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To parents

ABSTRACT

Nora Erkkola-Anttinen

Parental role in the diagnostics of acute otitis media

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Acute otitis media (AOM) and its suspicion are the leading pediatric reasons for physician visits. Tympanometry and spectral gradient acoustic reflectometry (SG-AR) are the traditional adjunctive tools to detect middle ear effusion (MEE), a prerequisite for AOM. Smartphone-enabled otoscopy is a novel tool for consumer use. This thesis aimed at assessing parent-performed examinations in the diagnostics of AOM.

Parents were taught to examine their child (6–35 months) with these devices. The diagnostic accuracy of 423 tympanometric (I) and 614 SG-AR (II) parent-performed examinations were compared to physician-performed examinations. SG-AR level changes between 361 paired SG-AR measurements were examined and related to changes in middle ear status (III). Physician-performed pneumatic otoscopy served as the diagnostic standard (I-III). The diagnostic quality of 1,500 parent-performed smartphone otoscopy videos were analyzed (IV).

Parents performed home examinations with high success rates. Parents detected and excluded MEE with a flat and any peaked tympanogram as reliably as physicians. In symptomatic children, the positive predictive value of SG-AR levels 4–5 to detect MEE was 88%. If there was no change in the SG-AR level in an initially healthy ear, AOM was effectively excluded. In symptomatic children, physicians detected or excluded AOM in 87% of parent-performed smartphone otoscopy videos.

Parent-performed home examinations could be useful in the diagnostic chain of AOM. Future studies should assess their clinical usefulness and resource savings within primary care and families if children who need a visit to a physician because of suspected AOM could be identified by parent-performed home examinations.

Key words: acute otitis media, middle ear effusion, tympanometry, spectral gradient acoustic reflectometry, smartphone otoscopy, diagnostics, telemedicine, children, parents, primary care.

TIIVISTELMÄ

Nora Erkkola-Anttinen

Vanhempien rooli lapsen äkillisen välikorvatulehduksen diagnostiikassa

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastentautioppi, Turun kliininen tohtoriohjelma; Lasten ja nuorten klinikka, Turun yliopistollinen keskussairaala, Turku, Suomi

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Lapsen äkillinen välikorvatulehdus ja sen epäily ovat yleisimpiä lääkärille hakeutumisen syitä. Tympanometri ja akustinen reflektometri ovat perinteisiä välikorvaeritteen, äkillisen välikorvatulehduksen diagnostisen kriteerin, havaitsemiseen käytettäviä apuvälineitä. Älypuhelinotoskooppi on kuluttajien käyttöön suunnattu uusi korvatutkimusmenetelmä. Väitöskirjan tavoitteena oli tutkia vanhempien tekemiä tutkimuksia äkillisen välikorvatulehduksen diagnostiikassa.

Vanhemmat opetettiin tutkimaan 6−35 kuukauden ikäinen lapsensa näillä laitteilla. Vanhempien 423 tympanometri- (I) ja 614 reflektometritutkimuksen (II) diagnostista luotettavuutta verrattiin lääkärin vastaaviin tutkimuksiin. Kahden reflektometrimittauksen välistä tasomuutosta tutkittiin välikorvan statuslöydöksen muutoksen merkkinä. Lääkärin pneumaattinen otoskopia toimi diagnostisena standardina (I-III). Vanhempien suorittamien 1,500 älypuhelinotoskopiavideoiden diagnostinen laatu analysoitiin tutkimuksessa IV.

Vanhempien onnistumisprosentti kotitutkimuksissa oli korkea. Vanhemmat havaitsivat tasaisella ja poissulkivat huipukkaalla tympanogrammilla välikorvaeritteen yhtä luotettavasti kuin lääkärit. Oireisella lapsella reflektometritasojen 4−5 positiivinen ennustearvo välikorvaeritteen toteamiselle oli 88 %. Alkujaan terveessä korvassa parimittauksien muuttumaton reflektometritaso käytännöllisesti katsoen poissulki äkillisen välikorvatulehduksen kehittymisen. Oireisella lapsella lääkärit pystyivät toteamaan tai poissulkemaan äkillisen välikorvatulehduksen 87 %:ssa vanhempien älypuhelinotoskoopilla kuvaamista videoista.

