency and emotional status (FFQ item 'Feeling nervous, agitated, or irritable') as independent variables. This resulted in four different regression models (see Table 2).

Caregiver HRQoL was assumed to influence their judgement of the child's HRQoL, but not the frequency of AOM episodes (Figure 1). To study whether caregiver HRQoL also modified the association between AOM frequency and child HRQoL, interaction terms (either AOM frequency × caregiver HRQoL, or AOM frequency × emotional status) were included in the regression analyses.

To enhance insight in the influence of caregiver HRQoL and emotional status on their rating of the child's HRQoL, stratified case-summaries of child HRQoL and FHS were given for different levels of AOM frequency, caregiver emotional status, and HRQoL.

Results

Caregiver HRQoL and family functioning

At baseline, lack of sleep, concerns, and feeling agitated, nervous, or irritable due to their child's rAOM was reported as a frequent problem by 22%, 13% and 10% of the caregivers, respectively (Table 1a). On a scale ranging from 0 to 100, they rated their own overall HRQoL as a consequence of their child's rAOM as 63 and family functioning as 81 (Table 1b). Most caregivers shared the opinion that the other siblings were not much affected by the recurrent ear infections of the sibling with rAOM.

[b] For the regression analyses a modified version of the OM-6, i.e. the OM-5, was used, excluding the question addressing caregiver worries and inconvenience

Caregivers of 'otitis-prone' children, who had 4 or more AOM episodes in the year prior to inclusion, reported more adverse consequences for family functioning than caregivers of children with fewer (2-3) AOM episodes per year: the FFQ total scores were 78 and 85, respectively (p=0.001). Their overall HRQoL (NRS Caregiver) did, however, not differ (61 vs. 66, p=0.11).

Since there were no significant differences between the pneumococcal and control vaccine group in caregiver HRQoL and emotional status at any assessment moment, both groups were combined in the follow-up analyses. Alongside the reduction in AOM incidence in their children, caregivers reported improvements

Table 1a. Caregiver worries and family functioning related to rAOM*.

	t = 0 mo		t = 7 mo		t = 14 mo		t = 26 mo	
	n = 371	95% CI	*n* = 354	95% CI	*n* = 346	95% CI	*n* = 241	95% CI
Family Functioning Questionnaire								
Lack of sleep	22%	18-26	6%	4-8	4%	2-6	0.4%	0-1
Having to stay at home	2%	0.6-3	0.8%	0-2	0.3%	0-0.9	0.4%	0-1
Canceling family-activities	7%	4-10	2%	0.5-3.5	0.6%	0-1	0.8%	0-2
Changing appointments	2%	0.5-3	0.8%	0-2	0.9%	0.1-2	2%	0.2-4
Changing daily activities	6%	4-8	3%	2-4	0.9%	0.1-2	0.4%	0-1
Feeling nervous, agitated or irritable	10%	7-13	3%	2-4	1%	0-2	0.4%	0-1
Siblings feeling neglected	6%	4-8	1%	0-2	1%	0-2	0.5%	0-1
Siblings asking for extra attention	9%	6-12	2%	0.5-3.5	1%	0-2	0.5%	0-1
OM-6								
Being worried, concerned or inconvenienced	13%	10-16	5%	3-7	2%	0.5-3	0.5%	0-1

* = reflected by % caregivers reporting the issue as a frequent problem, or as mostly/certainly true for sibling items (item 7 and 8 of the Family Functioning Questionnaire).

on all items of the FFQ. Caregiver concerns and inconveniences (one item of OM-6) and caregiver ratings of their global HRQoL related to their child's ear infections improved accordingly (Table 1a and 1b). Improvement in family

Table 1b. Family functioning and caregiver HRQoL at baseline, and 7, 14, and 26 months follow-up (mean score on 0-100 scale).

	t = 0 mo		t = 7 mo		t = 14 mo		t = 26 mo	
	n = 371	SD	*n* = 354	SD	*n* = 346	SD	*n* = 241	SD
Family Functioning Questionnaire	81	*18*	93	*13*	96	*10*	97	*9*
Caregiver subscale	73	*25*	90	*19*	94	*14*	95	*12*
Sibling subscale	83	*25*	94	*16*	96	*12*	97	*13*
NRS Caregiver*	63	*18*	81	*17*	83	*16*	81	*15*
AOM frequency	5.0	*2.7*	1.8	*2.2*	1.2	*1.7*	0.7	*1.2*

* *n* = 146, 149, 145 and 42 at 0, 7, 14, and 26 months follow-up, respectively.

functioning and caregiver HRQoL was largest during the first 7 months of follow-up, when the reduction in AOM incidence was largest as well. Largest relative improvements were reported in caregiver concerns and inconveniences (OM-6), in FFQ caregiver items 'lack of sleep', 'feeling nervous, agitated or irritable' and 'canceling family activities', and in one item about sibling emotional functioning: 'asking for extra attention' (Table 1a).

Caregiver HRQoL and their rating of child HRQoL

Multiple regression analyses (see also models under Table 2) indicated that caregivers with a better emotional status or HRQoL rate their child's HRQoL higher than caregivers with a poorer emotional status or HRQoL ($p < 0.001$ and $p \leq 0.002$, respectively). In these regression models, caregiver HRQoL appears to be the best predictor of child HRQoL ($R^2 = 0.61$), whereas caregiver emotional status is the best predictor of child FHS ($R^2 = 0.55$). In addition, caregiver HRQoL modifies the association between AOM frequency and child FHS (OM-5) ($p = 0.01$), whereas caregiver emotional status modifies the association between AOM frequency and child HRQoL (Child NRS) ($p = 0.03$) (Table 2).

Table 2. Child HRQoL (NRS Child) and FHS (OM-5) stratified by caregiver emotional status and HRQoL.

AOM frequency	Caregiver Emotional status#	HRQoL#	*n*	Child OM-5	*95% CI*	NRS Child	*95% CI*
0	1	--	0	NA		NA	
0	2	--	5	11.8	9.1-14.5	6.0	5.4-6.6
0	4	--	143	19.2	18.9-19.5	9.1	8.9-9.3
2	1	--	4	11.5	8.9-14.1	3.8	1.0-6.6
2	2	--	4	11.8	9.5-14.1	4.8	2.9-6.7
2	4	--	82	18.7	18.3-19.1	7.7	7.2-8.2
0	--	40	1	20.0		6.0	
0	--	60	4	13.5	11.0-16.0	6.3	5.4-7.2
0	--	100	30	18.4	17.2-19.6	9.8	9.6-10.0
2	--	40	0	NA		NA	
2	--	60	5	17.4	15.0-19.8	5.4	4.9-5.9
2	--	100	9	19.0	17.9-20.1	9.4	8.7-10.1

higher scores resemble better emotional status or HRQoL

Model 1. FHS Child = OM-5

1a. FHS Child = 6.6 – 0.14 x AOM frequency + 3.2 x caregiver emotional status – 0.035 x AOM frequency x caregiver emotional status $R^2 = 0.55$
p = 0.61 p < 0.001 p = 0.65

1b. FHS Child = 13.4 – 1.32 x AOM frequency + 0.59 x caregiver HRQoL + 0.15 x AOM frequency x caregiver HRQoL $R^2 = 0.34$
p = 0.003 p = 0.002 p = 0.01

