Assessment of
Tympanic Membrane
A study of children with otitis media in general practice

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Umeå 2014
To my wife Pernilla, children Adam and Amanda and my mother Svea
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Abstract

Background Acute otitis media (AOM) is a common disease in children and is causing great discomfort and disability worldwide but many areas are underserved regarding skilled professional. Tele-otology offers a promising technique to provide ear health globally. Diagnostic accuracy of AOM has regardless of method been found to be low. Grading the severity of AOM may offer a guide in decision on antibiotic treatment, however grading systems need improvement.

Aim To describe and evaluate imaging of the tympanic membrane (TM), develop an image based grading scale for AOM and to study the characteristics and the course of acute otitis media (AOM) episodes in children with the use of telemedicine techniques.

Method This thesis is based on two study populations, 63 children attending with othalgia at four primary health care centers in rural Sweden (papers I, II, IV) and 140 children attending a health clinic from a township in Johannesburg, South Africa, (paper III).

**Paper I:** Image quality of endoscopic imaging of TM’s, from the Swedish study was assessed by an otologist and two general practitioners together with an evaluation of important characteristics of assessing TM appearance.

**Paper II:** In development and validation of an image-based grading scale of AOM two expert panels of otologist’s evaluated the proposed grading scale stepwise and in a test and retest validation process.

**Paper III:** A test of the scale in a clinical situation was set up, an otologist otomicroscopically examined children and used the grading scale, and his diagnoses were set as gold standard. A specially trained ear and hearing facilitator then recorded videos of the TM using video-otoscopy. Videos were remotely assessed by the same otologist and by a general practitioner twice; 4 and 8 weeks after the otologist’s on-site grading.

**Paper IV:** Children with othalgia were followed with assessments of their symptoms and signs over a period of 3 months. An assessment group of two general practitioners and one otologist evaluated TM images, tympanograms and recorded symptoms and make a diagnose.

Results The results from paper I show that image quality was good and the position and transparency of the TM was found to be the most important characteristics when assessing TM. In paper II the new grading scale (OMGRADE) was developed and validated. The image-based scale focuses on the position and transparency of the TM. The results from paper III showed that the OMGRADE scale could discriminate the normal ear as well as ears with otitis media with effusion (OME) in an unselected pediatric population. Paper IV showed that the bilateral AOM had more severe symptoms. The children with chagrated TM’s took the longest time to resolve regarding TM appearance and tympanograms. Furthermore, symptoms resolved quicker than TM changes and tympanograms during the first week.

Conclusions TM images or video recordings taken by a trained nurse or facilitator are sufficient for remote evaluation. The new grading scale of TM appearance is valid and reliable and may function as a diagnostic guide together with evaluation of middle ear effusion. TM appearance may be of importance in grading the severity of an AOM episode.
Original Papers

This thesis is based on the following papers:


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Abbreviations

AAP  American Academy of Paediatrics
AOM  Acute Otitis Media
AOM-FS  Acute Otitis Media – Faces Scale
AOM-SOS  Acute Otitis Media – Severity Of Symptoms scale
bAOM  AOM with bullous myringitis
BM  Bullous Myringitis
CO  Clinical Otological score
CSOM  Chronic suppurative otitis media
ENT  Specialist in Ear, Nose and Throat disease
GP  General Practitioner
HCC  Health Care Centre
MEC  Middle Ear Cavity
NPD  Not Possible to Determine
OM  Otitis Media
OME  Otitis Media with Effusion
ORL  Oto-rhino-laryngologist
OS-8  Otitis media Scale – 8
pAOM  AOM with chagrinated TM or evidence of acute perforation and drainage
rAOM  recurrent Acute Otitis Media
TM  Tympanic Membrane
URI  Upper Respiratory tract Infection
WHO  World Health Organization
Sammanfattning på svenska

Bedömning av trumhinnans utseende - en studie på barn med öroninflammation i primärvård

Akut öroninflammation är den näst vanligaste infektionen hos barn och har varit den vanligaste orsaken till antibiotikabehandling hos barn i Sverige. I utvecklingsländer är öroninflammation vanligare än i Sverige och ofta av allvarligare slag, dessutom råder i dessa länder en stor brist på kvalificerad vårdpersonal. Telemedicinsk teknik kan erbjuda patienter bedömningar på distans av läkare.

Hög förskrivning av antibiotika bedöms bidra till en ökad resistensutveckling hos bakterier vilket i sin tur riskerar att försämra behandlingsresultatet vid allvarligare infektioner. Man försöker därför på olika sätt att minska antibiotikaförbrukningen. En förbättrad diagnostisk säkerhet av öroninflammation hos barn antas kunna minska antibiotikaförskrivningen till dessa barn och en förbättrad kvalitet på trumhinnebedömningar är en förutsättning för detta. Öroninflammationens svårighetsgrad har tidigare studerats och diskuterats ur behandlingsynpunkt och i samband med detta har olika former av graderingssystem, av varierande kvalitet använts.

Mål
Att utvärdera kvaliteten på bilddokumentation av barns trumhinnor utförd av assistent eller sköterska och att utveckla ett bildbaserat graderingsverktyg för trumhinnebedömningar samt att testa detta på barn. En annan målsättning var att följa symtom och studera trumhinneutseende hos barn i åldern 2-16 år som sökte på hälsocentral för öronvärk och att följa deras tillstånd utveckling över tid.

Metod
Denna avhandling är baserad på 2 olika studiepopulationer.


Resultat
Delarbete I: Bildkvaliteten av stillbilder tagna via ett rakt endoskop från Lapplandsstudien undersöckes och bedömdes vara av acceptabel eller mycket god kvalitet i 82% av bildmaterialet. Bildkvaliteten förbättrades under studietiden och var bättre hos de äldre barnen.
**Delarbete II:** Viktiga karakteristika för trumhinnebedömning vid öroninflammation identifierades. 124 trumhinnebilder sorterades i svårighetsgrad, från normalt trumhinneutseende till kraftigt påverkat och en bildbaserad skala framtogs. Expertgrupp A (3 öronläkare) granskade utvalda karakteristika samt skalförlag enligt en metod för att erhålla "content validity", innehållsvaliditet. Ett slutgiltigt skalförlag presenterades bestående av 6 grundsteg: 0=transparent, normalståld trumhinna; 1=transparent trumhinna i normal position med klar vätskenivå eller lätt indragen trumhinna; 2=transparent, indragen trumhinna med klar vätskenivå eller med grumlig vätskenivå; 3=hela trumhinnan opak men i väsentligen normal position; 4=opak och buktande trumhinna; 5=opak trumhinna med blåsbildningar eller med en chagrinerad och fuktig yta, alternativt en misstänkt perforation med dränerande pus. Studiegruppen korrigerade skalan efter upprepade genomgångar som utmynnade i ett slutgiltigt skalförlag (OMGRADE). Expertgrupp B (4 öronläkare) testade skalan på trumhinnebilder vid två separata tillfällen och god till mycket god överensstämmelse påvisades. OGRADE-skalan korrigerades slutligen en sista gång.

**Delarbete III:** Öronläkaren graderade öronen vid öronmikroskopundiöndersökningen. 180 videofilmer bedömdes på distans efter 1 och 2 månader med nämnda graderingsskala. Den nya graderingsskalan visade på god överensstämmelse mellan öronläkarens öronmikroskopiska bedömning och distansundersökningarna av video-filmerna. Sensitivitet och specificitet av skalan förmåga att detektera normalt öra eller vätskefyllt mellanöra (OME) beräknades mellan öronläkarens bedömningar till 65-70%, respektive 97-100%.

**Delarbete IV:** 63 barn med anamnes på öronvärk undersöktes. Nitton procent hade normala öron, 33 % vätskefyllt mellanöra (OME) och 48% akut öroninflammation av något slag. Trumhinnan bedömdes som buktande i 18%, med blåsbildningar i 11% och med chagarinerat utseende i 19%. En uppföljning genomfördes av 29 av dessa barn vid sammanlagt 3 tillfällen - efter 3 och 7 dagar samt efter 3 månader. Symtomen visade sig gå tillbaka snabbare än trumhinneförändringarna och tecken på eventuell vätska i mellanörat. Majoriteten av barnen var helt symtomfria redan dag 3. Barn med chagarinerad trumhinna hade längre tid till utläkning och efter 3 månader hade de fortfarande i 40 % ett avvikande tympanogram.

**Sammanfattning av resultat**
Prologue

Directly after medical school I started to work in general practice and had to assess tympanic membranes in children with otalgia. I had never seen a child with otitis media during my medical education, and I believed it to be a simple diagnosis to handle. The surprise was apparent when I examined the first child with earache. Somewhere in the darkness of the external ear canal something that could be the tympanic membrane was seen, was it red? Asking senior colleagues confirmed me that it was red, and yes, an acute otitis media (AOM). After a number of tympanic membranes had passed my otoscope and a number of colleagues had been consulted I started to realise that there was a discrepancy between the different colleagues assessments of the tympanic membranes. They all based their diagnosis on various important tympanic membrane characteristics.

During a research course for general practitioners (GP) I was introduced to professor Sten Hellström, specialist in otorhinolaryngology (ORL) and professor Göran Westman, specialist in family medicine (GP), who had outlined a draft for a study on AOM using telemedical equipment in rural areas of Lapland, north of Sweden. Together with my main tutor associate professor Herbert Sandström (GP) we started the planning and preparing of a study to follow the course of signs and symptoms in children with earache. A pilot study on six children at the Tegs health care centre was performed to evaluate the equipment and method. Thereafter, I took the first steps on my scientific journey. I was going to plan, start and control a clinical study that began in 2003 at four health care centres 150 to 200 km away from my hometown Umeå.

Now it is time to present where these first scientific steps led me and to describe my journey. It is my hope that this thesis can shed some light on the tympanic membrane and help us general practitioners in the interpretation of the changes of the tympanic membrane appearance.

“Before going out on a hunt, hunters discuss all the information at their disposal and work out a strategy that will maximise their chances of success. With a detailed knowledge of the country, they will be able to identify areas regularly visited by animals, such as waterholes, pans, dense thickets and the animal paths that connect them. Their knowledge of the habits of animals will also enable them to predict what their movement may be and at what times they may visit certain areas. They will discuss hunts of the recent and distant past, and apply the knowledge they have gained from them. Each hunt is therefore a continuation of previous hunts, taking advantage of experience gained over many years.”

Principles of tracking – Louis Liebenberg
Introduction

Otitis media – a common disease

Otitis media is the second most common disease in childhood as well as the most common reason for antibiotic treatment in children. The majority of acute otitis media (AOM) episodes occur under the age of 3 years [1]. Up to 70% of children under age 2 are expected to have at least one AOM episode and 20% of the children will have at least three AOM episodes before the age of 5 years. However, the burden of disease around the world differs greatly [2]. AOM is more common in developing countries. In sub-Saharan Africa the incidence rate (new episodes per 100 people per year) of AOM of all age groups is estimated to be 43% compared to 11% in central Europe. The incidence in the sub-Saharan children aged 1-4 year is greater and every child in these areas will have AOM at least once every year. When it comes to the chronic suppurative otitis media (CSOM) the difference between developing and developed countries is also large. Globally, the incidence is 5 per 1000 people; in Oceania and sub-Saharan Africa 7–9 per 1000 people. In the first year of life the highest incidence rate is found in Oceania (33%). Children in developing countries with otitis media suffer from more complications and even deaths [2].

In a study by Liese et al. [3] the incidence rate in Sweden was found to be 344 per 1000 person-years (34.4%) in the age group 0-2 years and 174 in 3–5 year olds (17.4%). Neumark et al. [4] found a decline by 50% of visits for AOM in the age group 2-16 years between 2000 and 2005. The highest risk of developing AOM is in the age from 0.5 to 2 years, and if the child develops AOM during the first 6 months of life the risk is higher for recurrent AOM.

What about the effects in daily living for children with otitis media? Among other causes, otitis media is one important reason for hearing impairment around the world. Monasta et al. [2] report prevalence to be that 6 of 1000 children by the age of five in south Asia suffer from hearing impairment related to otitis media. In Western Europe the figure is only 0.1 per 1000. Mortality related to AOM is estimated to be approximately 21 per 10 million children worldwide, by WHO estimated to be 28000 deaths annually due to complications of otitis media. In wealthy areas in North America it is estimated at 1.6 per 10 million compared to the highest mortality in the Oceania region with 101 per 10 million [2].

What is otitis media?

Otitis media (OM) is divided into three major diagnoses: acute otitis media (AOM), otitis media with effusion (OME, in Scandinavia more often described as secretory otitis media – SOM) and chronic suppurative otitis media (CSOM).

Acute otitis media (AOM)

AOM is defined as a fluid-filled middle ear cavity (MEC) together with acute inflammatory signs and symptoms. Bacterial colonisation of the middle ear fluid is often found but sometimes viruses occur. The majority of AOM is secondary to a upper respiratory tract
infection (URI). In a study by Kalu et al. [5] a mean of 5 days with URI preceded the AOM. A bulging TM has high diagnostic certainty. The American Academy of Paediatrics (AAP) states that the diagnosis of AOM can be made in presence of a bulging TM or with acute onset of otorrhea. The diagnosis may also be set if there is a mild bulging of the TM together with recent onset of ear pain or intense erythema of the TM [6]. The appearance of the TM is usually described as a thickened and opaque TM with a more irregular structure and with a white-grey-yellowish discoloration. Increased vascularisation is mainly found along the malleus and annulus fibrosus but has lower diagnostic value than the previously mentioned signs.

Symptoms such as otalgia, irritability, tugging of the ear, disturbed sleep may indicate AOM but cannot function as definite diagnostic estimates. They can all also be symptoms together with many other symptoms in an URI.

The TM can perforate and pus be pulsating out through the TM, known as perforated AOM. Furthermore, bullous formations can be found on the TM and is mainly associated with an AOM [7] and rarely occurs solely without purulent middle ear fluid as a local inflammatory process in the TM (bullous myringitis – BM) [8]. Furthermore, the AAP, in their guideline published 2013, present a grading of the AOM in non-severe and severe AOM [6]. The severe AOM is defined as an AOM with moderate to severe otalgia together with fever ≥39°. In Sweden the Medical Products Agency also added the terms “certain diagnosis of AOM” and “uncertain diagnosis of AOM” to their guidelines in 2010 [9].

Known risk factors for developing AOM are for example age below 2 years, AOM before 6 months of age, day-care centre attendance, many siblings and genetic factors as well as the winter season [1].

**Recurrent AOM (rAOM)**

Recurrent AOM is defined as three separate AOM episodes within six months or four in one year with at least one AOM episode within the last six months [6].

**Otitis media with effusion (OME)**

OME is defined as a fluid-filled MEC but limited signs of bacterial infection or inflammatory signs of TM. Medial to a translucent TM fluid levels and air bubbles can be seen as evidence of middle ear effusion. An opaque TM is a sign of OME together with the indirect measure of middle ear fluid using tympanometry or pneumatic otoscopy (impaired mobility of the TM). However, the OME is a dynamic process and may be a result of a preceding AOM, thus a distinct separation between OME and AOM is in some cases difficult. OME is often seen in association with a URI [8, 10].

**Chronic suppurative otitis media (CSOM)**

Chronic suppurative otitis media (CSOM) indicates a chronic disease in the middle ear as well as the mastoid mucosa with increased secretion together with a perforation of the TM. The CSOM diagnosis also include the dry ear with a perforated TM since it is believed to be a stage of the disease and CSOM can also be associated with cholesteatoma [11]. The cause of
COME has been under debate. Today however the predominant theory is that it starts with an AOM that leads to a chronic infection and alterations of the mucosal layer with increased secretion together with Eustachian tube dysfunction [10, 11]. Risk factors are frequent URI, overcrowding, poor living standards such as poor hygiene and nutrition. [11]

**Basic anatomy**

Otitis media is defined as an inflammation in the middle ear cavity (MEC) and the tympanic membrane (TM). Various factors have been found to be involved in the development of OM.

**Tympanic membrane**

The TM separates the middle ear cavity from the external ear canal and consists of the larger acoustic portion, pars tensa, and the smaller portion, pars flaccida. Pars tensa is a thin and inward cone-shaped structure made up of a three layers with a thickness of 64-95um [10]. The TM consists of an outer epidermal layer covered by a keratinising squamous epithelium, the middle layer (lamina propria) by one radial and one circular array of densely packed collagen fibres and an inner mucosal layer. In adults the TM measures on average 9 mm in diameter and it is angled in 140 degrees with the external ear canal and with a lesser angle in children. The handle of the malleus and the short process of the malleus are attached to the TM and can be seen through TM canal (fig. 1). The central part of the TM is called the umbo. The TM is attached to the ear canal via the annulus fibrosus.