Vanhempien tekemät kotitutkimukset voisivat olla käyttökelpoisia äkillisen välikorvatulehduksen diagnoosiketjussa. Tulevien tutkimusten tulisi selvittää niiden kliinistä käyttökelpoisuutta, perusterveydenhuollon ja perheiden resurssien säästöä, kun vanhemmat voisivat kotitutkimuksin tunnistaa ne lapset jotka tarvitsevat lääkärivastaanottoa äkillisen välikorvatulehduksen epäilyn vuoksi.

Avainsanat: äkillinen välikorvatulehdus, välikorvaerite, tympanometri, akustinen reflektometri, älypuhelin otoskopia, diagnostiikka, telelääketiede, lapset, vanhemmat, avoterveydenhuolto

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ABBREVIATIONS

AOM	acute otitis media
CI	confidence interval
CSOM	chronic suppurative otitis media
daPa	deca-Pascal
ENT	ear-nose-throat
ET	Eustachian tube
GP	general practitioner
MEE	middle ear effusion
mHealth	mobile Health
nMEP	negative middle ear pressure
NPV	negative predictive value
OCT	optical coherence tomography
OM	otitis media
OMGRADE	image-based grading scale for AOM
OME	otitis media with effusion
PCV	pneumococcal conjugate vaccine
PPV	positive predictive value
RTI	respiratory tract infection
SAA	static acoustic admittance
SG-AR	spectral gradient acoustic reflectometry
SWIR	shortwave infrared light otoscope
TEOAE	transient evoked otoacoustic emissions
TPP	tympanometric peak pressure
VO	video otoscopy

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-IV. Some unpublished data are also presented.

I. Erkkola-Anttinen N, Tähtinen PA, Laine MK, Ruohola A. Parental role in the diagnostics of otitis media: can parents be taught to use tympanometry reliably? *Int J Pediatr Otorhinolaryngol.* 2014; 78:1036-9.

II. Erkkola-Anttinen N, Laine MK, Tähtinen PA, Ruohola A. Parental role in the diagnostics of otitis media: Can layman parents use spectral gradient acoustic reflectometry reliably? *Int J Pediatr Otorhinolaryngol.* 2015; 79:1516-21.

III. Erkkola-Anttinen N, Tähtinen PA, Laine MK, Ruohola A. Can changes in parentally measured acoustic reflectometry levels predict the middle ear status? *Int J Pediatr Otorhinolaryngol.* 2017; 95:72-74.

IV. Erkkola-Anttinen N, Irjala H, Laine MK, Tähtinen PA, Löyttyniemi E, Ruohola A. Smartphone otoscopy performed by parents. Submitted.

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1 INTRODUCTION

Otitis media (OM) is one of the most frequent causes for families to seek medical care for their young child and places a great burden on both families and primary health care systems worldwide (Monasta et al. 2012, Greenberg et al. 2003). Children are most susceptible to acute otitis media (AOM) during the three first years of their life because AOM is usually related to a respiratory tract infection (RTI) (Klein 1994, Heikkinen and Ruuskanen 1994, Chonmaitree et al. 2008a). In Finland in 1990's, some 500,000 annual episodes of OM occurred in children aged six months to seven years (Niemelä et al. 1999). According to a Finnish primary care report, the annual number of OM-related physician visits in 2014 at health care centers was over 130,000 (Saukkonen and Vuorio 2016).

Because the symptoms of AOM and RTI overlap, young children are often brought for consultation when parents suspect AOM. AOM cannot be predicted only on the basis of the child's symptoms, and only approximately half of the children do have AOM when parents suspect it (Laine et al. 2010). Parents have no tools to distinguish children who actually need to see a physician because of AOM from those who do not.

One of the three diagnostic criteria of AOM is the detection of middle ear effusion (MEE); the two others are acute inflammatory signs on the tympanic membrane and rapid onset of symptoms (Lieberthal et al. 2013). Physicians perform pneumatic otoscopy to examine the middle ear. The tympanometer and the spectral gradient acoustic reflectometer (SG-AR) are non-invasive, handheld devices physicians may use to detect MEE. Neither of these devices provides visual access into the ear canal or the tympanic membrane. Rather, they provide objective, quantitative and graphic information related to the presence or absence of MEE (Brookhouser 1998, Kimball 1998). As diagnostic tools, they are easy to use in the clinical setting, provided that the child is cooperating.