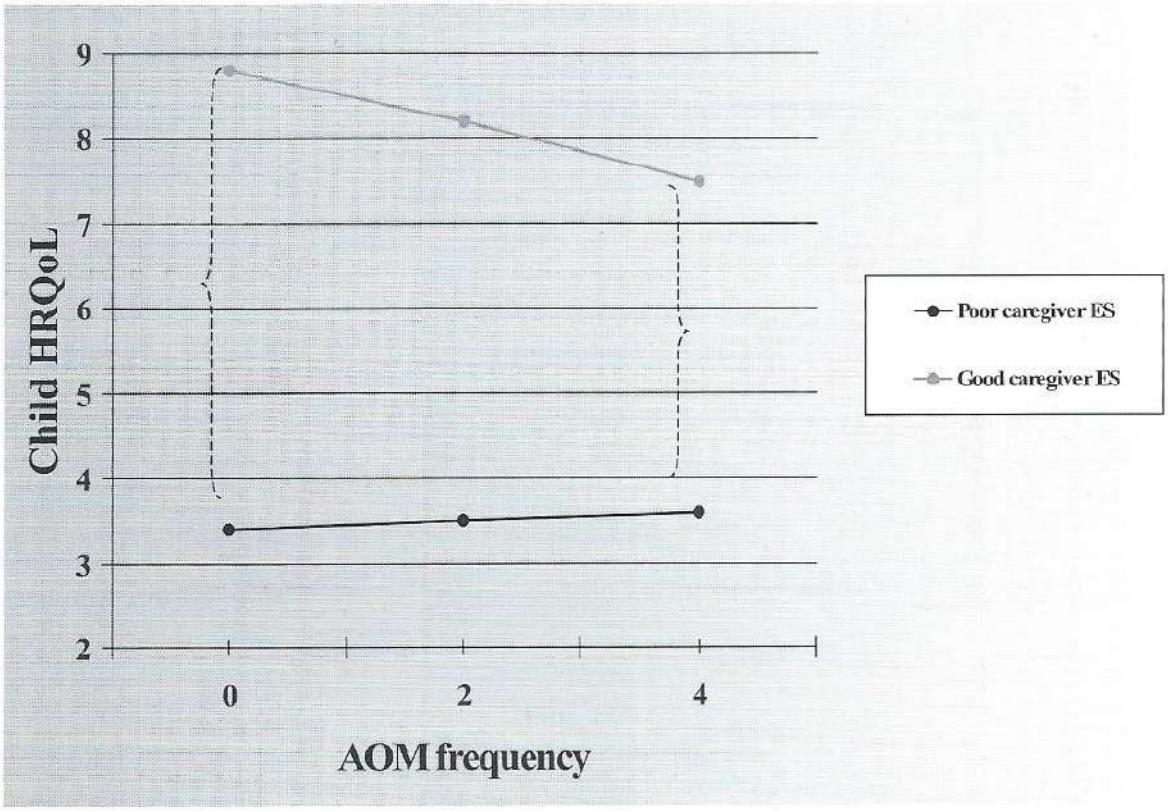
Model 2. HRQoL Child = NRS Child

2a. HRQoL Child = 1.6 + 0.18 x AOM frequency + 1.81 x caregiver emotional status – 0.13 x AOM frequency x caregiver emotional status $R^2 = 0.39$
p = 0.39 p < 0.001 p = 0.03

2b. HRQoL Child = 0.26 + 0.12 x AOM frequency + 0.95 x caregiver HRQoL – 0.031 x AOM frequency x caregiver HRQoL $R^2 = 0.61$
p = 0.59 p < 0.001 p = 0.28

Three of the four modifiers examined were inverse, indicating that the difference in caregiver rating of child HRQoL between caregivers with poorer versus better HRQoL becomes less prominent when AOM frequency raises (see Figure 2).

Figure 2. Child HRQoL by AOM frequency – effect modification by caregiver emotional status (ES).



Stratified case-summaries (Table 2) show that rating of child HRQoL and FHS increases with improvement of caregiver emotional status and HRQoL for both 0 and 2 AOM episodes per year. Likewise, when entering a hypothetical child with 2 AOM episodes in regression model 2, the child's HRQoL score is 4.1 on a 0 – 10 scale, when caregiver HRQoL is poor, and 9.4 when caregiver HRQoL is good.

Discussion

The results of the present study show that recurrent AOM in a child appears to have a negative effect on caregiver HRQoL and family functioning. In addition, caregiver HRQoL and emotional status appear to influence the relationship between rAOM and child HRQoL. To our knowledge, this is the first study to evaluate the complex interactions between child HRQoL on the one hand, and caregiver HRQoL and emotional status on the other hand.

Some limitations of this study need to be addressed. First, an index score on a numerical rating scale was used to assess caregiver HRQoL, whereas caregiver emotional status was assessed by one item of a family functioning questionnaire. These measures may have been too crude to adequately reflect caregiver HRQoL and emotional status. On the other hand, in previous studies single symptom scores of standardized questionnaires were found to satisfactorily assess psychological status.[11, 18]

Second, since we did not include a control group of healthy children, norm-scores were not available. In addition, we were not able to assess to what extent improvement in caregiver HRQoL and family functioning was caused by general factors other than improvement in rAOM. However, all caregiver questionnaires were disease-specific and therefore should reflect improvement in aspects of HRQoL that are mainly relevant to rAOM.

Third, the numbers in the strata were small, which may affect reliability of the case-summary scores. Trends reflected by the scores, however, were consistent and in agreement with the results obtained by entering hypothetical cases in the regression models.

Up to 13% of the caregivers in this study reported to be worried, concerned or inconvenienced for at least a good part or most of their time, which is considerably less than found in previous studies. In children with chronic otitis

media with effusion (COME) or rAOM referred for tympanostomy tube placement, concerns or inconveniences were reported by more than 50% of parents.[14, 15, 19] This may be explained by the fact that many of these children were referred for surgery because of hearing impairment accompanying COME, which is a major concern to parents of children with COME and rAOM.[7] The difference may also reflect a cultural difference in illness perception between Dutch and U.S. caregivers.

Lack of sleep and feeling irritated, agitated, and nervous were the items rated highest by caregivers in this study. Previous qualitative studies have identified frustration over the cyclical nature of infections and concurrent sleeplessness leading to stress, as important problems in rAOM.[6, 19] Besides, feelings of helplessness, guilt and frustration over the child's suffering may also affect a caregiver's emotional well-being.[6]

Caregivers in the current study judged siblings to be relatively unaffected by their brother's or sister's ear infections. Asmussen et al.[6] found sibling responses in rAOM to be very variable. In previous studies of siblings of children with other chronic conditions, the majority was found to have behavioral or emotional problems. However, unawareness of caregivers of a sibling's perceptions towards the chronically sick child appears to be a risk factor for maladjustment in a sibling.[2, 5] Since we did not obtain information directly from siblings of the children in the current study, it remains unclear whether the low impact on their functioning is real or a consequence of unawareness by their caregivers.

Previous studies in psychology have demonstrated associations between caregiver emotional or mental status and their reports of depression, psychological adjustment and behavior both in healthy children and children with a chronic illness.[10, 11, 12, 18] So far, however, no studies have been published on the effect of HRQoL or emotional status of the caregiver on their judgement of the child's HRQoL. In the current study, poor caregiver HRQoL or emotional status was associated with poorer caregiver reports of HRQoL children with rAOM. Part of this association between caregiver and child HRQoL may be explained by the

influence of caregiver HRQoL or emotional status on caregiver-child interaction, which in turn, affects HRQoL of the child. The association between rAOM and HRQoL of the child however, also appears to be modified by caregiver HRQoL or emotional status through their changed perceptions of the child's HRQoL (Figure 1 and 2).

Similar to previous psychological studies on caregiver psychological adjustment, caregiver HRQoL and emotional status appear to influence reported child HRQoL and FHS. Since assessment of HRQoL and FHS in children aged 7 years and younger mainly relies on caregiver report, it is important to obtain an idea of the magnitude and mechanism of this influence by modeling the influence of caregiver HRQoL and its interaction on child HRQoL. We therefore recommend to include questionnaires assessing caregiver HRQoL in studies using caregiver reported HRQoL or FHS of children.

In conclusion, our findings provide empirical evidence for the view that rAOM in a child has a negative impact on family functioning, and especially on caregiver functioning. HRQoL and emotional status of the caregiver influences caregiver reported HRQoL and FHS in a child, which appears to be partly due to perceptions of the caregiver with regard to their child's HRQoL and FHS. Assessment of caregiver psychological adjustment and HRQoL should therefore be included in studies on HRQoL and FHS in children.

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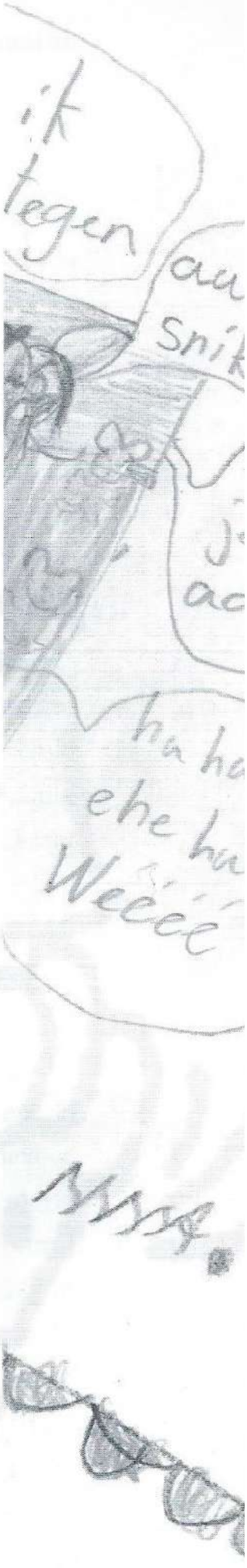
Chapter 8

General discussion



"You may give them your love but not your thoughts.
For they may have their own thoughts.
You may house their bodies but not their souls,
For their souls dwell in the house of tomorrow, which you cannot visit,
Not even in your dreams."