**Middle ear cavity**

The MEC is a gas-filled pocket medial to the eardrum (TM), connected to the nasal part of the pharynx via the Eustachian tube. MEC is lined with a mucosa. Passage of air occurs intermittently via the Eustachian tube, for example when we swallow, but the gaseous milieu of the MEC is also a function of the gaseous exchange over the mucosal wall [12, 13]. The mucosa is acting as a first line of the defence against infection. In the MEC we also find the
membranous relation to the inner ear, the oval window and the round window. The ossicle chain, malleus, incus and stapes, transduces sound waves received by the tympanic membrane to the footplate of stapes. The mucosal lining consists of both secretory and ciliary cells. These mucosal cells are involved, for example, in the gaseous exchange of the middle ear, production of mucins, lysozyme as well as immunoglobins. The secretory cells are few in number in the normal MEC but proliferate rapidly in response to infectious and inflammatory processes, in the MEC and nasopharynx [10].

**Eustachian tube**
The Eustachian tube is lined with a mucosal layer and the three main functions are pressure regulation, protection of the middle ear from sounds and secretion from the nasopharynx, and drainage of fluid from the middle ear [8]. Thus the tube allows air to pass into and fluid to escape from the MEC. In children the tube is shorter than in adults and at a straighter angle from the nasopharynx, this is held by many professionals to be the reason OM is being more common in children [14]. The opening and closing mechanism of the tube occurs through the tensor and levator palatine muscles. In children with cleft palate, for example, this muscle function is impaired and often leads to Eustachian tube dysfunction with a fluid-filled MEC [8].

**The normal tympanic membrane and middle ear cavity**
In the normal state the MEC is a gas-filled pocket and the TM is pinkish/greyish and transparent. “For clinicians the TM is the window into the middle ear” (PO Eriksson, Developing otitis media. Experimental studies in particular regarding inflammatory changes in the tympanic membrane) and its appearance can reflect various pathological processes in the MEC. The triangular reflex, a cone of light, in the lower anterior quadrant is a good landmark to look for in a healthy middle ear. If the TM is positioned differently, for example bulging or retracted, the reflex is smaller, irregular or absent. The evaluation of TM transparency is a judgement based on the colour and the appearance of the TM.

Through a transparent TM it is often possible to locate the promontory of the cochlea in the centre of the TM, the fossa of the round window in the postero-inferior quadrant and the orifice of the Eustachian tube in the antero-superior quadrant. The chorda tympani nerve can be identified between the pars flaccida and the pars tensa. An opaque appearing TM may be due to a thickened and inflamed TM and turbid fluid in the MEC. Fluid in the middle ear may vary in colour and viscosity and be purulent, serous, mucous or mixtures of these.
Methods for diagnosing otitis media

In clinical practice OM is based on visual evaluation of the TM and audiological measures of middle ear status.

Otoscopy and otomicroscopy

Otoscopy and otomicroscopy are traditionally used for the visualisation of the TM, the first step in the diagnosis of OM. The otomicroscope gives better illumination, higher magnification and a bifocal image that allows for a perception of depth that is important in the assessment of TM position. The use of endoscopes brings the lens closer to the TM. The inspection of the TM can be combined with testing of the mobility of the TM, known as pneumo-otoscopy and pneumo-otomicroscopy. The mobility test is performed using Siegel’s funnel.

Audiometric tests

An objective test of TM stiffness is called tympanometry, which measures the TM’s response to different air pressure in the external ear canal and its reflection at 226 Hz tone [15]. The tympanometer is basically a loudspeaker and a microphone together with a pressure regulator in a small probe that can be introduced into the external ear canal. The loudspeaker sends a tone at 226 Hz towards the TM that to some extent will reflect the tone back towards the tympanometer probe. The tympanometer’s microphone receives the reflected tone and this is analysed together with the actual air pressure produced in the external ear canal.

In a normal ear the TM can respond to and adjust to different air pressures in the external ear canal, known as compliance. A TM in normal position reflects less while a stiff TM reflects more sound. These measures result in a curve with a peak that actually is the inverted measure of the sound reflection; the less reflection, the higher the curve (figure 2, type A). The peak position on the x-axis of the diagram reflects the middle ear pressure while the height and form of the curve reflects the reflectivity of the TM. When the MEC is filled with effusion the TM mobility is obstructed, thus compliance is reduced, no difference in the sound reflection is found and it results in a flat curve (figure 3). If the middle ear pressure is affected the peak of the curve will move along the x-axis. Thus, the tympanogram can measure the air pressure in the middle ear together with the compliance of the TM.

AOM and OME may temporarily impair hearing in that TM mobility is decreased due to middle ear effusion. The traditional method for testing hearing is pure tone audiometry, which measures the threshold to detect the lowest level of tone loudness (dB) in a variety of tone frequencies (Hz). Moreover, specialised methods such as acoustic impedance audiometry and auditory brain stem response can be used to assess hearing, middle ear status and the auditory reflex pathway, although this is not used in general practice.
The gold standard for making the diagnosis of AOM is to verify middle ear fluid through myringotomy and tympanocentesis. The TM is incised, myringotomy, with a thin needle via which middle ear fluid can be obtained for laboratory examination, tympanocentesis. The incision is performed under local or general anaesthesia. In clinical practice this technique is nowadays mostly used on children who are severely ill and where hospitalisation is needed.

**How to assess tympanic membrane appearance and middle ear status**

**Important characteristics of the tympanic membrane**

The diagnosis of AOM is based on a number of different characteristics of the TM appearance, for example the position of the TM, transparency, colour, mobility and surface structure of the TM. A cloudy and bulging TM are strong indications of AOM together with impaired mobility of TM [16] with adjusted positive likelihood ratio ranging from 31 to 51. In comparison, a positive likelihood ratio of 8.4 was found for the distinctly red TM and 1.4 for the slightly red TM.

**TABLE 1. Diagnostic method for detecting otitis media with myringitomi as Gold standard method. From SBU – Swedish Council on Health Technology Assessment [17]**

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otoscopy</td>
<td>61</td>
<td>61</td>
<td>[18]</td>
</tr>
<tr>
<td>Pneumatic otoscopy</td>
<td>94</td>
<td>80</td>
<td>[19]</td>
</tr>
<tr>
<td>Otomicroskopy</td>
<td>91</td>
<td>93</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>89</td>
<td>[21]</td>
</tr>
<tr>
<td>Tympanometry, B-tympanogram</td>
<td>81</td>
<td>74,5</td>
<td>[19]</td>
</tr>
<tr>
<td>B + C-tympanogram</td>
<td>94</td>
<td>62</td>
<td>[19]</td>
</tr>
<tr>
<td>Pneumatic otoscopy</td>
<td>98</td>
<td>93</td>
<td>[22]</td>
</tr>
<tr>
<td>+ tympanometry</td>
<td>93</td>
<td>95</td>
<td>[23]</td>
</tr>
</tbody>
</table>

**Middle ear effusion**

The second step in the diagnosis of OME and AOM is an evaluation of middle ear effusion. An effusion can be seen through a transparent TM as fluid levels and air bubbles. A highly bulging TM can be attributed to pronounced middle ear effusion. The colour of the TM might give guidance in the matter as well where the whitish-yellowish discoloration of an AOM is due to purulent effusion. In an opaque TM in a fairly normal position, however, it is more difficult. Here pneumatic otoscopy can be of help (table 1). With the use of an air-filled balloon connected to the otoscope (or otomicroscope) the air pressure in the external ear canal can be increased repeatedly to assess the mobility of the TM, an indirect sign of fluid behind the TM preventing its mobility. An airtight seal of the otoscopic funnel and ear canal is required, which may be difficult to achieve handheld otoscopes.

Takata et al. [19] reviewed the literature and found sensitivity and specificity to be 94% and 80% respectively for pneumatic otoscopy to detect middle ear effusion. Similarly, Jones et al.
Aims

[18] showed that pneumatic otoscopy increased sensitivity and specificity by 24% and 42% respectively in comparison to otoscopy. However, the actual use of pneumatic otoscopy may be low. In a survey in Sweden only 20-40% of the GP’s used pneumatic otoscopy to detect OME or AOM (figure 3) [17].

Otomicroscopy gives a binocular view as well as a higher magnification of the TM. In a study by Young et al. [24] otomicroscopy performed by experienced otolaryngologists without the use of a Siegle’s speculum and mobility assessment of the TM had a sensitivity and specificity of 94% respectively. However, this study was performed in a highly selected population of children in a secondary care setting with high prevalence of middle ear effusion. Furthermore, otomicroscopy is rarely used in general practice and paediatric clinics due to the cost, immobility and the more tedious procedure compared to otoscopy.

Tympanometry was introduced in the middle of the 20th century and has developed over the years. Now there are small, easy-to-use models, that can be used in general practice, paediatric practice as well as in otology specialist practice. Tympanometry has been found to have a sensitivity and specificity ranging from 81% to 97% and from 62% to 74%, respectively [19]. If a combination of pneumatic otoscopy together with tympanometry is used, the sensitivity and specificity are further increased, ranging from 93% to 98% and from 93% to 95%, respectively [22, 23]. In a study by Saeed et al. [25] on children with AOM, tympanometry was found to have a sensitivity of 97% in predicting middle ear effusion with tympanocentesis as gold standard. Tympanometry, however, is seldom used in general practice in Sweden. Tympanometry can be used as a screening tool for middle ear effusions [26]. If a normal tympanogram is found, the risk of middle ear effusion is very low. Tympanometry performed by a nurse/clinical facilitator has been found to have better sensitivity than a general practitioner using otoscopy to detect middle ear effusion [27].

Diagnostic inaccuracy
The assessment of TM appearance is difficult and depends on personal skills, experience and the equipment used. Agreement on the evaluation of for example, colour is fairly low. In a study by Shaik et al. [28] various TM characteristics were compared between different physicians. The agreement was best for assessment of the position of TM and lowest for redness. Furthermore, a number of characteristics of the TM have to be assessed together with symptoms.

The difficulty of assessment is reflected in the diagnostic inaccuracy that has been found in several studies [29-33]. Picciciero et al. [30] performed a study on the diagnostic accuracy of OM by paediatricians in four different countries and found a mean accuracy of 36-54%. Blomgren et al. [29] compared the diagnosis made by a general practitioner (GP) with an ear-nose-throat (ENT) resident examining the same 50 children. The GP found AOM in 64% compared to 44% by the ENT. The proportion of reported characteristics between the GP and the ENT showed that the GP to a higher degree used colour as the basis for the diagnosis. Redness or vascularisation can be found in many other situations and research has shown it to have a low diagnostic value for the AOM.

In the study by Shaik et al. [28] characteristics of 135 TM images were reported by 7 otoscopists. The most common characteristic of the AOM ears was an opaque TM (100% of ears) and almost as common was a bulging TM (93% of the ears). The third most common characteristic of the TM was a white or yellow colour (64% of the ears) with redness coming fourth (58% of the ears). In OME ears opaque TMs were reported in 97% and redness in 22%. In normal ears redness was reported in 13% compared to white/yellow in 1%. When discriminating between slight or marked redness, the latter was more often associated with AOM. It should be noted that irritation of the external ear canal, a screaming child, a viral myringitis of the TM or trauma can also cause redness/vascularisation of the TM [16]. Thus, the colour assessment should focus on white or yellow rather than the redness. In a study by Neumark et al. [34] 76-89% of spontaneously draining ears were reported to have swollen keratin patches on the TM, a term we in Sweden sometimes call chagrinated. The TM is reddish with white and elevated keratin patches together with a wet appearance.

To improve diagnostic accuracy in general practice the most important factor appears to be the use of pneumatic otoscopy and or tympanometry together with learning to assess position and transparency rather than colour (redness). Training in diagnosing OME and AOM can also increase the accuracy [35-37]. Rosenkranz et al. [38] also showed that a multimodal and interactive workshop significantly increased the GP’s confidence in diagnosing OME as well as in pneumatic otoscopy and tympanometry. Clinical decision support as well as performance feedback can also be valid methods to improve diagnostic accuracy indirectly by strengthening the adherence to clinical practice guidelines [39]. The diagnostic inaccuracy might lead to over-diagnosing AOM of as much as 30% and the use of tympanometry in general practice to decrease the diagnosis of AOM by 30% [29]. Blomgren et al. [40] showed that the number of diagnoses of AOM decreased in 80% of otitis-prone children with the use of correct diagnostic criteria and clinical methods. However, the diagnostic inaccuracy is not
solely a clinical problem. In a review by Chandler et al. [41] compliance with the AAP’s three diagnostic criteria was found to be uncommon in studies on children with AOM, as only 20% used all three of these criteria to make an AOM diagnosis.

Cerumen
Diagnosing OM would be much easier without the cerumen problem, the earwax obstructing the external ear canal. Cerumen is a natural part of the external ear canal, which keeps the canal healthy, lubricated and clean, and it’s acidic pH gives it antimicrobial properties. The sebaceous and ceruminal glands of the external ear canal skin are constantly producing cerumen [42]. However, the biggest portion of the wax is desquamated keratin [43]. Cerumen can be wet or dry in its consistency. The dry type is inherited recessively and is more common in people from Asia or Native Americans [44, 45]. The epithelium lining the TM as well as the external ear canal is constantly migrating laterally at a slow pace cleaning the ear canal of debris with the sticky wax bringing dirt out [42]. In the daily practice as a GP, cerumen-related problems are common [46]. Traditional ways to remove cerumen are mechanical removal with instruments, oily detergents to soften the cerumen, water irrigation and removal with suction equipment under an otomicroscope. Furthermore, it is important to have assistance from an experienced nurse, who can keep the child’s head in a soft but steady grip.

However, a doctor in general practice with a full waiting room and a young child with otalgia, fever and a fear of doctors is a true challenge for the doctor, the child and the caregivers. The experienced nurse or facilitator is busy with other tasks. The chance of success is limited. Water irrigation in this child should be avoided. Waiting for oil treatment is seldom applicable. For the GP using an otoscope, mechanical removal in a distressed child can be harmful and jeopardise child compliance. Recently plastic removal instruments with LED light and a magnification glass have been introduced and shown to work in difficult cases. Sometimes you have to accept that a decision has to be made without having seen the TM.

Tympanometry can be a guide in certain cases with not totally obstructing cerumen. With a normal tympanogram an AOM is highly unlikely. With a type B tympanogram the attempt to clean the ear canal must continue.

Characteristics of acute otitis media

Symptoms of acute otitis media
Symptoms associated with AOM can be otalgia, irritability, tugging of the ear, vomiting as well as symptoms of URI such as rhinitis, fever, sore throat and cough. In order to identify the most important symptoms in AOM Shaik et al. used an expert panel and parent interviews [47]. They presented otalgia, ear tugging, irritability, decreased play, decreased appetite, disturbed sleep and fever as most important symptoms on which they based their AOM-SOS symptom scale. In a study by Arola et al. [48] various symptoms in children with AOM were registered. Rhinitis was the most commonly reported symptom (90%), followed by cough (78%), irritability (56%), fever (42%) and otalgia (47%). Hayden et al. [49] found severe earache in 42% and mild to moderate in 40% of children with AOM. Kontiokari et al. [50]
showed earache in relation to risk of AOM to be highest among symptoms, e.g. fever, sore throat, disturbed sleep. Earache was also found to be an important symptom for a parent to decide to seek medical aid immediately [51]. However, AOM may also present without otalgia and otalgia may be present without ear disease [52]. Hence, otalgia can be a guide to predicting an AOM but cannot confirm it [49, 50, 53, 54]. The sensitivity and specificity of otalgia were found to range from 54 to 60% and from 82 to 92% respectively compared to the rhinitis range from 75 to 96% and from 8 to 43% respectively [16]. Fever occurred in 34% of the AOM cases in children above 2 years of age in the study by Arola et al. [55].

Scoring systems and grading scales for severity assessment of acute otitis media

Scoring systems

A variety of scoring systems have been developed to differentiate severity of AOM and to follow and evaluate, for example, treatment effect (table 2). However, the scoring systems have been in use in a variety of styles and have not been thoroughly validated. The scoring system by Dagan et al. [56] can be regarded as the “standard” scoring system and is based on signs of the TM appearance; redness and bulging and symptoms; fever, irritability and tugging of the ear. Each characteristic is given 0–3 points with a total of 15 points. Thus a TM with severe redness has been given the same score as a TM with severe bulging. Friedman et al. [57] developed a symptom scoring system, the AOM faces scale (AOM-FS). It is based on 7 drawings of a child in increasing discomfort ranging from “not a problem” to “extreme problem”. They found excellent sequence validity as well as concurrent correlation and reliability.