The value of implementing telemedicine into pediatric care has been emphasized (Marcin et al. 2015). Mobile technology has produced devices and applications which improve access to care and provide rapid answers to questions on health and diagnostics. New and innovative smartphone-enabled otoscopes which generate video recordings or images from the tympanic membrane have been introduced.

Primary care resources are limited and there is a growing need to reconsider how society best provides primary care services. If parents could reliably exclude or detect MEE by tympanometry and SG-AR or AOM by smartphone otoscopy, primary care resources could be reallocated and the family burden reduced.

However, there is a lack of research on how well parents perform such examination.

The aim of this thesis was to examine parental use of tympanometry, SG-AR and smartphone otoscopy in the diagnostic chain of AOM. The three first studies are parts of a large AOM trial among children 6–35 months of age (Tähtinen et al. 2011). The fourth study, the MobiiliKorva-study, is the first study to examine parental smartphone otoscopy in the diagnostics of AOM.

2 REVIEW OF LITERATURE

2.1 Definitions of otitis media

Otitis media (OM), also known as middle ear inflammation, is an umbrella concept for otitis media with effusion (OME), acute otitis media (AOM) and chronic suppurative otitis media (CSOM) (Bluestone and Klein 2007). Common for these conditions is the presence of MEE (Bluestone et al. 2002, Bluestone and Klein 2007), but their symptoms, clinical findings, diagnostic criteria and treatment differ significantly.

MEE is defined as liquid in the middle ear of any etiology, consistence or duration (Bluestone and Klein 2007).

OME is traditionally defined as the presence of MEE behind a tympanic membrane without signs or symptoms of acute infection (Rosenfeld et al. 2013). OME complicates approximately 25% of RTI episodes (Chonmaitree et al. 2008b). OME is defined as chronic when MEE has persisted for more than 3 months (Rosenfeld et al. 2013).

AOM is defined as MEE behind a tympanic membrane with acute inflammatory signs and a rapid onset of symptoms. AOM is defined as recurrent when three or more separate episodes of AOM have been diagnosed within the preceding 6 months or four or more episodes within the preceding 12 months with one or more episodes in the past 6 months (Lieberthal et al. 2013).

CSOM is defined as a chronic inflammation of the middle ear and mastoid mucosa with persistent discharge through a perforation of the tympanic membrane, usually caused by AOM (Verhoeff et al. 2006). There is, however, no consensus on the mean duration of the ear discharge which may vary from two to six weeks (Goycoolea et al. 1991, Acuin 2006, Roland 2002).

2.2 Pathogenesis

The pathogenesis and etiology of OM are multifactorial. There are overlapping etiological factors related to the host (anatomy, age, genetics and immature immunity system) and to the environment (siblings, seasonality, day care, viral and/or bacterial microbial predisposition). Immaturity of the immune system together with Eustachian tube (ET) dysfunction are the most essential factors involved in the pathogenesis of OM (Bluestone 1996, Rovers et al. 2004).

In general, pathogens must overcome several barriers before active disease develops. They must adhere, invade and enter the epithelium, and finally overcome the defensive mechanisms of the epithelium and immune system.

2.2.1 Anatomy

The human ear can be divided into three parts: the outer, middle and inner ear **(Figure 1)**. The outer ear includes the ear lobe (pinna) and the external ear canal. The tympanic membrane (eardrum) separates the outer ear from the middle ear. The middle ear comprises the gas-filled middle ear cavity and the ossicles (malleus, incus and stapes). The malleus is attached to the tympanic membrane. The oval window connects the middle ear with the inner ear (cochlea and vestibular system). Gas-filled mastoids are connected to the middle ear. The ET connects the middle ear cavity with the nasopharynx (Bluestone and Klein 2007).

The anatomical dimensions of the ET differ with age. In children less than 1 year old, the length, width and orientation of the ET, which is still not full-grown, predispose the youngest to OM (Bluestone and Klein 2007). The angle and length of the ET increase during the child's growth from 10° to 45° and from 13 mm to 35 mm, respectively (Proctor 1967, Ishijima et al. 2000). The mature dimensions are achieved by age 7–10 years (Sadler-Kimes et al. 1989, Bluestone and Klein 2007).