Kahlil Gibran

In this thesis we aim to assess health-related quality of life and functional health status in Dutch children aged one to seven years with recurrent acute otitis media.

In *Chapter 2* we have shown that in spite of several attempts to measure health-related quality of life (HRQoL)[a] in children with otitis media (OM), there are few adequately validated generic and disease-specific instruments for HRQoL assessment in children with OM. For our study we selected four generic instruments (RAND[1-3], FSQ Generic, FSQ Specific[1, 3-5], TAIQOL[6, 7]) that were available in Dutch and translated two disease-specific instruments (OM-6 and NRS Child[8, 9]). To assess HRQoL in family and caregivers we composed two disease-specific instruments (FFQ and NRS Caregiver). This broad set of instruments was then validated for our population (*Chapter 3* and *Chapter 4*).

Most instruments were found to be highly reliable and valid. However, the two numerical rating scales assessing global health-related quality of life for the child and for the caregiver, as well as the TAIQOL - the only true HRQoL questionnaire in this study - were found unable to discriminate between children with different frequency of AOM episodes. In *Chapter 4* it was shown that the TAIQOL also had a very poor responsiveness and therefore could not be used to evaluate our trial results. Overall, the generic RAND and disease-specific OM-6 and FFQ demonstrated highest reliability and validity.

The impact of rAOM on HRQoL of the children in our study appeared to be considerable: their HRQoL was poorer than that of children from a general population and children with mild to moderately severe chronic illnesses such as allergy, asthma, eczema, and gastro-intestinal conditions *(Chapter 5)*. We found no benefit from pneumococcal vaccination compared to a hepatitis control vaccine on HRQoL of our children with rAOM. HRQoL improved remarkably in *both* intervention groups during follow-up alongside a reduction in AOM frequency *(Chapter 6)*.

[a] To enhance legibility 'health-related quality of life' in this chapter also refers to 'functional health status'.

In *Chapter 7* we showed that rAOM not only affects HRQoL of the child, but also that of the family and the caregiver, which in turn influenced the caregiver's judgement of their child's HRQoL.

Use of generic and disease-specific HRQoL instruments in rAOM

Were the instruments used in this study suitable for HRQoL assessment in young children?

Since most questionnaires in this study had not been specifically developed for pre-school children, one may question its feasibility to assess HRQoL of our study population with a median age of 2.2 years. To assess HRQoL in children, instruments need to be able to address age-appropriate functioning and to be sensitive to the changes that occur throughout a child's development.[10, 11] Based on their content and proven usefulness in previous studies, we expected that our set of questionnaires would be appropriate for HRQoL assessment in our study population.[1, 2, 5, 6] In addition, the possibility that age itself would affect HRQoL assessment across the broad age-range (1 - 7 years) of our study population[1] was refuted by our findings in *Chapter 5* that there was no significant effect of age on HRQoL ratings in our population.

Was the assessment of reliability and validity adequate?

Although there is general consensus on the best methods to assess internal consistency and discriminant validity, there is less agreement about assessment of test-retest reliability and construct validity[12-14]. Of the various statistics that are available to assess test-retest reliability, we chose Pearson's correlation coefficient and the intra-class correlation coefficient and found almost similar results for both statistics. However, although Pearson's correlation coefficient is a traditional and familiar statistic, we prefer the intra-class correlation coefficient since this statistic not only assesses the strength of a correlation between repeated measurements, but also whether there is systematic bias.[15]

Construct validity was estimated using a common strategy of testing hypothesized correlations between related instruments, between related dimensions of different instruments, and between instrument scores and external physical or psychosocial variables.[16] Selecting the appropriate external variables and formulating correct hypotheses, however, is troublesome *(Chapter 3)* and assessment of construct validity therefore continues to be an iterative process.

How to assess responsiveness in pediatric HRQoL?

To evaluate treatment effects, HRQoL instruments need to be responsive, i.e. they must be able to detect clinically important change over time. Since child HRQoL has been assessed for several chronic illnesses with the intention to then evaluate efforts to improve this HRQoL, it is remarkable that responsiveness has been assessed for only few pediatric HRQoL instruments.[17-21] Child HRQoL assessment should catch up with developments in *adult* HRQoL research, where the notion that the various methods to assess responsiveness may lead to different outcomes[13], has resulted in recent attempts to formulate plain recommendations regarding the use of multiple methods and interpretation of change.[14, 22] The consistency of our results regarding responsiveness of pediatric instruments in *Chapter 4* following these recommendations supports further application in pediatric HRQoL research. However, considering the ongoing discussion regarding (proper) assessment and interpretation of responsiveness, further harmonization of assessment methods and taxonomy and formulation of criteria for use in clinical trials is still needed.[23, 24]

Finally, the findings that the only true HRQoL instrument, the TAIQOL subscales, had a poor discriminant validity and a very poor responsiveness in our population demonstrates that it is essential to fully validate instruments before using them in clinical trials.

Health-related quality of life and functional health status in children with recurrent AOM

We believe that up to now the impact of rAOM on the child and its family has been underestimated, and that this may have contributed to the limited knowledge on HRQoL of children with this condition. AOM is a very common condition in childhood. Fortunately, in most children AOM episodes are infrequent and self-limiting, but in our study population of children who experienced recurrent episodes, however, the impact of rAOM on their HRQoL appeared to be considerable (*Chapter 5*).

How should the impact of rAOM on HRQoL be interpreted?

The absence normscores for most HRQoL instruments is a general problem in pediatric HRQoL measurement, limiting interpretation of results and statistical differences in scores across populations. Some questionnaires, such as the FSQ Specific have been applied in different pediatric populations, thus facilitating comparisons and producing surrogates for norm-scores. FSQ Specific scores, for example, were found to range from 96 (scale 1 to 100) for well children, to 87 for chronically ill children and 92 to 94 for children with mild to moderate asthma.[25, 26] In our population mean FSQ Specific score was 81, which places the impact of rAOM on HRQoL in the range of moderately severe chronic illnesses. To enhance further interpretation of HRQoL scores and to develop norm-scores, existing validated instruments such as in our study should be extensively used in various populations.

We realize that selection bias may have occurred, on the one hand because most children participating in the trial had suffered from very frequent AOM episodes (32% had 6 or more episodes in the year prior to inclusion) despite various medical and surgical therapies. The new pneumococcal conjugate vaccine was considered as the "last" option. On the other hand, many children were recruited through self-referral by the caregivers from various areas in the Netherlands.

Caregivers of children whom HRQoL had been more severely affected by rAOM probably were more likely to participate in this trial than other caregivers. Consequently, effects of rAOM on child HRQoL may be overestimated and may not be generalized to all children with rAOM or children with a single AOM episode.

The impact of treatment on HRQoL in rAOM

HRQoL of the pneumococcal vaccine improved considerably during follow-up alongside a reduction of AOM frequency. The hepatitis vaccine control group, however, showed the same improvement *(Chapter 6)*. This finding emphasises the importance of including a control group in studies evaluating treatment effects, and sheds the results of previous uncontrolled trials on the effect of tympanostomy tube placement and adenotonsillectomy[9, 27, 28] into a different light. Since HRQoL may also change as a result of advancing age, regression to the mean and non-specific effects of trial participation in itself[29, 30], examining the true magnitude of HRQoL improvements related to the intervention requires a controlled trial.

What does the influence of caregiver HRQoL on child HRQoL implicate?

Chapter 7 shows clearly that caregiver HRQoL affects caregiver reported child HRQoL, but it was found difficult to disentangle these reciprocal effects between caregiver and child HRQoL. This emphasises the importance of assessing both caregiver and child HRQoL as part of the evaluation of child HRQoL. Although it may prove impossible to eliminate the influence of caregiver HRQoL on their rating of child HRQoL, the first step is to gain more insight in these interactions by describing and quantifying them. We, however, would discourage the integration of questions addressing caregiver or family functioning in a child HRQoL questionnaire.