The clinical otological score (CO) described by Satran et al. [58] resembles that of Dagan et al. [56], but with a slightly different maximum score.

Hotomi et al. [59, 60] added decreased landmarks of TM to the signs and symptoms in their 12-point scoring system in attempts to differentiate between severe and non-severe AOM. AOM-SOS score is based on seven discrete characteristics: tugging of ears, crying, irritability, difficulty sleeping, diminished activity, diminished appetite, and fever [47]. The scale was thoroughly developed according to a conceptual model and showed an association with diagnosis of AOM as well as responsiveness to improvement over time [61].

In the 10-point scoring system for AOM developed by Casey et al. [62] three symptoms were recorded: fever at home, level of ear pain and irritability. They also included a temperature score based on physical examination. Scoring of TM signs was based on erythema, position, colour, mobility and otorrhea. Their system was found to have a sensitivity of 87% and a specificity of 98% in comparison with the diagnosis made by an experienced otoscopist. However, no diagnostic criteria for AOM were presented in this study, a limitation when discussing the applicability of the scoring system in other settings and populations. This recently developed scoring system, which includes both symptoms and TM signs, appears to be promising.
There are “weighting” problems with these scoring systems as each characteristic is given the same score without considering whether one characteristic has a lower diagnostic value than the other. Thus, for example, the red TM gets the same score as the bulging TM. Questions can also be raised about the validity of these scoring systems:  
1) how were they developed (communicative validity)?  
2) by whom were they developed and what were the developers’ education or clinical experience (face validity)?  
3) on what theoretical basis were these scoring systems developed (construct validity)?  
One has to bear in mind that scoring systems are not diagnostic standalone tools but mainly designed to grade the severity of disease, for example when evaluating treatment with antibiotics or no treatment.

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Symptoms</th>
<th>Score</th>
<th>Characteristics of TM</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Dagan (0-15 points)</td>
<td>Fever</td>
<td>0-3</td>
<td>Redness</td>
<td>0-3</td>
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<tr>
<td></td>
<td>Tugging of ear</td>
<td>0-3</td>
<td>Bulging</td>
<td>0-3</td>
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<tr>
<td></td>
<td>Irritability</td>
<td>0-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satran - CO (0-12 points)</td>
<td>Fever</td>
<td>0-3</td>
<td>Redness</td>
<td>0-3</td>
</tr>
<tr>
<td></td>
<td>Irritability/tugging</td>
<td>0-3</td>
<td>Bulging</td>
<td>0-3</td>
</tr>
<tr>
<td>Hotomi (0-12 points)</td>
<td>Ear pain/tugging of ear</td>
<td>0-2</td>
<td>Redness/erythema</td>
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<tr>
<td></td>
<td>Irritability</td>
<td>0-2</td>
<td>Bulging</td>
<td>0-2</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>0-2</td>
<td>Decreased landmarks</td>
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<td>Shaik - AOM-SOS (0-13 points)</td>
<td>Tugging</td>
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<td></td>
<td>Crying</td>
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<tr>
<td></td>
<td>Irritability</td>
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<td></td>
<td>Sleep disturbance</td>
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<td>Lower activity</td>
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<td></td>
<td>Lowered appetite</td>
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<tr>
<td></td>
<td>Fever</td>
<td></td>
<td></td>
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<tr>
<td>Casey (0-10 points)</td>
<td>Fever at home</td>
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<td>Erythema</td>
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<tr>
<td></td>
<td>Otalgia</td>
<td>0-1</td>
<td>Position</td>
<td>0-1</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>0-1</td>
<td>Colour</td>
<td>0-1</td>
</tr>
<tr>
<td></td>
<td>Fever at clinic</td>
<td>0-2</td>
<td>Mobility</td>
<td>0-1</td>
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<td></td>
<td></td>
<td></td>
<td>Otorrhea</td>
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<td>McCormick - OS-8 (0-7 points)</td>
<td>-normal ear</td>
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<td></td>
<td>-erythema only, no effusion (myringitis)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-erythema, air-fluid level, clear fluid;</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>-erythema, complete effusion, no opacification;</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
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<td>-erythema, opacification with air-fluid level or air bubble(s), (mild or no bulging TM);</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-erythema, opacification, complete effusion (mild or no bulging TM);</td>
<td>5</td>
<td></td>
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<tr>
<td></td>
<td>-erythema, bulging, rounded donut appearance of the TM,</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>-erythema, bulging, complete effusion and opacification with bulla formation.</td>
<td>7</td>
<td></td>
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</tbody>
</table>

**Image based grading systems**

An alternative way of scoring the characteristics of the TM is to use an image-based grading scale, the weight of different characteristics is thereby built in to the scale. Prior to ours an image-based scale was developed by McCormick et al, the OS-8 (otitis media score-8). It relies on 8 different appearances of the TM with redness being the main discriminating factor.
Introduction

After redness come transparency, middle ear fluid and position. The eight scores are described as: “0=normal ear, no AOM; 1=erythema only, no effusion (myringitis); 2=erythema, air-fluid level, clear fluid; 3=erythema, complete effusion, no opacification; 4=erythema, opacification with air-fluid level or air bubble(s), (mild or no bulging TM); 5=erythema, opacification, complete effusion (mild or no bulging TM); 6= erythema, bulging, rounded donut appearance of the TM, 7=erythema, bulging, complete effusion and opacification with bulla formation” ([63]. The scale does not specifically include the perforated AOM or the TM with wet appearance and keratin patches. An unknown number of photographs of TMs of children with and without AOM were sorted into different categories and ordered by severity and modified repeatedly until 6 panel members agreed on the scale steps. Then the images of the various scale steps were presented at different meetings to colleagues who ranked the images in order from normal to abnormal. As a last step the investigators were trained to use the scale. This scale has since been used in a number of studies [5, 57, 64-66] but it has to be noted that the description of the validation process is limited. However, the OS-8 lacks the perforated TM, and as described above, gives redness too much weight.

McCormick et al. introduced a scoring system for tympanometry with three steps [63]. A tymp-A is given 0 points, a tymp-C 4 points and a tymp-B 7 points (correlates to the max of 7 points given in the OS-8).

Quality of life scoring systems
Scoring systems for quality of life in children with otitis media based on questionnaires have also been developed. Rosenfeld presented a questionnaire for OME called OM-6 and showed excellent test-retest reliability as well as adequate construct validity [67]. Brouwer et al. [68] compared OM-6 with other questionnaires- both disease specific questionnaires and generic (e.g. TAIQOL – infant quality of life) and found good responsiveness as well as psychometric qualities for all of them.

Clinical presentation and course of various types of AOM
The course of an AOM and differences in the course of signs and symptoms is an important aspect of the discussion about whether to treat or not to treat. One of the first descriptions of the course of an AOM was published by Adam Politzer in his “The membrane tympani in health and disease” from 1869 [69]. In this study he describes how a medical student experiences otalgia shortly after a cold bath. The next day he is examined by Politzer who describes the ear canal as pinkish, with an abundance of vessels around the TM periphery as well as over the malleus. The TM appeared “dirty grey”. The patient received treatment with five leeches applied in front of the tragus and was followed for two weeks. On the second day the patient had no more otalgia. By day 4 the TM was unchanged but the hearing distance had sunk to 12 feet and by day 5 the TM was still described as injected with vessels and a “dull and greenish-yellow” colour. By day 13 the TM was back to normal; “The lustre and curvature, as well as the hearing distance, were perfectly normal”. In 1996, Glen Isaacson published an article with high-quality colour images of the course of TM changes in AOM [70].
Symptoms resolve quicker than signs [60, 71]. Hotomi et al. [59] showed that 91% of the recorded symptoms had normalised at day 5, whereas only 70% of the TM signs were normalised at day 28. Similarly, Harabuchi et al. [71] showed that 83% of children with AOM under antibiotic treatment were free of symptoms after 3 days but one month later only 60% of the children had normal TM. Younger children take longer to resolve symptoms than older children [72]. In a review by Thompson et al. [73] 50% of children with earache had normalised after three days and 90% by day seven.

Middle ear fluid is commonly found after an AOM episode. Teele et al. [74] followed children with AOM episodes and found persistent middle ear fluid in 70% of the children after two weeks, 40% after 1 month, 20% after 2 months and 10% after 3 months.

Children with AOM and bullous myringitis have been shown to report more otalgia and fever than children with an AOM without bullous myringitis [63] and to have a quicker resolution of signs [75]. *S. pneumonia* is reported to be more common in AOM and bullous myringitis [76, 77].

Some AOM episodes lead to a spontaneous perforation of the TM and draining pus. In a European multicentre study by Liese et al. [3] 26.5% of AOM was found to be associated with ear discharge in Sweden compared to 2.6% to 18.2% in other European countries. The perforations are often small, located in the pars tensa and mainly in the anterio-inferior quadrant [78]. Berger et al. [78] showed that 70% of the perforations had closed within one week. Middle ear effusion persisted longer than the perforations. Leibovitz et al. [79] examined 12617 AOM patients in Israel <3 years of age and found 15% to have spontaneous otorrhea. They were older than the AOM patients without otorrhea (15.8 months vs. 9.7 months of age) and children with previous AOMs and *Streptococcus pyogenes* were found in a higher proportion (5% vs. 1%).

Children with the perforated AOMs as well as the bilateral AOM have a more affected TM status and are regarded as more severe forms of AOM [80]. Hotomi et al. [59] studied severe and non-severe AOM and found that younger children and children with *S. pneumonia* had a longer normalisation time.

**Bacteriology**

AOM is generally a bacterial infection in the middle ear secondary to a viral URI. Children aged 0.5-3 years with URI developed AOM during the first week in 22% of cases [5]. Chonmaitree et al. [81] found an association between AOM and RSV, adenovirus and to a lesser extent influenza virus, parainfluenza, enterovirus and rhinovirus. Another study reported similar relations except for adenovirus [82]. Pettigrew et al. [83] described an association between AOM and RSV, bocavirus and adenovirus and also found an association between RSV and S pneumonia (OR 4.4) and H Influenza (OR 2.0). In contrast Kleemola et al. [84] could not find any association between a specific virus and type of bacteria. It has been estimated that 30–60% of children infected with influenza A virus will develop an AOM...
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[81, 85]. In the 10th Research Conference on Recent advances in Otitis media 2013 RSV and adenovirus were stated to be the most important viral infections associated with AOM [86].

There are two ways to examine bacterial aetiology; as a nasopharyngeal swab or obtained from middle ear fluid. Nasopharyngeal swabs are the most commonly used method as myringotomy is a relatively more complicated method and as nasopharyngeal colonisation is well correlated to colonisation of middle ear fluid [15]. Bacteria can be detected in 70–84% in middle ear effusion of children with AOM [8]. If both viral and bacterial diagnostics are used bacteria alone has been found in 55%, a combination of bacteria and virus in 15%, virus alone in 5% and no pathogens in 25% [87]. Bacteria are commonly found in the nasopharynx during childhood and thus the presence of bacteria may lead to an AOM under certain conditions [88]. Similarly, Ruohola et al. [89]* examined 505 children aged 6-35 months with symptoms suggestive of AOM and found 78% of the children without AOM to be colonised by S. pneumonia, H. influenza or M. catarrhalis compared to 96% among children with AOM.

Bacteria that are commonly found in children with AOM are Streptococcus pneumonia, Haemophilus influenza, Moraxella catarrhalis and Streptococcus pyogenes [15]. The most common bacteria found in children with AOM is S. pneumonia, which is known to present with a more severe clinical picture [15]. It is also shown that spontaneous resolution (without treatment) occurs only in 20% of AOM with S. pneumonia [15]. The panorama of bacteriology in AOM has changed since the introduction of penicillin. Before the 1950s S. pyogenes was the most common bacteria in AOM [15].

In the following section studies using nasopharyngeal swabs will be marked (*) and middle ear fluid studies with (**). Streptococcus pneumonia has been associated with younger age and higher TM scores on day 1 as well as prolonged symptoms [59, 60]*. A recent study in Taiwan showed that AOM with otorrhea was most commonly caused by S. pneumonia [90]** and presented with more severe symptoms. Harabuchi et al. [71]* found the outcome of AOM to be related to signs and symptoms at diagnosis as well as bacteriology. Children with S. pneumonia had significantly higher TM scores as well as tympanometry scores at days 8, 15 and 29. Segal et al [91]** studied S. pyogenes in AOM children aged 0–18 years and spontaneous drainage was common. S. pyogenes occurred less often in bilateral AOM and in children with less fever. S. pyogenes is also correlated to a higher risk of mastoiditis [92].

Treatment of acute otitis media

Antibiotics

Antibiotic treatment for AOM has been widely used ever since the antibiotic era started in the 1950s but the judicious use of AOM has been questioned over the last decades. The clinical presentation of AOM has changed and is nowadays a less aggressive disease than it was in the earlier half of the 20th century [93]. Due to the emerging bacterial antibiotic resistance the use of antibiotics needs to be diminished. Today many countries advocate watchful waiting as a
strategy, which means that antibiotic treatment of an AOM episode can be delayed, and if the AOM does not resolve spontaneously within 1–2 days antibiotics can be prescribed. The prescribing patterns, however, vary widely between countries [94]. The treatment regime also differs in, for example, developing countries or in populations in which the complications or prolonged course of disease can be expected. The indication for antibiotic treatment also differs with different ages, in children with other complicating diseases (e.g. cystic fibrosis) or if a child has anatomical anomalies in the upper respiratory system (e.g. cleft palate).

Treatment with antibiotics has been shown to give a slightly quicker resolution of signs and symptoms compared to placebo, more evident in younger children [95, 96]. Despite this, two thirds of the children in the non-treatment group resolved without treatment [95]. In a review of guidelines and management protocols Spiro et al. [97] concluded that immediate use of antibiotic treatment for AOM is needed in children younger than 6 months, “ill-appearing” (e.g. affected general condition), any sign of concurrent and complicating bacterial illness, recurrent AOM, compromised immunity, previous antibiotic use within 7 days, perforation of TM, poor access to medical care, hearing impairment and craniofacial anomalies.

The current Swedish guidelines recommend antibiotic treatment to any child below the age of 1 year and above the age of 12 years. Antibiotics is also recommended for children under the age of 2 years with bilateral AOM and also to any child with a perforated AOM [9]. It should be mentioned that the conventional treatment of recurrent AOM is not medical, but surgical by use of transmyringeal ventilation tubes.

**Vaccines for acute otitis media**

Vaccines that may affect AOM incidence are mainly directed towards *S. pneumonia*. Over the last few years pneumococcal vaccines have emerged and are shown to decrease the AOM incidence [98]. The decrease of AOM incidence is multifactorial and other factors such as the improved diagnostic criteria may be most important and may also contribute to the decrease. However, the early 7-valent pneumococcal vaccines have led to a subsequent increase in other serotypes, some of which have been found to be more resistant to penicillin V [99]. A 13-valent vaccine is now in use and a further development is expected. The general opinion today is that the introduction of pneumococcal vaccines has been important to lower the incidence of severe AOM but other serotypes of *S. pneumonia* and an increase of other bacterial species e.g. *H. influenzae* may hamper the positive effects [15].

**Complications and sequel**

AOM in children in developed countries rarely leads to complications but is more frequent in younger age groups and among children in developing countries. The most common serious complication is mastoiditis, an infection of the mastoid cells behind the ear. Mastoiditis should be suspected in a child with otalgia and a reddened swelling behind the ear and sometimes a visual displacement of the external ear, tenderness over the mastoid, high fever and an affected general condition. C-reactive protein is often raised in combination with leucocytosis. Rarer complications of AOM are peripheral facial paralysis, bacterial
meningitis, brain abscess, sinus-thrombosis and acute labyrinthitis [10]. Ossicular erosion or sensorineural hearing loss is uncommon in children with AOM [10].

Sequel of AOM and OME that may be discovered by TM assessment are myringosclerosis, atrophy, retraction pockets, atelectatic and/or adhesive TMs, chronic perforations and cholesteatoma[15]. Myringosclerosis is seen as a “chalky patch” in the TM and consists of inlays of calcium phosphate plaque in the fibrous layer in the TM [15]. Myringosclerosis is in particular seen in a TM, which has been subjected to insertion of a ventilating tube for treatment of OME. In some TMs, which has been subjected to OME and AOM the dense collagenous layer will be lost and replaced by a loose connective tissue [100, 101]. These thin TM atrophic areas will lose their tension and become more transparent and movable. Discret atrophic areas will form retraction pockets whereas a totally atrophic TM may become atelectatic. If collapsed and adhering to the promontory there will be an adhesive TM. Chronic TM perforations may occur after OM episodes, in particular after a longstanding CSOM. Cholesteatoma may present as a white mass of the TM, most commonly in the attic of the TM, and can be caused by otitis media or a retraction pocket. It is an accumulation of desquamating keratinising epithelium within the middle ear cavity [102].