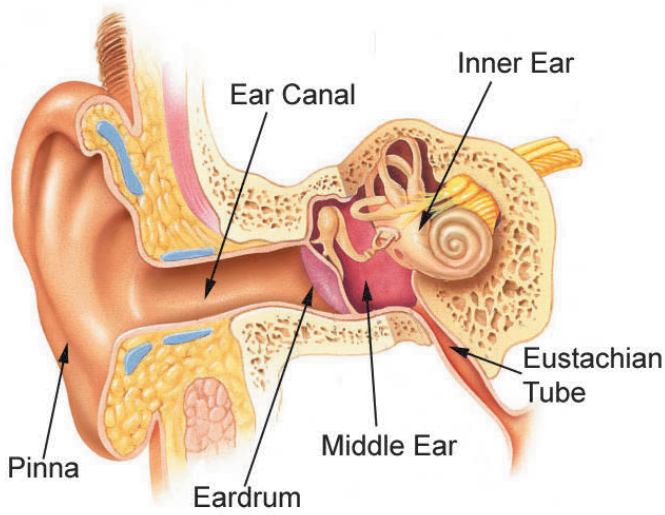


Figure 1. Anatomy of the ear. Source: http://www.kids-ent.com/pediatricent/ear_infections/

2.2.2 Function of the Eustachian tube

The ET serves as a channel between the middle ear cavity and the nasopharynx. It is a tube-shaped structure with a mucous lumen surrounded by cartilage, soft tissue, muscles and a bony support (Bluestone and Klein 2007).

The ET and middle ear cavity do not contain pathogenic bacteria during health, and normal function of the ET is important for maintaining a healthy middle ear (Lim et al. 2000, Bluestone and Klein 2007). The ET has three important functions: ventilation, protection and clearance (Bluestone and Klein 2007).

The ET is usually closed, but opens briefly when a person swallows or yawns. The ET functions as a pressure (ventilation) equilibrator and provides aeration between the middle ear and the ambient air (Lim et al. 2000, Bluestone and Klein 2007). This function is most important, because hearing is optimal when the pressure is the same within the middle ear cavity and the external auditory canal, *i.e.,* the atmospheric air (Bluestone and Klein 2007).

The anatomical structure and mucociliary defense of the ET protects the middle ear from secretions and from pathogens arising from the nasopharynx. In addition, the ET clears secretions which are produced in the middle ear and drains them to the nasopharynx by muscular pumping systems and mucociliary flow. These actions direct secretions from the middle ear cavity through the ET to the nasopharynx (Bluestone and Klein 2007). Respiratory mucosa composed of ciliated epithelial cells covers the middle ear and the ET. Together with goblet cells, they provide innate immunity molecules and mucoid and serous mucus (Lim et al. 2000, Schilder et al. 2016).

2.2.3 Viral respiratory tract infection

The common cold, *i.e.,* RTI, is usually a mild and self-limited, upper airway viral infectious disease. Usually it lasts for 5–10 days, but it may exceed a couple of weeks in duration. RTIs occur globally and create a substantial public health and economic burden throughout the world. In Finland, the average number of annual viral RTI episodes in children younger than 2 years was 5 in a prospective cohort study (Toivonen et al. 2016). A viral RTI usually precedes the development of AOM by causing ET dysfunction (Bluestone and Klein 2007).

The pathogenesis of a viral RTI is a cascade of events. The host must be exposed to a virus directly or indirectly. Usually this happens from person-to-person via released infective viral pathogens by air (coughing or sneezing) or hand transfer

(Hodinka 2016). After the virus has entered the host cell in the respiratory epithelium, it damages the mucosa of the respiratory epithelial cells, impairs the mucociliary function and induces cytokine activity and inflammatory mediators in the nasopharynx and ET (Massa et al. 2009, Patel et al. 2009, Schilder et al. 2016). Viruses also increase the number of host cell surface antigens to which bacteria can adhere (Bakaletz 2010). Because of this cascade, the normal function of the ET is disturbed which leads to a negative middle ear pressure. A negative middle ear pressure may enhance the invasion of viruses and bacteria into the middle ear and thus promote the development of AOM (Bluestone and Klein 2007).