The impact of rAOM on child and caregiver HRQoL (*Chapter 5* and *Chapter 7)* as well as the limited effectiveness of current AOM treatment strategies (*Chapter*

6), has implications for future care of children with rAOM. Considering the high level of caregiver concerns *(Chapter 7)*[31, 32] as well as lack of (social) support reported in previous studies[31], counselling of caregivers, while important in its own right, may also improve caregiver and child HRQoL in rAOM.[33]

The major advantage of this study has been the application of a battery of questionnaires. Use of generic as well as disease-specific instruments allowed to study the performance of both types of questionnaires in validation studies *(Chapters 3 and 4)* as well as in HRQoL assessment *(Chapters 5 and 6)*. Both generic and disease-specific instruments appeared to be valid in HRQoL assessment and give complementary information on HRQoL of children with rAOM and their family. The use of existing Dutch versions of the RAND, FSQ Generic, FSQ Specific and the recently developed Dutch TAIQOL has contributed to a deeper understanding of the applicability these questionnaires in general. In addition, translation of the disease-specific OM-6 from English into Dutch according to principles of backward-forward translation[34-37], as well as the composition of a new disease-specific questionnaire to assess family functioning (FFQ) has yielded two new instruments that appear to be valid for future use in AOM research in children.

Recommendations regarding HRQoL in clinical research and care

This study shows that health-related quality of life measurement in young children is complicated and still limited. Further HRQoL research in children should address the following topics:

- Pediatric HRQoL research should address the obvious lack of responsiveness assessment. For that purpose, recent guidelines regarding use of multiple methods and interpretation of change that have been developed in adult research should also be applied to responsiveness assessment in child HRQoL.

- Caregiver and family functioning should be assessed simultaneously with child HRQoL using separate, validated questionnaires addressing psychosocial adjustment and HRQoL. Although functioning of children is closely related to the quality of their environment, we would discourage the inclusion of questions addressing caregiver or family functioning in a child HRQoL questionnaire.
- A control group should be included in any trial evaluating the effectiveness of treatment or intervention on child HRQoL to control for non-specific effects.
- The possibility of developing valid multidimensional HRQoL instruments for *young* children by inclusion of emotional and social functioning should be explored as well as the possibility to include a value judgement of the young child's functioning.

Regarding HRQoL in children with rAOM:

- A combination of generic instruments and disease-specific instruments should be used to allow for comparisons between HRQoL of children with rAOM and that of healthy children or children with other medical conditions.
- Normscores for both generic and disease-specific instruments are needed.
- The instruments proven useful for HRQoL assessment in our children with rAOM (RAND, FSQ Generic, FSQ Specific, OM-6, NRS Child, FFQ and NRS Caregiver) should be incorporated in future studies to fully appreciate their usefulness in AOM as well as to put the results in a broader perspective.
- Since the impact of rAOM on child and caregiver HRQoL is considerable, and effectiveness of current treatments is limited, research into new directions for treatment and prevention is urgently needed.
- Following the above, the additional notion that caregiver HRQoL influences child HRQoL should urge health care providers to be (fully) alive to the expectations, views and concerns of caregivers of children with rAOM.

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Chapter 9

Summary

Samenvatting

"The time is right
I'm gonna pack my bags
And take that journey down the road
Cause over the mountain I see the bright sun shining
And I want to live inside the glow."

India.Arie

Acute otitis media (AOM) is the most common infection in childhood with five to fifteen percent of all children, depending on their age, suffering from *recurrent* episodes of acute otitis media (rAOM). These repetitive episodes cause considerable distress in the child and its family. Since effectiveness of current management options for rAOM, such as tympanostomy tubes, adenoidectomy or antibiotic prophylaxis is modest, attention has diverted to prevention through vaccination. In this thesis we describe the impact of recurrent acute otitis media on the health-related quality of life (HRQoL) of the child and its caregiver and the effects of pneumococcal vaccination.

In *Chapter 2* we reviewed the literature on HRQoL in otitis media (OM) to gain a better understanding of the impact of OM on HRQoL and to evaluate the applicability of existing HRQoL instruments in clinical practice and research. The majority of children with AOM were reported to experience physical suffering (pain, high fever), hearing, speech or behavioural problems, and emotional distress. Up to now a variety of instruments have been used. Most of them mainly address symptoms of AOM and physical functioning and therefore actually measure functional health status (FHS) instead of HRQoL. Furthermore, adequate data on reliability and validity are lacking for most of the instruments. As a result, our knowledge of HRQoL in children with recurrent or chronic OM is still limited. The OM-6 appeared to be the most appropriate instrument available for FHS assessment in children with OM based on its content validity and psychometric characteristics.

In *Chapters 3 to 7* the results of HRQoL assessment are described in 383 children with rAOM (2 or more documented episodes of AOM in the previous year) aged 1 to 7 years participating in a double blind randomized placebo controlled trial on the effectiveness of pneumococcal vaccination. One hundred and ninety children were vaccinated with heptavalent pneumococcal conjugate vaccine followed by

pneumococcal polysaccharide vaccine (pneumococcal group), 193 children received hepatitis A or B vaccines (control group).

Parents completed Dutch versions of eight HRQoL and FHS instruments assessing general FHS (RAND, FSQ Specific and FSQ Generic) and HRQoL (TAIQOL), and OM-specific FHS (OM-6), child HRQoL (NRS Child), family functioning (FFQ), and caregiver HRQoL (NRS Caregiver) during clinic visits at baseline and at 7, 14 and 26 months follow-up. In addition, data on the number of physician diagnosed AOM episodes and related treatment were collected at each clinic visit.

In *Chapter 3* and *Chapter 4* we evaluated the reliability and validity of four generic and four disease-specific HRQoL and FHS instruments. Internal consistency and test-retest reliability were found to be high for all instruments. Construct validity was demonstrated by moderate to strong correlations among the questionnaires and between items expected to address similar aspects of physical functioning. Construct validity was further supported by moderate to strong correlations between ratings of global FHS and HRQoL and the number of physician visits for upper respiratory tract infections, and between scores on disease-specific instruments and the number of AOM episodes in the preceding year. Discriminant validity for children with few versus frequent AOM episodes per year was good for most instruments, but poor for the examined subscales of the TAIQOL and both numerical ratings scales.

In *Chapter 3* responsiveness (i.e. the ability to detect clinically important change) was assessed according to recently developed guidelines recommending use of multiple strategies, and head to head comparison between generic and disease-specific instruments. Evaluation of responsiveness involved assessment of sensitivity to change and assigning meaning to change by estimating minimally clinical important change (MCID). Although sensitivity to change was better for disease-specific instruments, both generic and disease-specific instruments had adequate responsiveness to justify their use in clinical studies of children with recurrent acute otitis media. The otitis-related TAIQOL subscales however, had

very poor sensitivity to change, which made them inadequate for follow-up studies.

FHS and HRQoL of children with rAOM were assessed in *Chapter 5* using the generic and disease-specific questionnaires that we had validated for this particular population.

Subscales assessing physical problems, emotional distress, problem behaviour and parental concern were found to be most affected by rAOM. Caregivers of children with recurrent AOM not only judged their child's FHS and HRQoL markedly lower than caregivers of children from a general population, but also lower than those of children with mild to moderately severe chronic illnesses such as gastro-intestinal problems. FHS and HRQoL of our study population were similar to those of children with mild to moderate asthma and American children with chronic OME or recurrent AOM.

In *Chapter 6* the results of the randomized controlled trial are presented. During follow-up no substantial differences in HRQoL or FHS could be demonstrated between the pneumococcal and the control vaccine group, nor could sub-groups benefiting either more or less from pneumococcal vaccination be identified. HRQoL and FHS, however, improved substantially alongside a reduction in AOM incidence in both the pneumococcal and control vaccine group.

In *Chapter 7* we studied the impact of rAOM on family life, especially on the main caregiver. We also explored how caregiver HRQoL and emotional status influence their rating of HRQoL of children with rAOM. Recurrent AOM in a child negatively affected family life, especially caregivers' functioning. This impact of rAOM on caregivers HRQoL and emotional status also appeared to influence the caregiver reported HRQoL and FHS in a child. We therefore recommend to include measures of caregiver psychological adjustment and HRQoL in studies on HRQoL and FHS in children.

In *Chapter 8* we discussed the main findings of this study, and the difficulti assessing HRQoL in young children. We also suggested how to interpret findings and what the implications could be. Since our instruments were appropriate and had adequate reliability and validity, we believe them t suitable to assess HRQoL and FHS in our study population of children aged years with rAOM. HRQoL and FHS in children with rAOM were comparab that of children with other moderately severe chronic illnesses. Unexpect pneumococcal vaccination, had no beneficial effect on rAOM or HR Recommendations are given regarding future HRQoL research in young chi in general and children with rAOM in particular.