**TM documentation and examination in telemedicine**

**Historical resume**

Until 150 years ago the appearance and structure of the TM was based merely on autopsies since the TM is hidden deep in the darkness of the external ear canal. With better illumination techniques the first image documentation of the pathological appearance of the TM was published as black and white sketches by Pilcher; “Treatise on the structure, economy and diseases of the ear” – 1838 [69]. Some years later, in 1865, Adam Politzer published coloured drawings of various stages of otitis media. For the first time TM characteristics such as colour, position and TM pathology were described. The first photographs of the TM were documented by Stein in 1873 [69]. However, routine modern photography of TM did not become common not until the 1960s. Today the documentation technique has developed rapidly and can be offered at a lower cost and easily distributed digitally. Video-otoscopy is now available in small hand-held cameras attached to a laptop, with good illumination and high resolution at a relatively small cost. The latest invention, now under testing in USA, is an ear-scope funnel with a small lens that can be attached to a smartphone for TM imaging.

**Telemedicine providing health care to rural areas**

As mentioned in the Introduction, the burden of otitis media is unevenly spread over the world. Moreover, developing and low-income countries, as well as rural areas, lack a sufficient number of specialists providing health care. Approximately 32 million children around the world are suffering from hearing impairment with the highest proportion in South Asia, Asia Pacific and Sub-Saharan Africa. Infectious diseases and chronic ear infection are some of the causes of hearing impairment and early detection along with treatment is important to decrease the burden that otherwise may be lifelong [103].
Aims

The rapidly emerging digital technique over the last few decades has led to the development of telemedicine. Underserved areas are now offered a wide variety of medical services, ranging from education and training to medical assessments and even intervention options [104, 105]. Initial contacts via regular telephone lines are now switched to wireless connections with high speed and the capacity to transfer both sound and image. Telemedicine in otology, tele-otology, will now provide health service at a distance in many countries [104]. An image or a video-uptake of, for example, the TM can be obtained via video-endoscopy or video-otoscopy together with the patient history transferred to almost any part of the world for assessment by an experienced otologist or GP. Both hearing assessment [106] and video-otoscopy can be performed by a trained health care facilitator or nurse [107]. The telemedical assessments can be synchronous (live) with direct contact between the patient and clinician or asynchronous (store-and-forward) where the clinicians assess the stored information from a database, email or other forms of digitally stored and transferred information.

TM imaging

The usefulness and quality of digital imaging of the TM has been investigated in a number of studies. Aronzon et al. [108] demonstrated that digital images and tympanograms could be used for diagnosis of otitis media. In a rural Australian study Eikelboom et al. used tele-otology with digital images, tympanometrical and audiological data together with clinical history of children aged 0.5 to 16 years. They found the information sufficient for a confident and correct diagnosis of AOM, CSOM and cholesteatoma [109]. Regarding OME the diagnose was less confident and correct. The author argues that these diagnoses are hard to reach agreement on even in face-to-face examinations. Other studies on OME in children have shown tele-otology to give an accurate diagnosis with excellent sensitivity and specificity, 97.8% and 100%, respectively [110]. Telemedical assessment of video-otoscopy images has been shown to be comparable to in-person micro-otoscopy examination of follow-up of post-tympanostomy tube placement [111, 112]. Smith et al. [113] investigated the concordance between videoconference and face-to-face consultation regarding diagnoses and management plans in paediatric ENT surgery and showed close agreement between the two methods. Furthermore, a mobile telemedicine-enabled ear screening service was assessed for indigenous children in rural Australia and found to be an efficient screening method for children at risk of hearing impairment [114]. In a wider view of the benefits of telemedicine Smith et al. showed that the use of Telehealth saved travel for follow-up of burns injuries by 1.4 million km over a period of 6 years [115]. They compare the travel saved to two return journeys from earth to moon!

Validity and reliability - a short introduction

Validity and reliability are important aspects of science [116]. Validity gives insight in how a test is able to pinpoint what is important in for example a specific disease. Reliability is the ability of a test to give similar results on repeated measures. However, good reliability may still be non-valid if the test gives non-correct answers.

The validity is based on the following pillars:
Introduction

1) Face validity can be obtained if for example an expert group can give guidance on what aspects or characteristics of a specific disease would be important to test and how it should be measured.

2) Criterion validity is established if for example a new test is compared with an existing – “Gold standard”.

3) Construct validity means that a test needs to be based on clinical and empirical evidence as well as on a theoretical explanation. The basic and conceptual definition of what is being studied or measured is crucial for construct validity.

4) Communicative validity is the ability to show the process of developing a test and how logical the method of development appears.

5) Content validity can be referred to how well a test represents all sides of a clinical problem of interest and depends on the construct validity and face validity. There are different methods for validity assessments. Lynn et al. [117] have developed a method for establishing content validity.

Reliability is basically measured through repeated measures to see whether the individual measurements agree between different users (inter-rater) and between the same users but at different times (intra-rater). In other words, reliability is how consistent the specific test measurements are (consistency) [116]. Inter-rater reliability can be measured by letting several examiners use the test and measure how well they agree on their measures. With a test-retest the same person makes two or more tests on the same material, intra-rater reliability.

Agreement or concordance between two examiners, raters, can be measured as a percentage of agreement, that is, in how many of the ratings the examiners agree. This basic method lacks the correction for chance affecting the result. There are different approaches to calculate agreement with the correction for chance depending on the data being tested. For ordinal data (categorical values) the use of Cohen’s kappa is recommended to estimate agreement. Concerns have been raised about the kappa calculations being too conservative and underestimating the agreement, but the Cohen’s kappa is still the most widely recommended. When assessing agreement along an ordinal scale the weighted kappa can be used to compensate for the “distance” between two ratings. If agreement between multiple raters is assessed a variant of Cohen’s kappa can be used, the Fleiss kappa (multi-rater kappa) [118]. How do we then interpret our kappa values? For kappa calculations there are no definite values or classifications for agreement but a widely used classification was proposed by Landis and Koch [119]. Values 0–0.2 indicate slight agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate, 0.61–0.8 substantial and 0.81–1.0 almost perfect agreement. Fleiss [118] changed the classification slightly and proposed the categories to be poor agreement < 0.4, fair to good 0.4–0.75 and a kappa value above 0.75 to be regarded as excellent agreement. Intra-class correlation is preferably used for ratio data.
Aims

The overall aim of the present thesis was to, study the TM appearance in children with AOM in general practice by use of telemedicine technique and to identify any clinical aspects associated with the TM appearance.

The specific purposes were:

I) to describe and evaluate video-endoscopic digital imaging of TM and to highlight any important characteristics in assessing TM status at distance.

II) to develop and validate a grading scale for TM appearance in various stages of AOM.

III) to evaluate the validity and reliability of a newly developed grading scale for TM appearance in a clinical situation in children 2–16 years with or without ear symptoms.

IV) to elucidate the symptomatology, TM status, tympanogram profile in relation to diagnosis, in children attending primary health care for otalgia and to follow the course of symptoms and signs over time.
Methods

This thesis is based on four investigations from two major clinical studies (table 3). The first part of this chapter is an overview of the methods of the two studies with markings where applicable for each paper in brackets (I–IV). Then follows a more detailed section on the methods of the different investigations (papers).

TABLE 3. Overview of the Lapland and the South Africa study

<table>
<thead>
<tr>
<th>Manuscript</th>
<th>THE LAPLAND STUDY</th>
<th>THE SOUTH AFRICA STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Year of collection

Study population
Children 2–16 years with otalgia at HCCs in Åsele, Dorotea, Storuman and Malå in Lapland, Sweden

Children 2–16 years attending the Witkoppen health and welfare clinic, Johannesburg, South Africa

Study design
Observational, cross-sectional, prospective and consecutive study

Observational, consecutive study with a within-subject comparative design

Data collection
Patient questionnaire and diary. Clinical consultation by study nurse with documentation of symptoms and patient history together with endoscopic photo-documentation of TM and tympanometry.

Clinical consultation with documentation of TM examination using oto-microscopy and otoscopy performed by an ENT and a GP. Video-otoscopic recordings of TM collected by Telehealth facilitator.

Aim
Evaluate characteristics of TM and image quality of endoscopic TM images

Validate and develop a TM grading scale.

Follow the course of signs and symptoms in children with otalgia.

Clinical test of the grading scale. Further validation and a test of reliability

Study personnel
Study nurses. Research group. Assessment group: 1 ENT, 1 GP, 1 GP registrar

Research group. Expert panel A (3 ENT). Expert panel B (4 ENT)

Consensus (assessment) group (1 ENT, 2 GP)

Health care facilitator. Assessment group: 1 ENT, 1 GP

Data sources
Assessment groups grading of image quality

Questionnaire Expert panel A. Interviews Expert panel A. Result of test grading with proposed scale, Expert panel B.

Demographic data. Tympanometry types, OMGRADE gradings, symptom gradings.


Data analysis
Descriptive and frequency statistics. Agreement statistics with Cohen’s kappa

Descriptive statistics. Cohen’s kappa and Fleiss multirater kappa

Descriptive statistics. Frequency of scorings. Chi² statistics

Agreement statistics with weighted kappa. Sensitivity and specificity
Methods

The Lapland study (papers I, II and IV)

Study design
An observational, cross-sectional, prospective and consecutive study of a sample of children aged 2-16 years attending health care centres with othalgia and who agreed to participate during the years 2003 to 2005.

Population
The Lapland study was based on children from rural Sweden, Lapland, in the county of Västerbotten, during the study period 2003–2005. The health care centres (HCC) were located in Åsele, Dorotea, Storuman and Malå, located 150–200 km from Umeå. The population of the different communities during the study years ranged from 1500 to 6500 inhabitants with a range of 0.68–1.98 inhabitants/km² [120].

Study population, personnel, information material and protocols
Children attending HCC in Lapland with othalgia in the age of 2-16 years were offered participation in the study. At each health care centre a study nurse was assigned for patient history documentation, TM imaging, tympanometry and recording of all data in a PC-based protocol. Each HCC received a handout and a manual written by TL on how to perform and document the study examinations. Children and their caregivers received an information sheet specially written for this study by TL about AOM and the study.

Technical equipment
The connections between the different HCCs and the receiving unit at the Umeå University Hospital are set up within Sjunet, a secured IP-based health care network built on Ethernet VLAN technology.

Each HCC was equipped with a PC-based telemedicine system (Migra Bildanalysystem AB, Stockholm). The bandwidth for the network was 768kbit/s. Software for picture storage and analysis was used (Picsara). A straight fibre endoscope (Hopkins, by Karl Storz, 1218AT 0°) with a camera attached (Karl Storz Endovision, Telecam® SL, 30mm) was connected to the system (figure 4). Detergent was used to avoid mist on the lens. Each HCC was also equipped with a Maico Race Car Tympanometer.
Methods

A PC-based protocol was developed in which patient history data, clinical findings, and pictures of TM and tympanometry prints from each patient were registered as an individual “case”. These digital cases were then stored in a central database at the University Hospital, Umeå, and data could be exported in MS Excel format. The database was also accessible via a VPN-client. Images were stored in JPEG compression, 768x576 pixels. The protocol was not integrated in the ordinary PC-based medical journal but was a part of an already existing telemedicine system at each HCC. Entry to the protocol and database was secure and only the nurses in the study and study coordinator (TL) had access to the protocol and database, for which a username and password was required.

Setup and procedure

Any child aged 2–16 years attending the HCC complaining with othalgia within the last few days was offered participation in the study (figure 7). The child and caregiver received an information sheet about the study in the waiting room. A study nurse informed the child and its caregiver about the study and the child was enrolled in the study after the caregiver signed a written consent. Participants were informed that they could leave the study at any time. Information about of patient history and symptoms was registered (table 4).

### TABLE 4. Study variables

<table>
<thead>
<tr>
<th>Background data</th>
<th>Registered as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of visit</td>
<td>date</td>
</tr>
<tr>
<td>Examiner</td>
<td>name</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
</tr>
<tr>
<td>Sex</td>
<td>male/female</td>
</tr>
<tr>
<td>Family history of rAOM,</td>
<td>yes/no</td>
</tr>
<tr>
<td>Previous AOM</td>
<td>number of</td>
</tr>
<tr>
<td>Smoking in family</td>
<td>none/one/two</td>
</tr>
<tr>
<td>Day-care</td>
<td>yes/no</td>
</tr>
<tr>
<td>Last AOM</td>
<td>date</td>
</tr>
<tr>
<td>Last antibiotic treatment</td>
<td>date</td>
</tr>
<tr>
<td>Debut of URI</td>
<td>Previous days</td>
</tr>
<tr>
<td>Debut symptom</td>
<td>type</td>
</tr>
<tr>
<td>Othalgia prior to visit 1</td>
<td>hours</td>
</tr>
<tr>
<td>Ongoing antibiotic treatment</td>
<td>yes/no</td>
</tr>
<tr>
<td>Time of visit</td>
<td>date</td>
</tr>
<tr>
<td>Ear with predominant symptoms</td>
<td>left/right</td>
</tr>
<tr>
<td>Antibiotic treatment started at visit</td>
<td>yes/no</td>
</tr>
<tr>
<td>Further comments</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms of othalgia, fever and general condition, based on the child’s and caregiver’s information, were graded by the nurse in three grades: normal, fair and severe/high at face-to-face examination (table 5). An image of each ear was taken after which a tympanogram was obtained on each ear (figure 5). Then the doctor in service (but outside of the study) at the HCC examined and decided about any treatment, the study nurse recorded the doctor’s decision.
Methods

Follow-up visits
Follow-up visits after 2–4 days, 6–8 days and after 3 months were performed by the study nurse using the same procedure as described above.

<table>
<thead>
<tr>
<th>TABLE 5. Current symptoms reported by the child or caregiver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade of affected general condition</td>
</tr>
<tr>
<td>Grade of othalgia</td>
</tr>
<tr>
<td>Grade of reported fever</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Hearing impairment</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>

Ethical considerations
The Regional Ethical Review Board at Umeå University, Umeå, Sweden, approved the study. All collected data were handled within a secured network and data were stored in a separate database protected by username and password. Only the study nurses and the study
Methods

Coordinator had access to the database. Examination posed no harm to the child, but the examination can cause pain in the external canal. The endoscope is a long metal tube that is inserted into the external ear canal, and unlike an otoscope no funnel is normally used, thus it can pose some danger of damaging the TM if handled incorrectly. The child was normally positioned in a sturdy ear examination chair or lying down on the examination bunk and the study nurse was thoroughly trained and informed about the possible dangers of the examination method. Tympanometry can sometimes cause pain, especially in a child with acute otitis media. The more traditional examination method by pneumatic otoscopy, more often used in the routine examination of a child with otalgia, can also cause pain and is often needed to evaluate any middle ear effusion. The children attending with otalgia often had a concurrent URI, sometimes with fever, and thus the child might experience the examination as tedious and tiring. The child and caregiver could at any time stop participating in the study with no effect on the clinical care that was given outside of our study. The setup of the study was a first visit and following visits after three and seven days, which meant travel costs and time outlay for participants. The last follow-up visit at the time of the study was a normal follow-up after three months. No financial remuneration was given to the child or the caregiver.

The South African study (paper III)

Study design
An observational, consecutive study and a within-subject comparative design of a non-probability sample of children aged 2–16 years attending Witkoppen Health and Welfare Clinic for any reason and who agreed to participate during a two-week period. On-site examination with otomicroscopy and otoscopy by an otologist and a GP compared with their asynchronous assessments with video-otoscopic recordings of the same ears. A study designed to assess the quality of video-otoscopic recordings in a telemedicine setting as well as to evaluate the use of a new grading scale for otitis media in an “unselected population”.

Population
We offered an ear examination to all children aged 2–16 years who for any reason was attending the Witkoppen Health and Welfare Clinic. The Witkoppen clinic provides medical care to people from a poor township called Diepsloot in Johannesburg, South Africa. Diepsloot has a population of over 150,000 and is a settlement made up of government-subsidised housing, brick houses, and shacks made of scrap metal, wood, plastic and cardboard [121]. Around 90% of the population is unemployed and lacking basic services such as running water, sewage and rubbish removal. The prevalence of HIV and associated TB infection is high [121].