A viral RTI is very common among young children and is followed by bacterial complications, such as AOM, in 29–50% of RTI episodes (Heikkinen and Ruuskanen 1994, Koivunen et al. 1999, Winther et al. 2006, Chonmaitree et al. 2008a). This explains the high incidence of AOM worldwide. The development of AOM peaks within 3–4 days from the onset of RTI (Heikkinen and Ruuskanen 1994, Koivunen et al. 1999, Chonmaitree et al. 2008b). It is noteworthy that even viruses alone can induce AOM (Chonmaitree et al. 1986) and approximately 10% of AOM in children may be solely of viral origin (Revai et al. 2007). Although some viruses occur all year around, the seasonality of viral infections explains why RTIs and AOMs peak in the winter season (Vesa et al. 2001).

The most important respiratory viruses related to AOM are the respiratory syncytial virus, rhinoviruses, adenoviruses, human coronavirus, boca virus, influenza viruses, parainfluenza viruses, enteroviruses and human metapneumovirus (Chonmaitree et al. 2008b, Nokso-Koivisto et al. 2015). The signs and symptoms generated by infections caused by these viruses overlap and resemble one another. It is virtually impossible to determine which specific virus causes AOM by clinical examination alone and, in most cases, this it is neither necessary nor economically feasible, since the clinical course of RTI and AOM episodes is usually mild. However, specific viral diagnostics could be important for patients with immunodeficiency and the identification of a specific virus could guide patient care and optimize the use of antibiotics (Hodinka 2016).

The importance of viral vaccines against viral RTIs for the prevention of AOM has been discussed (Heikkinen et al. 1999, Heikkinen 2000). To date, influenza vaccine is the only vaccine against viral RTIs. A study on the efficacy of influenza vaccination for prevention of AOM associated with influenza virus reported an 83% decrease in the incidence of AOM associated with influenza A in the vaccine group compared to the non-vaccine group, and a 36% reduction in overall AOM morbidity in the vaccine group (Heikkinen et al. 1991). Heinonen and colleagues have found that when oseltamivir treatment is started within 12 hours of symptom onset, the incidence of influenza virus induced AOM is reduced by 85% in children

with any influenza and by 79% in children with influenza A (Heinonen et al. 2010). However, a pooled analysis of eight randomized influenza vaccine trials concluded that an intranasally administered live attenuated influenza vaccine reduced all-cause AOM only by 7.5% compared to placebo (Heikkinen et al. 2013). In conclusion, appropriate vaccination against influenza may affect significantly the frequency of AOM.

2.2.4 Bacterial pathogens

AOM is largely a bacterial disease. The usual bacterial pathogens causing AOM are *Streptococcus pneumoniae* (*S. pneumoniae*), nontypeable *Haemophilus influenza* (*H. influenzae*) and *Moraxella catarrhalis* (*M. catarrhalis*) (Coker et al. 2010, Ngo et al. 2016). However, it is noteworthy that none of these bacteria are capable of causing inflammation without immune dysfunction of the host or epithelial rupture. In other words, colonization is not a sufficient cause for an active infection (Peters et al. 2012).

S. pneumoniae is the most frequently detected (25–50%) bacteria in AOM (Klein 1994, Ngo et al. 2016). It is more likely to cause more ear pain and higher fever (≥ 38°C) than the other bacterial pathogens (Howie et al. 1970, Harley et al. 1997, Rodriguez and Schwartz 1999, Palmu et al. 2004).

H. influenzae is the second most common bacterium (15–30%) in MEE of children worldwide (Klein 1994, Ngo et al. 2016). *H. influenzae* is often related to chronic, recurrent or bilateral AOM, eye symptoms and failed antibiotic treatment (Howie et al. 1970, Palmu et al. 2004).

M. catarrhalis is often part of a polymicrobial infection, in contrast to *S. pneumoniae* and *H. influenzae.* A 7-year study found that *M. catarrhalis* relates more often to milder symptoms and the first AOM of younger children (Broides et al. 2009). *M. catarrhalis* is detected in 3–20% of AOM episodes (Klein 1994, Ngo et al. 2016).

Streptococcus pyogenes, or *group A β hemolytic streptococcus (Strep A)* has a history of predominating as an AOM pathogen (Bluestone et al. 1992). At present, it is found in 1−4% of MEE samples in children with AOM (Palmu et al. 2004, Segal et al. 2005). *Strep A* relates more often than other AOM pathogens to older children (≥ 24 months) with fewer signs of RTI symptoms, unilateral AOM, spontaneous perforation of the tympanic membrane and to the risk acute mastoiditis (Segal et al. 2005).