Otitis media acuta (OMA) ofwel acute middenoorontsteking is de meest voorkomende infectie bij kinderen en gaat gepaard met klachten van oorpijn, koorts en algemeen ziek-zijn. Vijf tot vijftien procent van alle kinderen, afhankelijk van hun leeftijd, hebben er veelvuldig (4 of meer keer per jaar) last van. Deze aandoening wordt recidiverende otitis media acuta genoemd (rOMA). Hoewel veel aandacht is besteed aan de gevolgen van middenoorontstekingen voor bijvoorbeeld gehoor, taalontwikkeling en algemene ontwikkeling, is er internationaal nog maar weinig bekend over de invloed ervan op het functioneren van het kind en het gezin. Dit functioneren kan in maat en getal uitgedrukt worden als kwaliteit van leven en functionele gezondheidstoestand. Met de functionele gezondheidstoestand bedoelen we het fysiek, cognitief, emotioneel en sociaal functioneren van gezonde en zieke kinderen. Als ook beoordeeld wordt hoe zij zich daarbij voelen, spreken we van kwaliteit van leven. Bij jonge kinderen wordt de kwaliteit van leven en functionele gezondheidstoestand meestal beoordeeld door hun ouders. Vragenlijsten die kwaliteit van leven en functionele gezondheidstoestand meten worden onderverdeeld in algemene en ziekte-specifieke vragenlijsten. Algemene vragenlijsten zijn gericht op een breed scala aan gezondheidsproblemen en het daarbij behorend functioneren, terwijl ziekte-specifieke vragenlijsten vooral gericht zijn op die onderwerpen die relevant zijn voor een bepaalde aandoening.

De huidige behandelingsmogelijkheden voor recidiverende middenoorontstekingen, zoals het plaatsen van trommelvliesbuisjes, het knippen van de neusamandelen of het geven van antibiotische profylaxe, blijken een gering effect te hebben op het verminderen van het aantal oorontstekingen. De laatste jaren is de aandacht dan ook verschoven van behandeling naar het voorkomen (preventie) van middenoorontstekingen door middel van bijvoorbeeld vaccinatie.

In dit proefschrift beschreven we de invloed van recidiverende acute middenoorontstekingen op de kwaliteit van leven van een kind en zijn ouders,

alsmede het effect van vaccinatie met pneumococcen vaccins op deze kwaliteit van leven.

In *Hoofdstuk 2* bespraken we de onderzoeken die tot nu toe zijn gedaan naar de kwaliteit van leven van kinderen met middenoorontstekingen. Het doel van dit systematische literatuuroverzicht was enerzijds een beter inzicht te krijgen in de gevolgen van middenoorontstekingen voor de kwaliteit van leven van een kind, en anderzijds de toepasbaarheid van bestaande instrumenten in de klinische praktijk en wetenschappelijk onderzoek te evalueren.

Lichamelijke klachten (pijn, hoge koorts), van streek of geïrriteerd zijn, en taal/spraak- of gedragsproblemen bleken veel voor te komen bij kinderen met een acute middenoorontsteking. De tot nu toe gebruikte instrumenten om de invloed van middenoorontstekingen op het welbevinden van een kind te meten bleken echter zeer uiteen te lopen. De meeste beschreven vooral (de ernst van) de symptomen van een acute middenoorontsteking en het lichamelijk functioneren en maten dus eigenlijk de functionele gezondheidstoestand in plaats van de kwaliteit van leven van een kind. Bovendien bleek dat de betrouwbaarheid en validiteit (meet de vragenlijst wat hij zou moeten meten) van de meeste instrumenten onvoldoende was onderzocht. Al met al was onze kennis over de kwaliteit van leven van kinderen met middenoorontstekingen dus beperkt. Van alle beschreven instrumenten leek de OM-6, op basis van zijn inhoud, betrouwbaarheid en validiteit, de meest geschikte vragenlijst om de functionele gezondheidstoestand van kinderen met middenoorontstekingen te meten.

In de *Hoofdstukken 3 tot en met 7* werden de resultaten gepresenteerd van ons eigen onderzoek naar de kwaliteit van leven van 383 kinderen, in de leeftijd van 1 tot 7 jaar, met recidiverende acute middenoorontstekingen (gedefinieerd als 2 of meer acute oorontstekingen in het voorafgaande jaar). Deze kinderen deden mee aan het OMAVAX onderzoek, een dubbelblind gerandomiseerde en placebo gecontroleerde interventiestudie naar de effectiviteit van pneumococcen vaccinaties in het voorkomen van middenoorontstekingen. De helft van de

kinderen (190) werd daartoe ingeënt met een heptavalent pneumococcen conjugaat vaccin, zes maanden later gevolgd door een booster met een pneumococcen polysaccharide vaccin (pneumococcen groep). De andere helft van kinderen (193) werd ingeënt met een vaccin tegen hepatitis A of B (controle groep).

De ouders van alle kinderen vulden bij begin van de studie en na 7, 14 en 26 maanden diverse vragenlijsten in. Vier vragenlijsten hadden betrekking op de algemene functionele gezondheidstoestand (RAND, FSQ Specific, FSQ Generic) en de algemene kwaliteit van leven (TAIQOL). De andere vier waren otitis media-specifieke vragenlijsten en maten de functionele gezondheidstoestand (OM-6) en kwaliteit van leven (NRS Child) van het kind, het gezinsfunctioneren (FFQ) en de kwaliteit van leven van de ouder (NRS Caregiver). Daarnaast werd op de bovengenoemde tijdstippen vastgesteld hoeveel acute middenoorontstekingen een kind in de tussenliggende periode gehad had en of, en zo ja welke, behandeling(en) het kind hiervoor ondergaan had.

In de *Hoofdstukken 3* en *4* hebben we de betrouwbaarheid en validiteit onderzocht van de bovengenoemde vragenlijsten over kwaliteit van leven en functionele gezondheidstoestand. De interne consistentie en de reproduceerbaarheid (test-hertest), beide maten voor betrouwbaarheid, waren goed voor alle instrumenten. In welke mate de instrumenten werkelijk kwaliteit van leven en functionele gezondheidstoestand meten werd getoetst door de samenhang ofwel correlaties tussen de diverse vragenlijsten te bestuderen. De correlaties tussen de vragenlijsten, alsmede tussen de items waarvan op voorhand verwacht werd dat ze vergelijkbare aspecten van fysiek functioneren zouden meten, waren matig tot sterk. Dit duidt op een goede construct validiteit. Deze construct validiteit werd gesteund door matige correlaties tussen globale beoordelingen van de functionele gezondheidstoestand en kwaliteit van leven van het kind (gemeten met de RAND, NRS Child en NRS Caregiver) en het aantal artsbezoeken voor bovenste luchtweginfecties, alsmede door matige tot sterke correlaties tussen de scores op de ziekte-specifieke instrumenten en het aantal

middenoorontstekingen in het voorgaande jaar. Het discriminerende vermogen tussen kinderen met weinig en kinderen met veel OMA episoden per jaar van de meeste vragenlijsten was goed. De subschalen van de TAIQOL en beide numerieke waarderingsschalen (de NRS Child en NRS Caregiver) bleken dit onderscheid echter niet te kunnen maken. In *Hoofdstuk 4* hebben we vervolgens het vermogen van de vragenlijsten om klinisch belangrijke veranderingen te meten (responsiviteit) onderzocht volgens recent ontwikkelde richtlijnen. Deze bevelen aan meerdere strategieën te gebruiken en directe vergelijkingen tussen algemene en ziekte-specifieke instrumenten te maken. Allereerst hebben we de gevoeligheid van iedere vragenlijst voor een verandering in de kwaliteit van leven vastgesteld. Vervolgens hebben we voor iedere vragenlijst bepaald welke verandering in de score nodig is om *klinisch* relevant te zijn. Hoewel de ziekte-specifieke vragenlijsten gevoeliger bleken te zijn voor verandering dan de algemene vragenlijsten, was de responsiviteit voor beide type vragenlijsten voldoende om ze te kunnen gebruiken klinische studies naar de kwaliteit van leven van kinderen met rOMA. Alleen met de otitis-gerelateerde subschalen van de TAIQOL bleek het nauwelijks mogelijk om verandering in kwaliteit van leven te meten. De TAIQOL lijkt daarmee geen geschikt instrument te zijn voor longitudinale studies naar kwaliteit van leven bij kinderen.