Study personnel
The authors trained an Ear and Telehealth clinic facilitator to perform video-otoscopy and save recordings on a laptop. An experienced otologist (>35 years of practice) together with a GP examined the children face-to-face.
Setup and procedure

**On-site assessment (face-to-face)**
Children aged 2–16 years who attended the Witkoppen clinic for any reason were offered an ear examination at entry. The otologist recorded the child’s sex and age together with any suffering from earache, drainage from the ear or hearing impairment during the last two weeks. The child was examined with otomicroscopy and a diagnosis was set based on the findings of TM status and symptoms. No evaluation of TM mobility was performed. The position of the TM, TM transparency, secretion and perforation of the TM was recorded together with a note as to whether wax was removed. If the TM was not possible to assess because of a distressed child or obscuring wax or any other reason, the diagnosis was set as “not possible to determine” (NPD). An image-based grading scale for AOM was used to grade the TM appearance and was recorded together with the above-mentioned characteristics. The GP then performed otoscopy by the same procedure before the child came to the Ear and Telehealth clinic facilitator who performed video-otoscopy on both ears; video-recordings of 10–30 seconds were stored on a laptop (figure 6). If any ear pathology was found that needed medical treatment or follow-up the doctor in service at the clinic was consulted for further care of the child.

**Asynchronous assessment**
The TM video-recordings were anonymised and sent over the Internet via Dropbox to be assessed at Umeå University by the otologist and the GP 4 and 8 weeks (test-retest) later. The video-recordings and the TM status were assessed using the same procedure as in the on-site assessment. An independent investigator at the University of Pretoria numbered the images in random order, which was also changed between test and retest. The assessors were blinded to each other’s gradings.

**Technical equipment**
A Leica M525 F40 surgical otomicroscope with a 6:1 zoom magnification (1.2 to 12.8×) and a 300-watt xenon fibre optic illumination was used for on-site otomicroscopy (figure 6). The video-otoscopic recordings were made with a Dino-Lite Pro Earscope with a LED light, a magnification of 10–20×, a frame rate of 30 frames/sec and a 1.3-megapixel resolution. The Dino-Lite video-otoscope was attached via a USB cable to a Lenovo ThinkPad 2.0 running Windows 7 via 2.0 interface or a Macbook Pro running OSX v10.7.5. DinoCapture 2.0 software (AnMo Electronics Corporation) version 1.2.7 was used to record and view the video-otoscopic recordings. Depending on the size of the external ear canal, a 3, 4 or 5 mm speculum was attached on the video-otoscope head. Recordings were between 9 and 33 seconds long (mean 25.6 secs) and were saved onto a laptop as MOV or WMV files (Macbook Pro and PC) and ranged from 0.85 to 7.61 MB size (mean = 3.6 MB). Via a foot-pedal connected to the laptop or a touch button on the video-otoscope recordings could be started and stopped. Analyses of the video recordings were made using a 24-inch Apple LED Cinema Display connected to a Macbook Pro.
Methods

FIGURE 6. Video-otoscopy performance

Ethical considerations
This study was conducted following approval from the institutional ethics committee at the University of Pretoria, South Africa. We did not record any personal information, only the child’s age, sex and symptoms. Video-recordings were made of TM only, and the child’s identity cannot be revealed in these recordings. The child’s caregiver was informed about the study and the procedure by the Telehealth facilitator who spoke seven languages (English and six different African languages) which was important with the wide diversity of languages being spoken in South Africa (11 official languages). The examination was done during a long waiting period for the participants for their ordinary visit. It was not unusual for the patients to spend 6–8 hours at the clinic waiting for their different examinations and prescriptions, thus our examination rarely delayed the examined children and their caregivers. No financial compensation was given, but balloons were offered each child at video-otoscopy. Otomicroscopy was performed by an experienced otologist (>35 years) according to standard procedures. Wax was mechanically removed when needed for visualisation of TM. If any pain was noted or discomfort for the child the examination was cancelled. Otoscopy was performed by a GP (15 years experience) directly after otomicroscopy using standard equipment. This examination procedure generally lasted no more than 10 minutes. Then followed a video-otoscopy examination by a Telehealth facilitator employed by the Witkoppen clinic, duration approximately 10 minutes. A new video-otoscope was used connected to a laptop via a USB cable. The otoscope has the same funnel as an ordinary otoscope and poses no other dangers compared to ordinary otoscopy. If any pathology was found in the examinations the research group arranged consultation with medical personnel on duty at the centre for immediate treatment or further examination.

Quality of video-endoscopic images (paper I)

Study design
One hundred and twenty-four TM images from the first visit were included in the study. The research group (two ENTs, one GP, one GP registrar) discussed and outlined important characteristics of OM diagnostics with digital imaging based on current knowledge about OM diagnostics. These characteristics were divided into two major categories: anatomical and image-related components, with each category subdivided into four different categories
(components) (table 6). An assessment group (one ENT, one GP and one GP registrar) was formed to assess these components in a selection of images of TM.

**Study variables and collection of variables**

The assessment group evaluated all digital video-endoscopy images of TM from the first visit. Images were assessed on a film screen and the reviewers of the assessment group sat together but were not allowed to discuss their gradings with each other. Each component was graded 0 for not possible to assess and 1 for possible to assess with a maximum of 4 points per category and a total score of 8. The image quality was graded in three grades (0–2) (table 7) From the research nurses’ notes, information on any problem with the examination, pain etc. was at hand for comparison.

**TABLE 6. Grading of important components of tympanic membrane images**

<table>
<thead>
<tr>
<th>Image-related components</th>
<th>Label</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus</td>
<td>Good focus</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Light</td>
<td>Good light</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Obscuring objects</td>
<td>No obscuring objects</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Composition</td>
<td>Important anatomic structures of TM are visible</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

**Anatomically related components**

| Surface structure of TM       | Surface structure of TM can be assessed | Yes/No                                                                      |
| Thickness of TM               | Thickness of TM can be assessed        | Yes/No                                                                      |
| Colour of TM                  | Colour of TM can be assessed           | Yes/No                                                                      |
| Position of TM                | Position of TM can be assessed         | Yes/No                                                                      |

**TABLE 7. Overall grading—grading scale for general image quality**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Label</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Excellent</td>
<td>Excellent image quality and easy to assess the status of the tympanic membrane</td>
</tr>
<tr>
<td>1</td>
<td>Acceptable</td>
<td>Possible to assess the status of the tympanic membrane</td>
</tr>
<tr>
<td>0</td>
<td>Not acceptable</td>
<td>Not possible to assess the status of the tympanic membrane</td>
</tr>
</tbody>
</table>

**Data analysis**

A comparison was made between overall grade and the different image components. Images with overall grade 2 were scrutinised to see whether any component was more or less important for excellent image quality. The same procedure was used for images with overall image quality grade 0. Additionally, each component was compared with image quality in cross tables; image quality was for this reason dichotomised into acceptable or not acceptable image quality.

Images were then grouped based on the child’s age into 3 age groups, 2–4 years, 5–7 years and 8–16 years, and any difference in image quality was assessed. Furthermore, images were also grouped based on time intervals when in the study period they were taken; two groups were formed (early and late group). Chi² tests were used for significance analysis.

Agreement on each component as well as overall grading between the assessors was calculated with Cohen’s kappa (k). We used Landis and Koch’s [119] grading of kappa values (table 8).
## Methods

### TABLE 8. Interpretation of agreement depending on different kappa values [119].

<table>
<thead>
<tr>
<th>Kappa values (k)</th>
<th>Interpretation of kappa values</th>
</tr>
</thead>
<tbody>
<tr>
<td>k=0–0.2</td>
<td>slight agreement</td>
</tr>
<tr>
<td>k=0.21–0.4</td>
<td>fair agreement</td>
</tr>
<tr>
<td>k=0.41–0.6</td>
<td>moderate agreement</td>
</tr>
<tr>
<td>k=0.61–0.8</td>
<td>substantial agreement</td>
</tr>
<tr>
<td>k=0.81–1.0</td>
<td>almost perfect agreement</td>
</tr>
</tbody>
</table>

### Development of a new grading scale for AOM (paper II)

Due to lack of a feasible grading scale to study the course of TM appearance in *paper IV* we initiated the development of an image-based grading scale.

### Study design

We used a method for establishing content validity based on a process outlined by Lynn et al. [117] together with adjustments of the method by Wynd et al. [122]. The development was set up in two stages, a development stage and a judgement/quantification stage.

### Study variables and method of collection of variables

The development stage was further divided into 2 steps. The first step was establishing construct validity based on current theoretical knowledge about TM and middle ear pathology together with the diagnosis of AOM. The research group categorised a selection of 66 images (32 children) of acceptable quality in sequences of increasing pathology of TM status and chose important characteristics of TM status (items). A provisional scale was established with typical images representing each scale step together with a description of each scale step and item (table 9).

### TABLE 9. Description of items

<table>
<thead>
<tr>
<th>Effusion</th>
<th>Fluid level visible or notable effusion in middle ear. Effusion can be transparent, opaque or haemorrhagic</th>
</tr>
</thead>
</table>
| Position | 1. Retracted TM with protruding lateral process of malleus, the reflex may be divided and the annulus fibrosus may be protruding.  
2. Normal position.  
3. Bulging TM with loss of normal anatomical structure, shattered or absent reflex |
| Vascularisation | Visible vascularisation with radiant arteries in pars flaccida, over handle of malleus, over entire TM and/or on the outside the margins of the TM |
| Bullae | One or more bullous formations on TM |
| Haemorrhagic (later described as Chagrinated) | Visible haemorrhage spread diffusely over TM, most often with keratin patches (highly deformed TM with keratin patches) |
| Perforation | Visible perforation of TM or the finding of purulent fluid in the ear canal |

The second step was to establish face validity and content validity. An expert panel (expert panel A) of 3 ENT specialists was formed with a range of 13–30 years of experience in their
professions. The expert panel A answered questions about the items and scale steps in a questionnaire (Appendix A). This was followed by a new discussion in the research group about the expert panel A’s assessment of the items and the provisional scale with subsequent alterations. A second round followed with the expert panel A with a new assessment according the procedure described above. A third round as described above followed until the research group agreed upon a proposed grading scale.

For the judgement and quantification stage, step 3, a new expert panel (expert panel B) was formed consisting of 4 ENT specialists with experience ranging between 15 and 35 years. The expert panel B using the proposed scale tested a sample of 24 images of TMs with different stages of TM status represented. The assessments were made with the expert panel B gathered in a conference room but with no ability to talk to each other or see their gradings. Each image was presented for 45 seconds as a glossy print randomly numbered, with a total test time around 45 minutes. The retest was made 4 weeks after the first test, with a new randomisation of the images. Consistency of the scale was calculated between test and retest and together with inter-rater agreement on the two tests.

**Data analysis**

Fleiss’ multi-rater kappa was used for calculation of expert panel A’s questionnaire and inter-rater agreement. Consistency (intra-rater agreement) was calculated with Cohen’s kappa. We used an online kappa calculator for both types of kappa calculations – http://www.statstodo.com/CohenKappa_Pgm.php.

**Test of the OMGRADE scale in a clinical and telemedical setting (paper III)**

**Study design of paper III**

A study designed to validate and test the reliability of the OMGRADE scale (Appendix B) from manuscript II in a clinical setting based in the South Africa study. Validity evaluated with a comparison of on-site and asynchronous assessments, establishing concordance as well as testing the reliability with a test-retest design.

**Study variables and method of collection of variables**

The diagnosis made by the otologist on face-to-face assessments was set as the gold standard. The asynchronous assessments were performed as a test and retest with an interval of four weeks between face-to-face and the first asynchronous as well as between the two asynchronous assessments. The OMGRADE gradings were compared between the face-to-face assessments and the otologist’s as well as the GP’s asynchronous assessments.

**Exclusions**

All ears that were rated as not possible to determine in any of the assessments were excluded for analysis.
Data analysis
Consistency (reliability) of the OMGRADE scale was determined by investigating the agreement between reviewer gradings at four and eight weeks using Cohen’s kappa. Weighted kappa statistics (κ) were used to quantify “strength of agreement” (or diagnostic concordance). Weighted kappa was also used to calculate the concordance of OMGRADE otomicroscopy by the otologist, and video-otoscopy assessments by the otologist and the GP. Diagnostic validity was calculated by dichotomising the diagnosis by the otologist and OMGRADE gradings into normal or abnormal. All ears diagnosed as SOM or AOM were grouped as abnormal. All ears diagnosed as CSOM were excluded for this calculation. The OMGRADE scale was grouped into normal (grade 0–1R) and abnormal (grade 1F–5C). Data analysis of frequencies and cross-tabulations was done using SPSS. An online Kappa calculator was used – http://www.statstodo.com/CohenKappa_Pgm.php – together with Excel and SPSS. An online calculator was also used for calculations of specificity and sensitivity – http://www.medcalc.org/calc/diagnostic_test.php.

TM appearance and the relation to the course of signs and symptoms (paper IV)

Study design
In order to evaluate TM-status, tympanometry, symptoms and background data an assessment (consensus) group was formed consisting of one otologist (>35 years experience), and two GPs (16 and 30 years experience respectively).

Study variables and method of collection of variables
Images of TM’s were assessed using the OMGRADE scale (appendix B) and the assessment group made a decision of the grading after a consensus discussion. The otologist evaluated the tympanograms and they were grouped into three types; type-A tympanogram with a peak above −150 daPa and compliance above 0.3 cc was considered type-A. If the compliance was less than 0.3 cc but the tympanogram had a visible peak above −150 daPa it was also regarded as a type-A tympanogram (restricted mobility of TM). A type-C tympanogram had a peak below −150 daPa and a flat tympanogram was set as type-B.

A diagnosis of each ear was set by the assessment group after a consensus discussion based on TM image, tympanometry together with the child’s reported symptoms (fever, otalgia, affected general condition). A translucent TM in a fairly normal position (OMGRADE scale step 0–1R) without signs of fluid in the middle ear together with a type A tympanogram was considered normal. A middle ear with visible fluid (OMGRADE scale step 1F–2) or an opaque TM in a fairly normal position (OMGRADE scale step 3) together with a type B or C tympanogram was considered SOM. The AOM diagnosis was based on a bulging TM (OMGRADE scale step 4) together with a type B tympanogram. A bullous myringitis (BM) was considered if TM presented with blisters (bullae) but a normal tympanogram (type A) and AOM with BM (bAOM) was set if bullous formations were found on the surface of the opaque TM (OMGRADE scale step 5B) together with a type B tympanogram. If a chagrinated, wet and contourless TM was found (OMGRADE scale step
Methods

5C) it was labelled pAOM. In some cases with OMGRADE scale step 3 and tympanogram B an AOM diagnosis was set after evaluation of registered symptoms (general condition, otalgia and fever). Ears lacking TM images or with poor TM image quality were classified as NPDs, as were ears with absent or non-interpretable tympanograms.

Exclusions
For first visit analysis all children with missing data on symptoms together with missing or poor-quality tympanograms and/or TM images of the most symptomatic ear were excluded from further analysis. For follow-up visits all ears with missing or poor-quality tympanograms and/or TM images of the ear with dominating symptoms were excluded.

Data analysis
The OMGRADE scale was transformed into a score from 0 to 8 points (0-1R-1F-1RF-2-3-4-5B-5C). A validated scoring system for tympanometry profiles is lacking. However, we decided to use the same scoring system as in the studies by McCormick et al. [64] and Le et al. [123] with a slight adjustment. Tympanograms were classified by scoring points from 0 to 4 and up to 8 depending on tympanogram profiles type-A, type-C or type-B.

Symptoms were scored 0 to 2 points (none=0, mild to moderate=1 and severe=2). A “sum of symptoms” score was calculated by adding the different scores (0–6 points). A “sum of signs” was calculated by adding the scores from the tympanograms and the OMGRADE scores (0–9 points). A median of scores was calculated for each diagnosis, for comparison between unilateral and bilateral AOM and between antibiotic treated and non-treated children. MS Excel and SPSS v22 were used for frequency tables and cross tables.

Study nurse
Day 1: Enrollment visit (n=63)
- Anamnestic info
- Endoscopic TM photography
- Tympanometry

Day 2: 2nd visit (n=29)
- Same procedure as day 1

Day 7: 3rd visit (n=29)
- Same procedure as day 1

3 months: 4th visit (n=29)
- Same procedure as day 1

Assessment group (asynchronous evaluation)
- Analyzing data from central database
- Grading of TM appearance
- Evaluation of tympanograms (otologist)
- Establishing diagnosis

FIGURE 7. Setup and procedure of the Lapland study
Results

In the Results section I will start by presenting a summary of the demographics of the two main studies. Then follows a more detailed presentation of the results of the four investigations (papers I–IV), based on the aims of the thesis such as image quality, telemedicine evaluation, grading scale development and testing as well as TM appearance and course of signs and symptoms.