Bacteria form biofilms attached to the mucosal surface of the respiratory epithelial cells. These biofilms probably explain the chronic nature of many otorhinolaryngologic infectious diseases and antibiotic treatment failures. Since these bacterial colonies reside in a matrix, they are protected from the immune system and the effects of antibiotic treatment (Cayé-Thomasen et al. 2013). Previous studies have shown that biofilms are present in the adenoids of children with chronic OME (Saylam et al. 2010), in removed tympanostomy tubes (Post 2001) and in the middle ear mucosa of children with recurrent OM (Hall-Stoodley et al. 2006). Although studies have identified the important role of biofilm formation for chronic OM, biofilms are probably also important in the pathogenesis of AOM (Bakaletz 2012).

Viral and bacterial coinfections are important in the development of AOM. Bacteria and viruses were present in 66% of the MEE and nasopharyngeal samples of children with AOM (Ruohola et al. 2006). Interactions between bacteria and virus infections may increase the severity of AOM. Viruses may induce increased production of inflammatory mediators, delay the clearance of bacteria and decrease the penetration of antibiotics to the inflammation site (Heikkinen and Chonmaitree 2003, Chonmaitree et al. 2016).

2.2.5 Immunology

The human immune system consists of innate and adaptive immunity. The innate immunity, functional already at birth, is nonspecific and reacts quickly, whereas the adaptive immunity needs sensitization and responds more slowly, only after recognition of the pathogen through antigen-specific antibodies.

The respiratory mucosa of the palatine, pharyngeal and lingual tonsils and adenoids form Waldeyer's ring (a circular lymphoid ring tissue), the primary defense against pathogens (Rovers et al. 2004). When bacteria, viruses or both invade the nasopharynx, this is the first barrier they meet. The pathogen induces an inflammatory reaction leading to mucosal epithelial damage, inadequate cilia function and upregulation of cytokine responses. The epithelial cells initiate first-line defense mechanisms by producing innate defense molecules (Mittal et al. 2014a) and pattern recognition receptors which rapidly recognize the pathogens, trigger pro-inflammatory responses and antimicrobial responses while simultaneously promoting the adaptive immune system (Skevaki et al. 2015, Mittal et al. 2014b). This cascade of events is needed for the innate immune system to rapidly clear the middle ear from the infection.

Lymphoid tissue produces agents of adaptive immunity, such as antigen-specific immunoglobulins, humoral and cellular factors, inflammatory mediators, oxidative enzymes and hydrolytic enzymes, in response to a bacterial or viral pathogen (Bluestone and Klein 2007).

2.3 Epidemiology

A systematic review by Monasta et al. (2012) estimates that the global AOM incidence rate (new episodes per hundred people per year) is approximately 11%. This estimate would equal 709 million episodes of AOM each year. Geographically, the global incidence rates vary from 3.6% in central Europe to 43% in sub-Saharan central Africa (Monasta et al. 2012). These figures reflect differences between the developed and the developing countries and the medical, social and economic burden caused by AOM to health care and families worldwide.

Strikingly, 51% of all AOM episodes occur in children less than 5 years of age. The highest incidence rates are in the age group 1–4 years (61%) and in children less than one year old (45%) (Monasta et al. 2012). In the US, 80% of all children experience at least one episode of AOM before their third birthday; the age-specific incidence peaks at age 6 to 23 months (Klein 1994, Chonmaitree et al. 2008b). More than 30% of the children will have three or more episodes of AOM (Teele et al. 1980). By age 5–9 years, the global AOM incidence declines to 22% (Monasta et al. 2012).

Infants aged less than 6 months have AOM less frequently than older children because they are protected by maternal antibodies which they acquired *in utero* (Pichichero 2013). Daly et al. (1999) followed 596 healthy infants from birth to 6 months. Of these infants, 39% had AOM during this time, and 20% developed recurrent AOM (two or more AOM episodes). The investigators found that innate and environmental factors were the most important determinants of AOM. Prenatal factors were not associated with early onset AOM (Daly et al. 1999).