In *Hoofdstuk 5* werden de functionele gezondheidstoestand en de kwaliteit van leven van de kinderen met rOMA gemeten met behulp van de in hoofdstuk 3 en 4 gevalideerde algemene en ziekte-specifieke vragenlijsten. Recidiverende OMA bleek vooral een negatieve invloed te hebben op de lichamelijke en emotionele gezondheidstoestand en het gedrag van een kind. Ook bleken de ouders zich hier aanzienlijk zorgen over te maken. De ouders van kinderen met rOMA in onze studie beoordeelden de kwaliteit van leven van hun kind niet alleen duidelijk lager dan ouders van kinderen uit een algemene populatie, maar ook lager dan ouders van kinderen met milde tot matig ernstige chronische aandoeningen, zoals allergie, oogafwijkingen, en gastro-intestinale aandoeningen. De functionele gezondheidstoestand en de kwaliteit van leven van de kinderen in onze studie

bleken vergelijkbaar te zijn met die van kinderen met milde tot matig ernstige astmaklachten en met die van Amerikaanse kinderen met chronische oorklachten.

In *hoofdstuk 6* werden de resultaten van onze OMAVAX studie naar het effect van pneumococcen vaccinatie op de kwaliteit van leven van kinderen met rOMA beschreven. De kwaliteit van leven van kinderen die gevaccineerd waren met de pneumococcen vaccins bleek niet te verschillen van de kwaliteit van leven van de kinderen die gevaccineerd waren met een controle vaccin. Ook hebben we geen subgroepen gevonden die meer of minder baat hadden bij de pneumococcen vaccinaties. De kwaliteit van leven en functionele gezondheidstoestand van *beide* groepen kinderen verbeterden echter aanzienlijk. Dit kon o.a. verklaard worden door de sterke daling in het aantal acute middenoorontstekingen in beide groepen gedurende het onderzoek.

In *hoofdstuk 7* hebben we de invloed bestudeerd van recidiverende middenoorontstekingen op het gezinsleven en met name de primaire verzorger, meestal was dat de moeder. We hebben ook onderzocht of en hoe de kwaliteit van leven en het emotionele welbevinden van de ouders hun beoordeling van de kwaliteit van leven van het kind met recidiverende middenoorontstekingen beïnvloedde. Recidiverende OMA bij een kind bleek het gezinsleven, met name het functioneren van de ouders, negatief te beïnvloeden. Dit uitte zich in slaapgebrek, gejaagdheid, spanningen, irritaties, en zorgen bij de ouders. Dit effect van rOMA op de ouders bleek ook de kwaliteit van leven van het kind zoals die door de ouder werd beoordeeld, te beïnvloeden. We pleitten er dan ook voor om vragenlijsten over het psychologische aanpassingsvermogen en de kwaliteit van leven van ouders op te nemen in studies naar kwaliteit van leven van kinderen.

In *Hoofdstuk 8* is beschreven hoe onze bevindingen geïnterpreteerd kunnen worden en wat hiervan de implicaties kunnen zijn voor toekomstig wetenschappelijk onderzoek en de klinische praktijk. Aangezien de door ons

gebruikte instrumenten betrouwbaar en geschikt zijn gebleken voor de kinderen in onze studie, zijn we van mening dat we met ons onderzoek daadwerkelijk uitspraken kunnen doen over de kwaliteit van leven en de functionele gezondheidstoestand van kinderen met recidiverende otitis media acuta in de leeftijd van 1 tot 7 jaar. De kwaliteit van leven van deze kinderen was vergelijkbaar met die van kinderen met andere chronische aandoeningen zoals astma. Pneumococcen vaccinatie bleek, in tegenstelling tot onze verwachting, geen gunstig effect te hebben, noch op het voorkomen van AOM noch op de kwaliteit van leven van de kinderen en hun ouders. Hieruit werd duidelijk dat verbetering van de kwaliteit van leven van kinderen met rOMA èn hun ouders een punt van aandacht moet blijven in toekomstig onderzoek en in de klinische praktijk. Tenslotte zijn aanbevelingen gedaan met betrekking tot toekomstig onderzoek naar de kwaliteit van leven bij jonge kinderen in het algemeen en bij kinderen met recidiverende otitis media acuta in het bijzonder. Het opdoen van uitgebreide ervaring met en grondige validering van de bestaande kwaliteit van leven vragenlijsten, alsmede onderzoek naar de invloed van de kwaliteit van leven van de ouders op die van het kind, waren hierbij belangrijke aanbevelingspunten.

Appendices

Appendix 1. Characteristics of HRQoL and FHS instruments used in the study

Generic instruments

RAND

Type	functional health status
Number of items	7
Score type	total
Score range	7-32
Construct(s) measured	general health; current health; previous health; resistance to illness
Applications in other studies	low-birth-weight children[1, 2]; survivors of childhood cancer[3]; asthmatic children[4, 5]

FSQ Generic

Type	functional health status
Number of items	14
Score type	total
Score range	0-100
Construct(s) measured	age appropriate functioning and emotional behaviour
Applications in other studies	low-birth-weight children[1, 6]; survivors of childhood cancer[7]; adolescents with cancer[8]; asthmatic children[5, 9-11]

FSQ Specific

Type	functional health status
Number of items	14
Score type	total
Score range	0-100
Construct(s) measured	age appropriate functioning and emotional behaviour: impact of illness
Applications in other studies	low-birth-weight children[1, 6]; survivors of childhood cancer[7]; adolescents with cancer[8]; asthmatic children[5, 9-11]

TAIQOL

Type	health-related quality of life
Number of items	35 (age < 15 months); 46 (age > 15 months)
Score type	subscale
Score range	0-100
Construct(s) measured	physical functioning (sleeping, appetite, lung problems, stomach problems, skin problems, motor functioning); social functioning (problem behaviour, social functioning); cognitive functioning (communication), emotional functioning (positive mood, anxiety, liveliness) Functional problems are weighted by degree of associated negative emotions.
Applications in other studies	low-birth-weight children[6]; children with chronic illness[6]; children with chronic OME[12]

Disease specific instruments

OM-6

Type	functional health status
Number of items	6
Score type	item ; total
Score range	1-4 ; 6-24
Construct(s) measured	physical suffering; hearing loss; speech impairment; emotional distress; activity limitations; caregiver concerns
Applications in other studies	children with recurrent AOM[13]; children with chronic OME[13-15]

Family Functioning Questionnaire

Type	functional health status
Number of items	8
Score type	total
Score range	0-100
Construct(s) measured	Parents: sleep deprivation; change of daily or social activities; emotional distress. Family: cancelling family plans or trips. Siblings: feeling neglected; demanding extra attention.
Applications in other studies	none

Numerical Rating Scale Child

Type	health-related quality of life
Number of items	1
Score type	index - direct
Score range	0-10
Construct(s) measured	global well being of child related to AOM episodes
Applications in other studies	children with recurrent AOM or chronic OME[13]

Numerical Rating Scale Caregiver

Type	health-related quality of life
Number of items	1
Score type	index - direct
Score range	0-10
Construct(s) measured	global well-being of parent related to child's AOM episodes
Applications in other studies	none

Appendix 2.

Otitis Media – 6 item (OM-6)

The following questions address the influences of middle ear infections on the well-being of your child, please check one box for each question below.

	greatly	reasonably much	little	none
1. How much pain or unease had your child suffered during the past six weeks as a result of middle-ear infections? *Here we have in mind earpain, ear discomfort, ruptured eardrum, high fever or poor balance.*	1	2	3	4
2. How much hearing discomfort has your child experienced in the past six weeks? *Here we have in mind difficulty hearing, questions must be repeated, frequently says "what" or television is excessively loud.*	1	2	3	4
3. How many problems with speech did your child experience in the past six weeks? *Here we have in mind delayed speech poor pronunciation, difficulty to understand, or unable to repeat words clearly.*	1	2	3	4
4. To what degree during the past six weeks was your child upset because of middle-ear infections? *Here we have in mind being irritable, frustrated, sad, restless, or poor appetite.*	1	2	3	4
	very often	regularly	sometimes	never
5. How often during the past six weeks was your child restricted in his or her activities by middle-ear infections? *Here we have in mind playing, sleeping, doing things with friends/family, attending school or day care.*	1	2	3	4
6. How often during the past six weeks have you as a parent or guardian been concerned about or inconvenienced by your child's middle-ear infections?	1	2	3	4

Appendix 3.