Characteristics of study populations

The Lapland study (papers I, II, IV)
Sixty-five children were examined at first visit (first visit group). Two children were excluded due to errors in the recording of data. Sixty-three children have data of age, sex and symptoms together with image and tympanogram of the ear with most symptoms, 35 boys and 28 girls (table 10). Mean age was 6.8 years (median 6) with a range of 2–16 years, 25 children were under 5 years, 33%. Rhinitis was the most common URI symptom, 75% (table 10 and 11).

<table>
<thead>
<tr>
<th>TABLE 10. Background data of First visit group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
</tr>
<tr>
<td>Mean (median)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
</tr>
<tr>
<td><strong>Previous AOM</strong></td>
</tr>
<tr>
<td>Mean (median)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td><strong>Duration of othalgia (hours) before visit 1.</strong></td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td><strong>Symptoms of URI</strong></td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Hearing impairment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 11. Symptoms of first visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>First visit group (n=63 children)</td>
</tr>
<tr>
<td>General condition</td>
</tr>
<tr>
<td>Not affected</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Missing</td>
</tr>
</tbody>
</table>

The diagnoses found were: normal ears in 19% of the children, 33% OME (table 3), 48% any type of AOM. However, 3 of the 7 children with BM/bAOM can be regarded as BM without evidence of middle ear fluid and thus not a true AOM (table 12).
All children reported othalgia prior to the first visit, 52% of them were not diagnosed as AOM. Current othalgia at first visit was reported in 68% (table 11). Ten children, 16%, reported severe othalgia, the mean age in this group was 6 years (unpublished data). Seven of these children were diagnosed as AOM of some type and 2 of them as normal ears. Of the AOM group with severe othalgia 2 were diagnosed as AOM, 2 as bAOM, 4 as pAOM, and 2 children had bilateral AOM. Seventeen children, 27%, reported no othalgia at the first visit.

Fever was reported in 22% of all children at first visit and in 33% of children with AOM (unpublished data). Four children reported fever >39°C, all reported moderate to severe othalgia: the mean age in these children was 5 years (unpublished data). One child with temperature >39°C had bilateral AOM.

**TABLE 12.** Diagnosis, tympanograms and OMGRADE grading at enrolment (visit 1). Total number of children count is based on most symptom-giving ear.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>First visit group (n=63 children, 126 ears)</th>
<th>Follow-up group (n=29 children, 58 ears)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of ears (n=128)</td>
<td>Total number of children (n=63)</td>
</tr>
<tr>
<td>Normal</td>
<td>40 (31%)</td>
<td>12* (19%)</td>
</tr>
<tr>
<td>OME</td>
<td>34 (27%)</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>AOM</td>
<td>15 (12%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>BM/bAOM</td>
<td>7 (6%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>pAOM</td>
<td>14 (11%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>NPD</td>
<td>16 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Tympanogram</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>43 (34%)</td>
<td>22 (35%)</td>
</tr>
<tr>
<td>Type C</td>
<td>10 (8%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Type B</td>
<td>38 (30%)</td>
<td>24 (38%)</td>
</tr>
<tr>
<td>NPD</td>
<td>35 (28%)</td>
<td>14 (22%)</td>
</tr>
<tr>
<td><strong>OMGRADE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33 (26%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>1R</td>
<td>9 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>1F</td>
<td>3 (2%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>1RF</td>
<td>2 (2%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>2</td>
<td>11 (9%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>3</td>
<td>18 (14%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>4</td>
<td>15 (12%)</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>5B</td>
<td>7 (6%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>5C</td>
<td>14 (11%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>NPD</td>
<td>14 (11%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*normal ears on both sides

Hearing impairment was reported in 17 of the children in the Lapland study and in 7 (23%) of the children with AOM. The children with reported hearing impairment were diagnosed as 2 AOM in, pAOM in 5, OME in 6 and as normal in 4 children but none was diagnosed as
Results

BM/bAOM (unpublished data). The HCC doctor prescribed an antibiotic treatment to 27 children.

The South Africa study (paper III)
The study comprised 140 children aged 2 to 16 years (range 2–15.8 years, mean age 6.4 ± 3.5 years, 44.4% females. Seventeen of these reported one or more symptoms from their ears during the last two weeks. Otalgia was reported in 10 children, and 3 children reported both earache and drainage of the ear. Eight of the seventeen children with otalgia were diagnosed as having normal ears. One hundred ears were excluded (figure 8). The otologist diagnosed 151 normal ears (84%), 20 OME ears (11%) and 9 ears with CSOM (5%) at on-site otomicroscopy.

Quality of TM imaging (papers I, III)
In paper I the study group (ENT, GP and GP registrar) reviewed 124 TM images. Image quality was graded as acceptable or excellent in 102 (82%) of them (grade 1 or 2). Image-related components were perfect with a total score of 4 in 41, 33%, while 99, 80%, had a total score of 2 or more. The different components differed slightly: “light” was acceptable in 72% of all images compared to 69%, 63% and 61% respectively for “no obscuring objects”, “focus” and “composition”. In 22 images, 18%, the quality was rated as not acceptable. Poor composition was most common in the images with unacceptable image quality, 87%, and obscuring objects was noted in 17 images, 77%.
Anatomically related components were given a maximum score of 4 in 74 images, 60%. Of images rated as not acceptable image quality, the position and thickness of TM could not be assessed in 95% of these images.
In *paper III* Image quality was rated as not acceptable in 24%, acceptable in 57% and excellent in 17% of all video assessments (unpublished data). Of the 68 ears rated as NPD in video assessments, 43 ears were still possible to assess in 1 or 3 of the total of 4 assessments (video-otoscopy 1 and 2 by OT and GP).

Any age-related differences of image quality were tested in *paper I* by grouping the participants in 3 age groups: 2–4 years, 5–7 and 8–16 years. Poor overall image quality was most common in the younger children (2–4 years). Obscuring objects, poor light as well as not being able to assess colour was most frequently reported in this group. In *paper III* we found 5% of the ears to have a better image quality in the age group 6–15 years compared to the lower age group 2–5 years (unpublished data).

One might assume that the skills of the nurse or the facilitators’ imaging technique would improve over time. In *paper I* image quality improved over time with a significant improvement of focus in the later half of the project. We also found a slight increase in image quality in the second week in *paper II*.

In *paper III* the otoscopist changed his diagnosis regarding CSOM at video-recording assessments 1 and 2 in 5 and 4 ears respectively, a change from 9 diagnoses of CSOM to 14 and 13 ears with CSOM.

**Telemedicine technique in children with ear related problems (papers I-IV)**

In *papers I and IV*, pain was recorded in 4 children, 8 images, as a problem in obtaining endoscopic images; three of these were in the youngest age group. Three children had difficulty complying with the examination, and their images were reported to be of unacceptable image quality in 3 images, acceptable in 2 images and 1 image was reported as missing. One child’s data and images were lost due to computer problems.

In *paper III* we excluded 11 ears due to non-compliance at examination with otomicroscopy or video-otoscopy.

**Agreement between examiners (papers I-III)**

The three reviewers (ENT, GP and GP registrar) in *paper I* examined the image quality of 124 images and the agreement between their assessments was found to be fair to substantial (table 13). Agreement was best for evaluating the quality of the component “no obscuring object”.

In *paper II* both the inter-rater and intra-rater agreement of the expert panel B was found to be moderate to almost perfect using the OMGRADE scale on the selected images. However, a discrepancy was found especially between the panel members’ interpretation of the item fluid levels and if the TM was retracted or not. We evaluated the images with the lowest agreement, 7 images, and found that these were mainly found in the range of transparent TMs,
Results

OMGRADE grades 1R, 1RF and 2OF. The item fluid level was what differed most between reviewers.

In paper III disagreement was evident in deciding whether TMs were slightly retracted or not, the otologist graded 1R in 14 and 7 ears respectively in video-otoscopy compared to the GP’s rating of 75 and 65 ears being 1R.

<table>
<thead>
<tr>
<th>TABLE 13. Inter-rater agreement on different components of image quality and grading. Cohen’s kappa (κ).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0.680</td>
</tr>
<tr>
<td>0.683</td>
</tr>
<tr>
<td>0.740</td>
</tr>
<tr>
<td>0.413</td>
</tr>
<tr>
<td>0.558</td>
</tr>
<tr>
<td>0.607</td>
</tr>
<tr>
<td>0.619</td>
</tr>
<tr>
<td>0.537</td>
</tr>
<tr>
<td>0.558</td>
</tr>
</tbody>
</table>

Viewer 1 ENT specialist, Viewer 2 Registrar in GP, Viewer 3 GP. For interpretation of kappa values see table 8.

Development and test of a new image-based grading scale (papers II, III)

By the process outlined in paper II we identified a list of items that are important in the diagnosis of otitis media (table 14). The item haemorrhagic was changed to chagrinated, a reddened TM with swollen keratin patches that appear white and elevated from the TM together with a wet appearance of the TM.

The proposed scale developed as described in table 15. The major changes during the process were adding the differentiation of clear or turbid fluid level behind a transparent TM and combining the chagrinated TM with the perforated TM as one scale step (5C). The AOM with bullous formations was “upgraded” to 5B instead of 4B.

The proposed scale was tested in paper II by expert panel B on a selection of 24 images of various stages of TM appearance ranging from the normal TM to the chagrinated TM. The four ENTs in expert panel B graded the images in random orders on two occasions, a test and retest. Inter-rater agreement between examiners was substantial to almost perfect between pairs of examiners, but overall agreement was only moderate (table 16). Intra-rater agreement was found to be substantial to almost perfect (table 17).
## Results

### TABLE 14. Description of Items, important characteristics of TM status.

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effusion</td>
<td>Fluid level visible or notable effusion in middle ear. Effusion can be</td>
</tr>
<tr>
<td></td>
<td>transparent, opaque or haemorrhagic</td>
</tr>
<tr>
<td>Position</td>
<td>1. Retracted TM with protruding lateral process of malleus, the reflex</td>
</tr>
<tr>
<td></td>
<td>may be divided and the annulus fibrosus may be protruding.</td>
</tr>
<tr>
<td></td>
<td>2. Normal position.</td>
</tr>
<tr>
<td></td>
<td>3. Bulging TM with loss of normal anatomical structure, shattered or</td>
</tr>
<tr>
<td></td>
<td>absent reflex</td>
</tr>
<tr>
<td>Vascularisation</td>
<td>Visible vascularisation with radiant arteries in pars flaccida, over handle</td>
</tr>
<tr>
<td></td>
<td>of malleus, over entire TM and/or on the outside the margins of the TM</td>
</tr>
<tr>
<td>Bullae</td>
<td>One or more bullous formation on TM</td>
</tr>
<tr>
<td>Haemorrhagic (later described as Chagrinated)</td>
<td>Visible haemorrhage spread diffusely over TM, most often with keratin patches (highly deformed TM with keratin patches)</td>
</tr>
<tr>
<td>Perforation</td>
<td>Visible perforation of TM or the finding of purulent fluid in the ear canal</td>
</tr>
</tbody>
</table>

### TABLE 15. Development of the scale developed from six basic grades.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Version 1</th>
<th>Version 2</th>
<th>Version 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0: Normal</td>
<td>0: Normal</td>
<td>0: Normal</td>
</tr>
<tr>
<td>1</td>
<td>1F: Transparent, retracted</td>
<td>1R: Transparent, retracted</td>
<td>1R: Transparent, retracted</td>
</tr>
<tr>
<td></td>
<td>1F: Transparent, clear fluid level</td>
<td></td>
<td>1F: Transparent, clear fluid level</td>
</tr>
<tr>
<td>2</td>
<td>2RF: Transparent, retracted</td>
<td>2OF: Transparent, opaque fluid level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2RF: Transparent, retracted</td>
<td>2OF: Transparent, opaque fluid level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2OF: Transparent, opaque fluid level</td>
<td></td>
<td>2OF: Transparent, opaque fluid level</td>
</tr>
<tr>
<td>3</td>
<td>3: Opaque, normal position</td>
<td>3: Opaque, normal position</td>
<td>3: Opaque, normal position</td>
</tr>
<tr>
<td>4</td>
<td>4: Opaque and bulging</td>
<td>4: Opaque and bulging</td>
<td>4: Opaque and bulging</td>
</tr>
<tr>
<td></td>
<td>4B: Bullous formation</td>
<td>4B: Bullous formation</td>
<td>4C: Chagrinated</td>
</tr>
<tr>
<td></td>
<td>4H: Haemorrhagic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5: Perforation</td>
<td>5B: Bullous formation</td>
<td>5C: Chagrinated or perforation</td>
</tr>
</tbody>
</table>

### TABLE 16. Inter-rater agreement, first and second test. Cohen’s kappa for all pair of raters

<table>
<thead>
<tr>
<th>Rater</th>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>0.7251</td>
<td>0.8297</td>
</tr>
<tr>
<td>2</td>
<td>0.768</td>
<td>0.7483</td>
</tr>
<tr>
<td>3</td>
<td>0.8575</td>
<td></td>
</tr>
</tbody>
</table>

*Overall kappa test 1: 0.5213. Overall kappa test 2: 0.5159. Overall kappa test 1-2: 0.5352*

### TABLE 17. Intra-rater agreement between first and second test, rater 1–4.

<table>
<thead>
<tr>
<th>Rater</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa</td>
<td>0.6808</td>
<td>0.7277</td>
<td>0.8947</td>
<td>0.7333</td>
</tr>
</tbody>
</table>
**Results**

Furthermore, based on the images (ears) with lowest agreement (7 images) a last and minor revision of the scale was made as presented in appendix B. We transferred these changes of the scale to the original gradings. For example, if the otologist originally had graded an ear as 2RF it was changed to 1RF. A recalculation of inter-rater agreement based on these transfers resulted in an increase in overall kappa from 0.5352 to 0.6409.

In *paper III* the new scale (Appendix B) was tested in a clinical setting in a selection of children with a disease prevalence expected to be low. With a temporary adjustment of the OMGRADE scale the grade CSOM was incorporated and labelled as grade t6. We found substantial agreement between otologists on-site gradings and video-otoscopy gradings as well as inter-rater agreement between video-otoscopy sessions 1 and 2 (table 10). After converting the OMGRADE scale in to diagnostic groups (Normal – 0–1R, OME – 1F–3, AOM 4–5, CSOM – t6 a comparison between the otologists’ gold standard on-site diagnosis and the otologists’ video-otoscopy OMGRADE gradings we found inter-rater agreement ranging k: 0.75–0.80. We tested the capability of the OMGRADE to discern between a normal ear and OME and found a specificity of 97.3% and a sensitivity of 67.5% between gold standard and the otologists’ video-otoscopy assessments (table 18). Disease prevalence was 12%.

**TABLE 18. Sensitivity/specificity of otomicroscopic diagnosis and otologist’s assessment of video-otoscopic recordings**

<table>
<thead>
<tr>
<th>OMD–OMg</th>
<th>OMD–VOOT1</th>
<th>OMD–VOOT2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>95% Cl</td>
<td>%</td>
<td>95% Cl</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85</td>
<td>62.1 – 96.6</td>
<td>70</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>97.5 – 100</td>
<td>96.6</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>100</td>
<td>59.3 – 93.1</td>
<td>73.7</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>98</td>
<td>94.2 – 99.6</td>
<td>95.9</td>
</tr>
</tbody>
</table>

*Disease prevalence 12%. Abbreviations: OMD=Otomicroscopic diagnose (normal or OME). OMg=Otomicroscopic grading with OMgrade (grouped 0–1R as normal and 1F–3 as abnormal/OME). VOOT=videootoscopic assessment by Otologist. Cl=Confidence interval.*

In *paper IV* the OMGRADE scale (Appendix B) was used for grading the TM status. The gradings by the assessment group at first visit are shown in table 12. Twenty-six per cent of the ears examined were graded as normal, grade 0, and grade 1R was found in 7%. Fluid levels of any kind were found in 13% of the ears, a completely opaque TM in 43% and 11% was rated as NPD. This can be compared to the findings of tympanometry; type-A was found in 26%, type-C in 8% and type B in 30%; 28% of the tympanograms, however, were rated as NPD. The correlation between OMGRADE and tympanograms is shown in table 19.

**TABLE 19. OMGRADE vs tympanograms.**

<table>
<thead>
<tr>
<th>OMGRADE</th>
<th>A</th>
<th>B</th>
<th>type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17 (74%)</td>
<td>4 (17%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>1R</td>
<td>3 (38%)</td>
<td>2 (25%)</td>
<td>3 (37%)</td>
</tr>
<tr>
<td>1F</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>1RF</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>2</td>
<td>7 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>3</td>
<td>7 (47%)</td>
<td>1 (6%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>5B</td>
<td>3 (43%)</td>
<td>1 (14%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>5C</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
<td>8 (89%)</td>
</tr>
</tbody>
</table>

...
TM appearance and the relation to the course of signs and symptoms (paper IV)

In paper IV, 29 children (58 ears) were examined at three follow-up visits (follow-up group). The proportion of normal ears was slightly higher than in the first visit group (table 12). Othalgia was reported in 21 children (72%) of this group compared to 68% of the first visit group. Six children, 21%, reported fever and 11 children, 38%, affected general condition compared to 22% and 38% respectively of the first visit group.

AOM was found in 14 children (48%) and a further 3 children with BM but without AOM. OME was found in 8 children (28%). The HCC doctor prescribed antibiotic treatment to 11 children (40%), 3 of whom were diagnosed by the assessment group as Normal, OME and BM and 8 as AOM.

Children with OMGRADE 5C (pAOM) showed longer recovery time of TM appearance and tympanograms than children with AOM but no difference in the course of symptoms (figure 9). Children with normal ears as well as children with any type of AOM were free of symptoms at day 3 except for 2 children who reported moderate effect of general condition and a further 2 with moderate othalgia.

### TABLE 20. Background data follow-up group

<table>
<thead>
<tr>
<th></th>
<th>Mean (median)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>6.8 (7)</td>
<td>2–14</td>
</tr>
<tr>
<td>Male gender</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Previous AOM</td>
<td>1.9 (2)</td>
<td>0 to &gt;5</td>
</tr>
<tr>
<td>Duration of othalgia (hours) before visit 1.</td>
<td>64.8 (48)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14 (48%)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>23 (79%)</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (28%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>8 (28%)</td>
<td></td>
</tr>
</tbody>
</table>
Results

a) Sum of symptom score

b) OMGRADE score

c) Type-B tympanograms

d) Sum of sign score

FIGURE 9. Median and proportion of scores at all four visits based on diagnosis at visit 1.
a) Median of sum of symptoms score 0–6p, b) OMGRADE median score 0–8p, b) proportion of
Tympanometry type B tympanograms, d) Median of sum of sign scores 0–16p. p<0.05 for each visit,
diagrams b and c.
Discussion

Main findings

The main aim of this thesis was to elucidate clinical aspects of the TM appearance, the important characteristics of a healthy and a pathological TM and to present a guide for how to assess TM status. Another aim was to evaluate new methods of documentation of TM status for use in telemedical practice.

This thesis showed that assessment of TM appearance is important for following the natural course of the AOM and that some characteristics of the TM correlate to prolonged middle ear pathology. A new, validated and reliable grading scale for otitis media, the OMGRADE scale, has been developed. Furthermore, I have presented the usability and quality of image documentation of the TM for use in a clinical context as well as in research. This thesis also showed that a trained nurse or a health facilitator could document the TM status along with other signs and symptoms for asynchronous evaluation at a distance in rural Sweden as well as in South Africa.

This chapter will discuss the findings, debate the generalisability and scrutinise the methods used in two main studies and in the four papers.

Methodological considerations

The Lapland study

The Lapland study was designed as an observational and prospective study of children aged 2–16 years with otalgia consulting general practice. The appearance of TM was followed in relation to otalgia, tympanometry and other symptoms. It was both a cross-sectional and a cohort study without interventions in a non-probability sample of children and caregivers who accepted participation, over a three-year inclusion period. The age group selected was based on the Swedish consensus guidelines published in 2000 on treatment of AOM [1]. This guideline had a watchful waiting approach for children aged 2–16 years with AOM. We asked ourselves how the important clinical signs and symptoms change over time and whether this knowledge could help us in the decision about treatment or not.

Table 21. Population statistics children aged 2–16 years

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malå</td>
<td>632</td>
<td>612</td>
<td>601</td>
</tr>
<tr>
<td>Storuman</td>
<td>1124</td>
<td>1106</td>
<td>1064</td>
</tr>
<tr>
<td>Dorotea</td>
<td>560</td>
<td>499</td>
<td>458</td>
</tr>
<tr>
<td>Åsele</td>
<td>580</td>
<td>572</td>
<td>557</td>
</tr>
</tbody>
</table>

The intention was to examine 200 children. With respect to the incidence rate of children with AOM, 2–5-year-olds being 171 per 1000 children per year [2] we could expect to examine approximately 500 children with AOM each year (table 21). Our population was somewhat older children with a mean age of 6.8 years, which may reduce the number of children to include annually. In reality the number of children was lower than calculated, for several reasons.

Although one nurse at each HCC was trained in the examination and study procedure, these nurses still had their ordinary working duties to cope with. This could, for example, be on-call service with ambulance, diabetic controls as well as home nursing. Therefore the study nurses were not always present during the HCC opening hours to recruit children with otalgia for the study. The procedure with follow-up visits was also difficult to maintain due to above-
mentioned working schedules. Furthermore, the examination with study questions, examination with endoscopy and tympanometry during the visit to the outpatient office was a tedious experience for some children and their caregivers. Long, time-consuming journeys in these rural areas were another common factor causing drop-outs.

The representativeness of the study sample can be questioned and this could have a negative effect on the external validity. A record of every child who came to the HCC with otalgia during the study could have given more information about our selection and guided us in evaluating whether our included cases were representative of children with otalgia aged 2–16 years. However, such a record is lacking.

Did the children in our study have more pronounced otalgia, higher fever or a more severely affected general condition than children who did not participate? One might argue that caregivers of those children would be more likely to agree to the study to get a more thorough examination of the child and a more careful procedure with revisits. In contrast, this study showed that the children reported a fairly low degree of symptoms.

We found that 19% of the children had a normal TM and middle ear status, which is somewhat lower than the results of a study by Kontiokari et al. who reported 34% of children aged 2–6.9 years with earache as not having AOM. However, we diagnosed another 31% as OME, leaving us with 49% children with AOM compared to 64% AOM reported by Kontiokari et al. [3]. Liese et al. showed that children aged 3-5 years reported ear pain in 84% of the AOM episodes compared to 57% in children under age 2, which is in line with our results of 87% with otalgia present in children with AOM in paper IV. Hence, our findings are in line with those of other researchers regarding otalgia in AOM children and support the generalisability and external validity of our findings.

During the study period, 2003–2005, the HCCs surprisingly noted a decrease in the number of children attending with suspected AOM. Similarly a retrospective study in Sweden showed the incidence of AOM decreasing by almost 50% in children aged 2–16 years from 2000 to 2005 [4].

Symptoms were recorded based on the caregiver’s or the child’s own grading of severity. Body temperatures measured at the HCC could have improved the accuracy. However, with the temperature measured at the HCC any antipyretic drugs given prior to the visit could affect the findings. In this respect a report from the caregiver about home temperature can be regarded as more appropriate.

The study inclusion criterion was otalgia, unlike other studies on AOM which have only included children with AOM, thus giving our study a broader perspective on signs and symptoms in the selected age group related to ear symptoms.

In paper I we used three clinicians to assess the image quality, one of whom was an ENT specialist with experience in assessing TMs using otomicroscopy, and one GP. We showed that the judgement of the GP without special experience in evaluation of TM imaging and with little experience of otomicroscopic examination agreed well with the ENT specialist, supporting the generalisability of our findings.

Paper II was based on a thorough validation method using two different expert groups consisting of otologists with wide experience of TM assessments.
The internal validity of *paper IV* is strengthened by some important factors. Diagnoses made after consensus decision in our assessment group may have higher accuracy than diagnoses made separately by different clinicians. The risk of assessment bias by the clinician is thus lower than if we had used one clinician at each HCC to assess the child. In addition, the Lapland study documented the TM status with digital imaging together with tympanometry. We used a combination of symptoms and TM appearance together with tympanometry to establish the diagnoses according to current guidelines. In this study a validated grading scale (OMGRADE) for otitis media was used that also encompasses the chagrinated and perforated TM as well as the bullous TM.

**The South Africa study**

The South Africa study was designed as an observational study, but unlike the Lapland study it was based on an unselected population with no requirements of specific symptoms for inclusion, which results in a low disease prevalence. This might be regarded as a limitation as well as a strength when evaluating a new grading scale. However, no children with AOM were found in this study.

The mobility of TM was not possible to assess at the clinic due to the lack of pneumatic otoscopy and tympanometry. Gold standard diagnosis was in this study based on the otologist’s otomicroscopic assessments. An evaluation of the TM mobility would have improved the diagnostic accuracy especially for the OME. However, the sensitivity and specificity for assessing middle ear effusion with otomicroscopy alone has been estimated at 87–91% and 89–93%, respectively [5, 6].

Since the developer (TL) was involved in the testing and evaluation of the OMGRADE scale, the generalisability may be lowered. The otologist was not part of the development process of the scale but trained to use it ahead of the study. If a scale is to be used a thorough training period is vital for giving accurate results. A common method is to let the examiners test the scale a number of times until an acceptable level of agreement between examiners is reached.

In *paper III* the use of video recordings for TM assessment indirectly offers a three-dimensional view of the TM with the possibility to examine the video over and over again and to stop and move frame by frame as well as to play the recording in slow motion. We evaluated an image-based grading scale originally developed for AOM in a fairly unselected group of children with low disease prevalence. The scale’s ability to discern the normal TM is thus thoroughly tested (grades 0–3). A low disease prevalence will however affect the positive predictive and negative predictive value of a tested scale. We found a positive predictive value of 77% and a negative predictive value of 96%. With a higher disease prevalence the positive predictive value would increase. Also, a highly unbalanced portion of disease, low disease prevalence, might possibly result in a somewhat lower sensitivity.

TM images with unacceptable quality lead to the loss of documented assessable ears in *papers III and IV*. This problem is found in other studies using digital imaging technique in tele-otology [7-9]. Obscuring cerumen is also a common clinical problem in ear examinations. However, the possibility to assess images repeatedly by several reviewers may give better accuracy of the assessments than using face-to-face assessments with for example otomicroscopy.
Discussion

General discussion

Image quality

In paper I we examined the image quality of digitally stored endoscopic images of the TM and found image quality to be good. We used images from the first visit of the Lapland study. The selection of important characteristics of image quality and TM status was based on literature studies and discussions in the research group. An assessment group was selected for the evaluation of image quality. Blur and insufficient light of the image were most common in images with unacceptable overall quality whereas blur and bad composition were recorded in 26% of images with acceptable overall quality. When images were rated as being of unacceptable quality it was not possible to assess position and thickness in 95% of these images. The problem with blur was identified as a problem that could be improved with functional improvement of the camera focus. Patricoski et al. [30] designed a focus tool for easier focus adjustment. Jones [31] suggested a lens with a wider depth of field to reduce the problem with focussing.

In paper III, in total four video-otoscopy assessments were made by the otologist and the GP at two occasions. The otologist and/or the GP labelled 68 ears as “not possible to determine” in at least one of in total four video-otoscopy assessments. In 43 of these ears an evaluation was possible to make in at least one to three assessments. Thus, a fair judgment of the TM status would have been possible in a clinical situation in more ears than was included in this study. The majority of ears (76%) in this study were judged to be acceptable or better on video-otoscopy recordings. We found similar numbers or slightly higher figures in other studies [20, 21, 22].

The two main reasons for NPD at video assessment in paper III were found to be obscuring cerumen or overall low image quality, 16–20%. These figures are comparable to a study by Smith et al. [8] who found 75% to be of acceptable image quality. In contrast, Biagio et al. [7] found only 10% of video-otoscopic images to be unacceptable. That study, however, was performed on adults. Any difference in image quality may be due to differences in study population, technical equipment, the skills of the examiner and/or different discriminating criteria. The criteria for unacceptable image quality was more stringent in paper III than in paper I.

Image quality was found to increase during the three-year Lapland study period, a result that can be suspected to be due to increased skills in the study nurses. In the South African study, performed during a limited time period, only a slight increase in excellent image quality was noted. In paper I the age of the child was found to be related to image quality; the lower the image quality, the lower the age. The link between age and image quality has also been found in other studies [9, 32]. The South African study did not reveal any age difference in image quality. In the Lapland study children suffered from URI and fever or otalgia and may thus be less cooperative in the examination procedure. Furthermore, the video-otoscope used in paper III is easier to use than the equipment used for endoscopic imaging, which might decrease the compliance of the child with the examination in the Lapland study.

Paper III also indicates that video-otoscopy recordings may provide more detailed information than otomicroscopy, at least in certain cases. In video-otoscopy assessments performed by the otolaryngologist 5 and 4 ears were identified with CSOM at 4 and 8 weeks, respectively, whereas they were classified as normal by conventional otomicroscopy. Additionally, in video assessments the otolaryngologist found 6 more CSOM ears than with
Discussion

Otomicroscopy. Recordings of the TM with high resolution have the advantage that they can be reviewed repeatedly and in slow motion or frame by frame without disturbing the child.

**Telemedicine**

All of the four papers involve the telemedicine technique in some way. The technique was evaluated as working well in both paper I and paper III. The telemedicine setting in paper III was based on a simple and less costly technique and the information was sent over an insecure Dropbox application. No personal data were sent in the South African study, but ensuring personal integrity in clinical use needs other systems for transfer. In paper I a secure VPN-based technique within an intranet was used.

In paper I we concluded that the technique could be reliable and that digital imaging may offer a more objective evaluation and grading of the TM status. Furthermore, the telemedicine equipment was found to work well. Only two children were excluded due to computer problems. The nurses reported a somewhat slow connection with the central database at times. Pain was reported in endoscopic imaging by 4 children and caused lower image quality in the Lapland study that might be due to the fibre endoscope being more difficult to handle than the video-otoscope used the South African study.

In paper III four children were not cooperating at otomicroscopy and were excluded from the study, whereas only two children at the video-otoscopic examination were excluded. Video-otoscopy recordings were performed by an EHTF with no formal health care education other than the training received for this study (two days before study start) utilising portable and inexpensive video-otoscopy equipment. No technical problems were reported using video-otoscopy and the remote assessment of video-recordings via Dropbox.

In paper IV all the assessments were made remotely and asynchronously based on personal data and background data together with TM images and tympanograms. No technical problems were reported although the problem with low image quality was in some cases evident (see Image quality).

As the present studies show, telemedicine, apart from providing rural areas with health care, can be feasible to use for multicentre studies for management and collection of data [33].

**OMGRADE – an otitis media grading scale**

The OMGRADE scale was developed and validated in paper II, tested in paper III and used in paper IV. In paper II we showed a moderate intra- and inter-rater agreement in expert panel B in a test and retest situation. Furthermore, the scale was developed in a careful and meticulous procedure ensuring validity. However, the grade 2RF, together with the grades 1R and 1F, was causing lower agreement between examiners, and therefore a small revision was made, changing grade 2RF to 1RF. The revised version was found in paper III to be valid for detecting normal TMs as well as ears diagnosed as OME and CSOM. However, the scale step 1R was found to cause disagreement between the GP and the otologist. This is believed to be due to insufficient training and calibration of the two examiners before the study start, as the intra-rater agreement of the scale step was considerably higher. Still, the scale step 1R is considered to be of low clinical value and may thus be transferred to grade 0R in a new revision of OMGRADE.

The OMGRADE can be used as a 6-grade scale (0–5), or as we used it in paper IV, as a 9-grade scoring system (0–5C). The scale may also be used as a diagnostic guide together with evaluation of TM mobility through pneumatic otoscopy or tympanometry. As shown in paper
III, the sensitivity was fair and specificity excellent for discriminating OME in comparison to diagnoses made by an otologist using otomicroscopy. The positive predictive value and negative predictive value was adequate but the generally low disease prevalence of paper III may have led to the lower positive predictive value.

Agreement and concordance on the grading of TM appearance using the OMGRADE scale found in our study was regarded as substantial and almost perfect although there was some disagreement between the examiners. Patricoski et al. [9] found kappa values ranging from 0.67 to 0.76 between face-to-face examination and assessment of video-otoscopic images. Intra-rater diagnostic agreement was 0.81. These agreement figures are in line with what we found in our study on grading TM status using the OMGRADE scale. Clinical evaluations that are based on sole visual findings are more difficult to reach reasonable agreement upon and will cause dispute about the interpretation of the findings to some degree. An image-based grading scale gives visual references for the reviewers to adhere to which will increase the precision of an assessment of the TM appearance.