Family Functioning Questionnaire (FFQ)

How often did you or your partner experience the following problems during the past 6 weeks as a consequence of a middle ear infection in your child?

	Often (5x or >)	Quite often (2-4x)	Sometimes (1x)	Never (0x)
1. Lack of sleep	1	2	3	4
2. Absence from work or education	1	2	3	4
3. Cancelling of family activities *(i.e. swimming, taking a walk, cycling)*	1	2	3	4
4. Changing or cancelling appointments with partner, family, friends or acquaintance	1	2	3	4
5. Changing daily activities *(i.e. house-keeping, shopping, voluntarily work, spend time with other siblings)*	1	2	3	4
6. Feeling nervous, agitated or tense	1	2	3	4

In case there are other children in the family:

During the past 6 weeks, when our child had a middle-ear infection,	Certainly true	Often true	Variable	Often not true	Certainly not true
7. Our other children felt neglected or excluded	1	2	3	4	5
8. Our other children demanded extra attention	1	2	3	4	5

Appendix 4. Formulas in Chapter 3

ES = mean change score $_{\text{changed group}}$ / SD (change score $_{\text{unchanged group}}$)*
ES_{np} = median change score $_{\text{changed group}}$ / interquartile range (change score $_{\text{unchanged group}}$)**

SEM = SD (change score $_{\text{unchanged group}}$) x $\sqrt{}$ (1 – ICC***)

SEM-MCID = 1-SEM

ES-MCID = 0.3 x ES

* = effect size (ES) calculated as Guyatt's Responsiveness Statistic
** = nonparametric effect size
*** = ICC = intraclass correlation coefficient

Appendix 5.
OM - Functional Status Questionnaire – disease specific[16]

	Always	Most of the time	Sometimes	Hardly any time	Never
1. How often did your child have signs or symptoms suggesting a middle ear infection (irritability, fussiness, fever) in the past six weeks?	1	2	3	4	5
2. How often did your child seem to have earache (tugging ears, pulling hair, unusual crying) in the past six weeks?	1	2	3	4	5
3. How often did your child have sleeping problems caused by a middle ear infection in the past six weeks?	1	2	3	4	5

1-16

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Dankwoord

Vele mensen waren op hun eigen manier betrokken bij de totstandkoming van dit proefschrift. Ik wil hen hier graag bedanken voor hun steun, begeleiding en hulp. Zonder jullie was het boekje niet geworden zoals het nu is.

Allereerst wil ik de kinderen die hebben meegedaan aan het OMAVAX onderzoek en hun ouders bedanken. Dankzij jullie enthousiaste en trouwe deelname is het OMAVAX onderzoek, ondanks het tegenvallende effect van het vaccin, een groot succes geworden.

Dan, onmisbaar bij het promoveren, wil ik mijn co-promotoren en promotor bedanken voor hun fantastische begeleiding. Dr. A.R. Maille, beste Rianne, de donderdag begon niet voordat we het wereldgebeuren en onze dagelijkse belevenissen van die week hadden uitgewisseld. Jij was het dan vervolgens, als ik ook verslag had gedaan van mijn ontwikkelingen in het OMAVAX onderzoek, die altijd vroeg "En hoe gaat het nu met jou?" Dit typeert je niet-aflatende belangstelling voor de mensen op je heen. Je besloot een 'sabbathical year' te nemen, een moedige en, naar bleek, een goede keuze. Dat je echter ook besloot om desondanks wel bij OMAVAX betrokken te blijven, heeft veel voor het kwaliteit van leven onderzoek van OMAVAX, maar zeker voor mij persoonlijk betekent, bedankt! Ik hoop in de toekomst van je kennis over 'kwaliteit van leven'-onderzoek gebruik te mogen blijven maken. Ik ga onze wereld-kritische gesprekken en kletspraatjes missen.
Dr. E.A.M. Sanders, beste Lieke, jij stond aan de wieg van het OMAVAX onderzoek. Als een soort spin in het web ben je bij de diverse activiteiten binnen OMAVAX betrokken. Je hebt dan ook zowel aan het klinische als het 'kwaliteit van leven'-deel van OMAVAX bijgedragen, al was dat lang niet altijd makkelijk met je vele en drukke werkzaamheden. Je bedachtzame opmerkingen wierpen in

de lastige eindfase weer net een ander licht op een onderwerp en haalde er de scherpe kantjes van af. Mijn dank daarvoor.
Dr. A.G.M. Schilder, beste Anne, je bent een meester in het puntiger, korter en krachtiger schrijven. Tussen je 1000 & 1 bezigheden vond je toch altijd weer tijd om mijn schrijfselen kritisch door te nemen. Ik werd er in het begin soms bijna moedeloos van als je met een welgemeend "Het is echt al heel goed!" me een artikel vol blauwe en rode strepen en bijgeschreven zinnen ter verbetering teruggaf. Maar ik heb er veel van geleerd, en als het even tegenzat was daar steevast het "Chin up!". Met hetzelfde optimisme ging je de diepe sneeuw in Alaska te lijf, de foto's moeten we nog steeds gaan uitwisselen. Ik wil je bedanken voor je kritische en motiverende steun, je gedrevenheid is inspirerend.
Tenslotte wil ik mijn promotor Prof. Dr. D.E. Grobbee, bedanken: beste Rick, onze eerste kennismaking liet even op zich wachten door overvolle agenda's. Ook daarna bleef het een kunst om iedereen voor het 'grote overleg' om de tafel te krijgen. Met rake en soms ontluisterend eenvoudige suggesties, bracht je dan ingewikkeld vraagstukken terug tot eenvoudige analyses. Dankzij je doeltreffende commentaar kregen de artikelen net die andere 'touch'. Dank je voor je stimulerende begeleiding.

Dr. M.M. Rovers, beste Maroeska, in Utrecht viel je meteen met je neus in de boter: van OME naar rOMA. In het afgelopen jaar ben je sterk betrokken geweest bij mijn promotieonderzoek, altijd rechtdoorzee en met een opvallend rechtvaardigheidsgevoel. Je kritische blik en je humor kenmerkten je begeleiding, bovendien was je altijd bereid om, waar nodig, bij te springen. En iedere keer kon ik met mijn vragen over de statistiek bij je terecht, al ging het alweer over hetzelfde. Veel dank daarvoor.

Beste Reinier, je passie voor het OMAVAX onderzoek was aanstekelijk vanaf de eerste avond dat je me uitleg gaf over het onderzoek. Ik heb veel van je geleerd, niet alleen doordat je me deelgenoot maakte in het klinische deel van het OMAVAX onderzoek, maar ook door je stimulerende begeleiding in de kliniek van

het Spaarne Ziekenhuis. Bovendien waren daar de gesprekken in de auto naar Utrecht en op de fiets om de neuswatjes bij het Streeklab af te leveren. Die gingen vaak over heel andere onderwerpen, waaruit bleek dat we een optimistische levensvisie deelden. Ik heb bewondering voor je enorme gedrevenheid en enthousiasme. Zonder jouw inzet was dit boekje er niet geweest, het is dan ook pas compleet met jouw proefschrift erbij; ik kijk ernaar uit.

Beste Ingeborgh en Anneke, jullie zorgden ervoor dat de poli-middagen zonder obstakels verliepen en dat de bijna 400 kinderen werden gevaccineerd met het juiste vaccin. Dank jullie wel voor jullie hulp bij het afnemen van de vele buisjes bloed en neuswatten en voor de gezelligheid en de kletspraatjes.
Beste Herma, regelmatig sprong je bij tijdens drukke poli-middagen in Haarlem, heel veel dank hiervoor.

De collega's van de artsen en verpleging in Spaarne Ziekenhuis Haarlem wil ik bedanken voor de leuke en leerzame tijd die ik op de Kinderafdeling heb gehad, voor jullie belangstelling voor het onderzoek, de leermomenten in de kliniek, de discussies, maar ook de humor en de gezelligheid.

Bep Verkerk en Bernard Slotboom wil ik bedanken voor hun ondersteuning bij het verwerken van de data. De mannen van de automatisering dank ik voor hun hulp bij alle computer-vragen & problemen.

Tenslotte wil ik mijn collega's, en met name de jonge onderzoekers van het Julius bedanken voor de leuke tijd het afgelopen jaar. Willemijn, Marianne, Irene, Lisette, Tali, Lydia, Linda, en Fleur: dank voor jullie humor, de gesprekken en kletspraat en het uitwisselen van frustraties.
Beste Henk, je hebt een essentiële bijdrage geleverd aan de artikelen over de validering van de kwaliteit van leven vragenlijsten. De besprekingen met Rianne en jou leverde altijd vruchtbare gedachtewisselingen op en we zijn nog lang niet uitgepraat.