**Study population**

We studied children aged 2 to 16 in the Lapland and the South African study; the mean age was 6.8 and 6.4 years, respectively. Both studies included more boys, 56%, than girls. Otitis media is slightly more common in boys than girls [10], which corresponds well to the findings of the Lapland study in which 57% of the children with AOM of any type were boys. The children with AOM of any type were found to have a mean age of 5.4 years, compared to the children with normal ears, mean age 8 years. In the South African study no AOM children were included but rather children with OME and CSOM.

In the Lapland study the children reported a median of 3 AOM episodes prior to the visit. However, we have no information about during which time span these occurred so no conclusions about rAOM can be drawn from these numbers. Other investigations have shown that 20% of children have experienced at least 3 AOM episodes before the age of 5 years [10]. In our study 11 of 27, 40%, younger than 5 years reported to have experienced 3 or more previous AOM episodes (unpublished data) indicating that the children included in our Lapland study may be a selection of more otitis-prone children.

**Symptoms**

In paper IV otalgia was reported to be present in 73% of the children at the first visit. Rhinitis was the most commonly reported URI symptom (75%) followed by cough (48%). These findings are in line with those of Arola et al. [11] except for otalgia (47%), which is obviously due to our inclusion criteria. In the study by Heikkinen et al. [12] 40% of children with AOM did not report any otalgia.

One may question that only 73% reported otalgia at the first visit. However, all the children included in our study suffered from otalgia when deciding to seek health care. Thus, otalgia was present in all children at least 48 hours before the first visit. From clinical experience it is common that children are affected by otalgia during the night but that the otalgia may have resolved the next morning when the doctor sees the child.

The finding in paper IV that 51% of the children with otalgia were not diagnosed with AOM is interesting. Niemela et al. [13] found that ear-related symptoms were found in 72% of children without AOM compared to 90% in children with AOM. In line with other studies [3, 12, 14, 15] our results seem to indicate that otalgia can be found in children with URI but without ear disease.
In *paper IV* fever was reported at the first visit in 22% of the children and in 33% of children with AOM (unpublished data). In comparison, other studies [11, 12] show that fever was found in 30–69% of children with AOM. However there is a difference in age representation compared to these other studies as we studied older children.

In the present study high fever, temperature >39°C, was found in only 4 children, all diagnosed as AOM. Hearing impairment was reported by the children with AOM, pAOM and OME, but not by the children with normal ears or BM/bAOM.

### Diagnoses

Of the 63 children in the Lapland study AOM was diagnosed in 48%. Of the various AOM types 37% was AOM, 10% BM, 13% bAOM and 40% pAOM. The chagrinated and wet TM seen in pAOM children in our study may be regarded as signs of TM perforation. In the study by Liese et al. [2] an AOM with ear discharge was found in 26.5% of all AOMs of the Swedish children aged 0-5 years. In contrast, Leibovitz [16] found a perforated AOM in 15% of children under age 3 in Israel. In the retrospective study of medical charts by Liese et al. no descriptions of the TM status were presented and it is not clear if they defined the ear discharge based on ear examinations, as in our study, or if it was based on parent reports.

The bullous AOM, or the bullous myringitis, is estimated to be present in less than 10% of AOMs [17, 18]. These figures are in line with our findings of 14% diagnosed as BM/bAOM.

We diagnosed 20 children, 32%, as having OME. In children with URI Chonmaitree et al. [19] found that 24% experienced OME and 37% AOM. These authors used acute onset of symptoms, inflammation of TM and middle ear fluid as the criteria for the AOM diagnosis. The inflammatory signs of the TM were not described, however. In a study by Shaik et al. 7 experienced physicians examined 135 TM images and diagnosed and described the appearance of an inflammatory TM using specified characteristics of which redness was one. Marked redness was found in 58% of AOM and 22% of OME. An opaque and reddened TM in a normal position was more often diagnosed as OME than AOM, 10.6% versus 1.2%.

Marked redness together with a bulging, opaque and discoloured TM was found in 43% of AOM and 0.5% in OME in comparison to no redness but a bulging, opaque and discoloured TM in 29.9% and 2.2% respectively. The TM appearance of the OME children in *paper IV* was in the range OMGRADE scale step 1F–3, that is, a transparent TM with a visible fluid level or an opaque TM in a normal position.

In *paper III* we examined the TM status in children attending an HCC for any reason. With the inclusion and exclusion criteria applied no AOM was found. On-site CSOM was oto-microscopically diagnosed in 5%, OME in 11% and normal ears in 84%. This high number of CSOM is in line with prevalence figures presented for Africa by WHO: 3–6% [20]. The high prevalence of HIV in this area may have an impact on the number of CSOM. The low number of AOM is somewhat surprising but may be explained by the low access to health care in this area of Johannesburg. Furthermore, it is feasible to assume that ear pain in contrast to e.g. a draining ear is not a reason for seeking health care in this population. Considering the risk factors that the study population lives under, such as overcrowding, poor hygiene, poor nutrition, exposure to charcoal and wood smoke, we expected more AOM to be found in this study.
Severity
The AAP guidelines [21] describe a severe AOM as a unilateral/bilateral AOM in a child older than 6 months presenting with severe symptoms such as moderate or severe otalgia and a temperature of $\geq 39^\circ C$. Of the 13 children in paper IV who reported severe otalgia and or temperature $>39^\circ C$, 11 were diagnosed as AOM of any type, but two with severe otalgia were diagnosed as normal ears. The four children in our study who reported a temperature $>39^\circ C$ all reported moderate to severe otalgia and were diagnosed as AOM, pAOM or bAOM.

Children with bilateral AOM reported slightly more fever and otalgia than children with unilateral AOM. McCormick et al. [22] studied laterality in children, mean age 1.7 years, and found no differences in reported symptoms or measured temperature but slightly higher TM scores (OS-8). Rovers et al. [23], in a meta-analysis of 6 randomised trials, showed that children under 2 years with bilateral AOM were more likely to report persistent symptoms. Uitti et al. [24] showed that children with bilateral AOM reported more fever than children with unilateral AOM. In our study 3 of 6 children with bilateral AOM also reported hearing impairment.

Course of signs and symptoms
We followed 29 children at 4 visits and identified the children with a chagrinated TM (as described in OMGRADE scale step 5C and diagnosed as pAOM) as having prolonged TM changes and type B tympanograms. Forty per cent of them still had type B tympanograms after 3 months. In the study by Teele et al. [25] only 10% of children with AOM had middle ear effusion after 3 months. Our finding is important; just by evaluating the TM appearance a more severe course of AOM was identified. A common view among otologists is that a chagrinated TM is a sign of a perforated AOM. This is supported, for example, by Neumark et al. [26] but more studies may be needed to certify this assumption. The chagrinated TM, with swollen keratin patches and a highly deformed structure of the TM, might be a sign of a more locally aggressive infection. Attempts to identify clinical differences between different bacterial pathogens have been made although no study has shown a strong correlation between pathogen and the clinical presentation of the AOM.

We found that symptoms such as fever and otalgia resolved more quickly than TM changes and tympanograms. This is in line with the findings of Hotomi and Harabuchi [28, 29]. Based on these findings a conclusion may be drawn that TM appearance and TM mobility are more important to evaluate than symptoms in grading the severity of AOM as well as setting the diagnose AOM.

Clinical implications
Grading the severity of AOM by signs and symptoms has been evaluated in a number of studies [28, 29, 34-38]. We showed that a chagrinated TM took longer to normalise regarding TM appearance as well as tympanometry. Children with bilateral AOM were more likely to report high fever and severe otalgia and children with high fever and/or severe otalgia were more likely to be diagnosed with AOM. Interestingly, children with normal ears also reported severe otalgia. As in other studies [52, 54], we were able to show that otalgia is common among children with URI without apparent ear pathology.

In line with other studies, my thesis shows that evaluation of symptoms may be of minor value in determining the diagnosis AOM. In this perspective an image-based grading scale such as OMGRADE may contribute to improving the diagnostic accuracy. I have shown that
the OMGRADE scale can be used as a grading instrument to follow TM appearance in clinical routine as well as research, and both at the outpatient office and at a distance by tele-otology.

Additionally, this thesis has shown the usability of tele-otology in providing rural areas with otological health care, areas in which the alternative may be no otological health care at all. Together with my collaborators, I have shown that a trained nurse or health facilitator may provide high-quality images of TM, tympanometry and clinical patient reports over the Internet.

**Future research**

The rapid emerge of new imaging technology that provides high quality at a lower cost is promising. Smartphones can now be used in a telemedical setting for otoscopy, hearing screening, CD4 counts of HIV patients or as a stethoscope, spirometer, pulse oximeter, to mention just some clinical extensions. This opens an enormous possibility to serve rural and poor areas with better health care in general as well as otological health care. This new area needs further development and research before it is implemented in the everyday clinic. The focus must be on bringing health care closer to the ones with the most needs. A study using smartphones for TM imaging and hearing test is planned at the University of Pretoria.

The OMGRADE scale has been validated and tested. Still, more research on its usefulness, reliability and validity is needed. A further investigation of the scale’s responsiveness to change of TM appearance is one aspect as well as testing the scale versus the OS-8 or the more traditional scoring systems. Can the OMGRADE scale be used to improve the clinician’s diagnostic accuracy?

The chagrinated TM and the difference in the course of the illness that is shown in this thesis need to be elucidated further. Furthermore, the course of the AOM would be interesting to study further in the aspect of severity grading of AOM in relation to the need for antibiotic treatment.
Conclusions

• Video-endoscopic images by a trained nurse were found to be of good quality for possible remote assessments.

• Video-otoscopic recordings taken by a trained facilitator of the tympanic membrane were found to be of good quality, with findings indicating that video-otoscopic recordings on some occasions may be more informative than otomicroscopy.

• TM characteristics such as position and transparency were found to be important for the evaluation of acute otitis media, and wax was a common problem in TM assessment.

• The OMGRADE scale, a new grading scale for acute otitis media, was developed, validated and tested in a telemedical setting.

• The OMGRADE scale was found to correlate well to diagnosis made otomicroscopically by an experienced otologist for normal ears and OME.

• The OMGRADE scale together with tympanometry was efficient in diagnosing a variety of otitis media conditions in children.

• The chagrinated TM was found to be associated with a prolonged course of TM changes and abnormal tympanometry indicating a more severe form of AOM compared to the bulging AOM or the bullous AOM.

• Symptoms resolved more quickly than TM changes, and otalgia was common not only in children with AOM but also in children with normal ears.
Acknowledgements

I would like to express my sincere gratitude to everyone who have helped, encouraged and supported me on my scientific journey. In particular, I would like to thank:

The children and caregivers for their patience and willingness to participate in these studies.

Herbert Sandström, my main supervisor, for your gentle and positive academic and scientific guidance, your endurance during all these years and your sound thoughts on my, sometimes, erratic ideas. Thank you for your support and encouragement in managing the projects as well as your friendship and being an excellent travel companion.

Sten Hellström, my second supervisor, for your everlasting energy in making science, your scientific skills and your wide knowledge about the tympanic membrane. Thank you for your calm and wise guidance and encouragement into the scientific world of otitis media during these years.

Claude Laurent, my third supervisor, for boosting the project with your positive energy, everlasting enthusiasm and wide knowledge about the TM and middle ear, for showing me the African sun and opening my eyes to a new world. Thank you for your friendship, hospitality and superb travel guidance.

Lars-Hjalmar Lindholm, for encouragement and everlasting enthusiasm and for inspiring to do research in Family medicine.

The National research School in Family Medicine, for boosting with scientific knowledge, inspiring meetings with other research students in Family medicine and keeping the spirit up. Special thanks to Maria Boström for keeping the sheep on track with a smile and all your help, to Olov Rolandsson and your colleagues for keeping the research school running and of course to Lars-Hjalmar Lindholm for the launch and start-up of the excellent school.

Peter Berggren and Carina Keskitalo (Storuman), Anders Wennberg (Malå), Eva Mårtensson (Dorotea) and Pia Edlund (Åsele) for your help and all your excellent work at the HCC’s in the Lapland study. Thank you for taking care of the children and their caregivers as well as reporting and keeping track of the data transfer.

Per-Olof Eriksson, for our interesting discussions about the tympanic membrane and its appearance and for your skilled assistance in paper I and II.

Hans Stenlund, for gentle but important statistical advice.

Violet Mugodo, for your cheerful kindness and for your help with recruiting children and performing video-otoscopy at the Witkoppen health and welfare clinic, Johannesburg.

De Wet Swanepoel, for your inspiring scientific rigour and our rewarding collaboration. Thank you for your hospitality and friendship and for letting me get to know your beautiful family.
Acknowledgements

Leigh Biagio, for being a patient co-research student and for your help with writing science. Thank you for your delighted companionship, friendship and superb hospitality. Good luck with your thesis!

Eva Westman, Lars Hallen, Ann Hermansson, Ove Söderström, Britt-Inger Wennberg and Joakim Grendin for your help in the expert groups and for enthusiastic and interesting discussions about TM appearance.

Anitha Groth, for your enthusiasm, encouragement and wise comments.

Sonja-Lis Westman, for your support on this scientific journey when patients and colleagues perhaps needed me more at the HCC.

Colleagues Gunnar Åström, Zeynab Terhani, Benny Holmberg, Thomas Ek, Peter Lindblom, Maria Öhman and Cajsa Portin and all co-workers at Backens Hälsocentral for putting up with my scientific leaves and for taking care of my patients so well.

Colleagues and co-workers at Tegs Hälsocentral.

Jean Bassett, (executive director) and the rest of the Witkoppen Health and Welfare Clinic management, staff, and patients.

Headley Isserow at Tecmed South Africa for providing the Leica otomicroscope to the Witkoppen clinic.

The Department of Speech-Language Pathology and Audiology, University of Pretoria, for inviting me to your department and for your hospitality.

Marie Hammarstedt and The Division of Family Medicine, Department of Public health and Clinical medicine, Umeå University for support and scientific guidance.

My supportive in laws, Sigrid and Mårten

My caring mother and father, Svea and Harry

Adam and Amanda for being who you are and supplying our house with music, life and new aspects of the world.

Last but not least, thank you Pernilla for your energy, love and enthusiasm.

This work was supported by grants from:
The County Council of Västerbotten Forskning och utveckling – FoU, Umeå ITHS2
The Kempe foundation
References


References


References

120. SSB, Folkmångd i hela riket, länen och kommunerna 31 december 2005.
121. J., C., Dainfern And Diepsloot: Environmental Justice and Environmental History in Johannesburg, South Africa. . Environ Justice [Internet]., 2008 Sep

Appendix A

Description of expert panel A questionnaire. Each Item and Scale step were reviewed with these questions.

<table>
<thead>
<tr>
<th>Item description</th>
<th>Not relevant</th>
<th>Can not assess relevance without revision</th>
<th>Relevant but needs slight revision</th>
<th>Very relevant</th>
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<td>Wording of Items</td>
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</tr>
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<td>Clarity of the description of each item</td>
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<td>Item reflect clinically defined entity of inflammatory changes in TM</td>
<td></td>
<td></td>
<td></td>
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<td>Image of scale step correlate to description of scale step</td>
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### Appendix B

**OMgrade scale**

<table>
<thead>
<tr>
<th>OMgrade</th>
<th>Opaque TM</th>
<th>Opaque FL</th>
<th>Fluid level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Transparent TM in normal position and with no visible fluid level</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>1F</td>
<td>Retracted FL</td>
<td>Transparent fluid level AND retraction</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>1RF</td>
<td>Retracted</td>
<td>Transparent FL with visible fluid, with or without retraction</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>2</td>
<td>Opaque</td>
<td>Opaque FL</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>3</td>
<td>Opaque</td>
<td>Opaque and bulging</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>4</td>
<td>Bulging</td>
<td>Bulging</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>5B</td>
<td>Bullous</td>
<td>Bullous</td>
<td>Viable fluid level</td>
</tr>
<tr>
<td>5C</td>
<td>Chagrinated</td>
<td>Chagrinated with opaque, wet surface</td>
<td>Viable fluid level</td>
</tr>
</tbody>
</table>

- **5B**: Bullous
  - TM is completely opaque and with fluid.
- **5C**: Chagrinated
  - TM is completely opaque, wet surface and with fluid.
- **4**: Bulging
  - TM is completely opaque and bulging.
- **3**: Opaque
  - TM is completely opaque and in a fairly normal position.
- **2**: Opaque FL
  - Transparent TM with visible fluid.
- **1F**: Retracted FL
  - Transparent fluid level AND retraction.
- **1RF**: Retracted
  - Transparent position.
- **0**: Normal
  - Transparent TM in normal position and with no visible fluid level.