Lieve Daniel en Tjalling, met jullie kan ik drinken en praten tot diep in de nacht over de wereld, de mooie dingen in het leven, onze dromen en zieleroerselen. Tot het de volgende ochtend weer licht wordt. Jullie zijn mijn soulmates, ik ben trots dat jullie mijn paranimfen willen zijn.
Lieve Karin, dankzij jou ziet het boekje er prachtig uit. Geen idee was voor jou teveel. Daarnaast ben je echter vooral ook een vriendin waarmee ik heerlijk kan kletsen over alles wat ons bezighoudt, de leuke en de minder leuke dingen. Ik waardeer je openheid. Dank je wel.
Lieve Lucille, we hebben een bijzondere vriendschap. Je lef om niet alleen in je dromen te geloven, maar ze ook waar te maken, inspireert me. Je hebt een plekje in mijn hart.
Lieve Shani-Qwa en Jenayden, dank jullie wel voor jullie tekeningen. Super!
Lieve Lieke, je was minder betrokken bij deze fase in mijn leven, maar niet minder in mijn hart, we'll catch up!

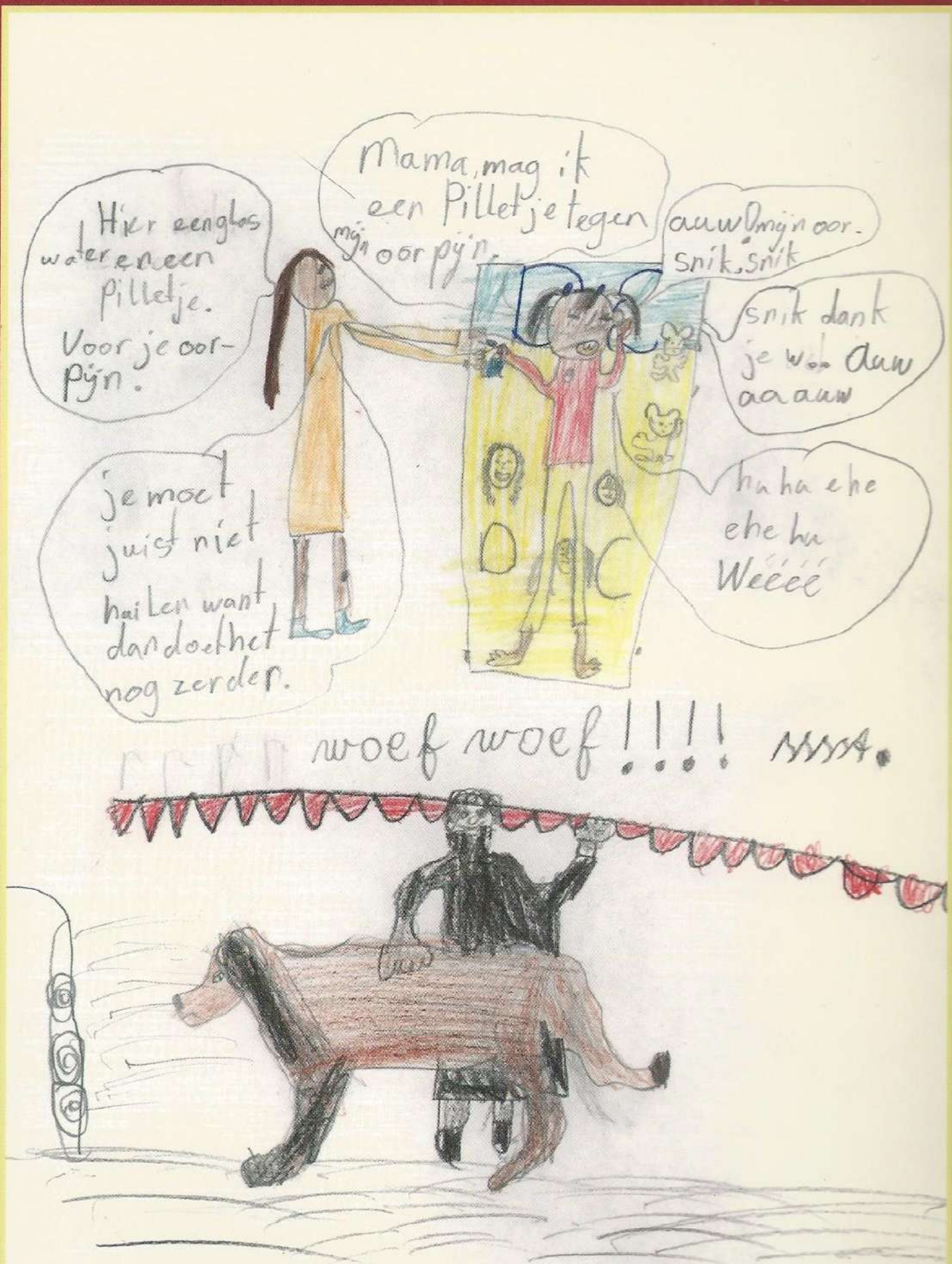
Lieve Mpho, Stefan, Misja, Christa, Hank, Robert, Luda, Zenja, Christianne, Maarten, Manje, Daniel, Sven, Remco, Martha, Mieke, Judith, Died en Daphne, dank jullie wel voor de nodige belangstelling, afleiding en steun via de telefoon, de mail, de kroeg, een concert, onder een etentje of gewoon op de bank. Jullie vriendschap maken me rijk.
Dear Diana, Vicky, Walter and Francesca, you are my friends at a distance, but no less friends, thanx for your mails, calls and live support! It is good to know that there is always a place with you to stay.
Tenslotte mijn voetbalvriendjes en vriendinnetjes; door een spontane loop van gebeurtenissen, heb ik jullie nog niet zo lang geleden leren kennen. Dank jullie wel voor jullie spontaniteit en lol, de discussies en verhalen na het voetballen. Altijd in voor een feest,.... als we het halen na de middernachtelijke shoarma.

Lieve oom Jan en tante Willy, dank jullie wel voor jullie altijd warme belangstelling. Jullie hebben een speciaal plekje in mijn hart.

Lieve Arjan, onverstoorbaar volg jij je eigen pad. Ik ben er trots op dat je mijn broer bent. Lieve Angelique, met je vrolijke aard tover je altijd vanzelf een glimlach op mijn gezicht. Lieve Linda, ik heb bewondering voor je doorzettingsvermogen en gedrevenheid. Je bent al lang niet meer mijn kleine zusje, al blijft je hartje klein. Ik hoop dat ik met je mee blijf groeien.
Lieve paps en mams, jullie stonden en staan altijd voor me klaar. Jullie steun en onvoorwaardelijke geloof in mij maken me sterk en de gedrevenheid waarmee jullie je inzetten voor de dingen die jullie raken, is mijn voorbeeld. Waar ook ter wereld zal ik mijn huis kunnen vinden, want ik weet dat ik altijd een thuis heb.

Curriculum Vitae

The author was born on March 12th, 1974, in Badhoevedorp, Haarlemmermeer polder. After graduating secondary school at the Rijnlander Oegstgeester Scholengemeenschap in Oegstgeest in June 1992, she started Medical School at the Free University in Amsterdam and obtained her medical degree in February 2000. From February to May 2000, she worked in a guesthouse for children with a mental handicap. Subsequently she worked from May 2000 to November 2000 as a community health care doctor for children in several centres for asylum seekers. In November 2000 she started the research that is described in this thesis (supervised by Prof. dr. D.E. Grobbee, Dr. A.R. Maillé, Dr. E.A.M. Sanders and Dr. A.G.M. Schilder) and worked part-time as a senior house officer in Pediatrics at the Spaarne Hospital in Haarlem, where the research was carried out, until December 2001. From January 2002 she continued the research at the Julius Center for Health Sciences and Primary Care in Utrecht. In April 2003 she started her training in Pediatrics at the VU medical center in Amsterdam (supervised by Prof. dr. J.J. Roord).


Hier een glas water en een Pilletje. Voor je oor-pijn.
Mama, mag ik een Pilletje tegen mijn oor pijn.
auw! mijn oor. snik, snik
snik dank je wel auw aaauw
je moet juist niet huilen want dan doet het nog zerder.
ha ha ehe ehe ha Weeee
woef woef!!!! ssss.