Vaccinations to prevent invasive pneumococcal diseases and AOM have been implemented. In 2000, seven-valent pneumococcal vaccination (PCV7) was introduced in the USA, but the AOM pathogens have remained essentially the same when compared to pre-PCV7 era. There seems, however, to have been a shift towards non-vaccine pneumococcal serotypes and *H. influenzae* seems to have surpassed *S. pneumoniae* as an otopathogen (Casey et al. 2010). In 2010, PCV13 vaccination was implemented to cover all the PCV7 and six additional serotypes. Again, a 9-year prospective study of young children demonstrated that the non-

vaccine serotypes replaced the vaccine serotypes as nasopharyngeal colonizers of these children (Kaur et al. 2016).

In Finland, a double-blind randomized clinical trial examined the effect of PCV7 on reducing AOM in young children 6 to 24 months of age (Eskola et al. 2001). The results showed that the vaccine reduced the overall number of AOM episodes by 6%. The number of AOMs caused by the vaccine serotypes decreased by 57%, while the non-vaccine serotype AOMs increased by 33%. In 2010, PCV10 vaccination for children has been introduced into the Finnish national vaccination program.

2.4 Risk factors and genetics

OM is a multifactorial disease. The risk factors are diverse and relate to the host and to the environment. The most important risk factors are young age, genetic susceptibility and environmental factors affecting the otopathogen load in the nasopharynx (Schilder et al. 2016).

The most important risk factor for AOM is a RTI at young age. In the age group 6 to 35 months, the incidence of RTI episodes per child in the US was approximately 5 per year. Of these episodes 37% were complicated by AOM and 24% by OME. Thus, the overall incidence of RTI followed by any OM was 61% (Chonmaitree et al. 2008b).

Genetic susceptibility has a significant impact on the occurrence of OM. Twin studies have shown that the susceptibility varies from 50% to 70% (Kvaerner et al. 1997, Casselbrant et al. 2004, Hafrén et al. 2012). By ethnicity, Australian aboriginal children and Arctic Inuit children are more susceptible to AOM and its complications than children of other ethnic background (Leach 1999, Morris et al. 2007, Koch et al. 2011). A Finnish family-based study showed that genetic determinants affect significantly the risk of recurrent and chronic OM (Hafrén et al. 2012).

Nasopharyngeal colonization with otopathogens in early childhood increases the risk for OM (Faden et al. 1997). Correspondingly, young age, exposure to tobacco smoke, poor nutrition and a history of short breastfeeding predispose a child to impaired immunity and colonization with bacterial otopathogens at an early age. Male gender, black ethnicity, day care and low socioeconomic status increase the risk for any OM according to a large epidemiologic study covering the first two years of life (Paradise et al. 1997). Adenoid hypertrophy has been considered to serve as a reservoir and a culture platform for bacteria and to affect the ET

unfavorably, increasing the risk for OM (Bluestone and Klein 2007). Additionally, gastroesophageal reflux might be a risk factor for OM, since pepsin has been identified in the MEE of children undergoing tympanostomy tube placement (O'Reilly et al. 2008).

Alho et al. (1993) found that the major AOM risks are day care and a history of an episode of AOM especially within the three preceding months (Alho et al. 1993). Older siblings subject the child to high rates of bacterial transmission and this increases the AOM risk (Uhari et al. 1996). The use of a pacifier increases especially the risk of recurrent AOM (Rovers et al. 2008). A study aiming to restrict the use of a pacifier to those moments when a young child was falling asleep found that the occurrence of AOM was 29% lower in the intervention than in the control group (Niemelä et al. 2000). A meta-analysis found that the risk of AOM is related to daycare attendance, parental smoking and having siblings. On the other hand, breastfeeding for at least 3 months decreases the risk of AOM (Uhari et al. 1996). A long duration of breastfeeding seems to relate to higher maternal education, and probably reflects an above average socioeconomic status of the family.

The spectrum of risk factors for OM in the developing countries is different from that in the developed countries. In developing countries overcrowding, poor hygiene, contaminated water, malnutrition, poor access to health care and a different occurrence of conditions that impair immunity (*e.g.,* human immunodeficiency virus infection and tuberculosis) predispose children to chronic complications of OM, such as chronic suppurative otitis media (Taipale et al. 2011).

2.5 Diagnostics

An accurate diagnosis of AOM is based on clinical examination with pneumatic otoscopy and other instruments. It is important that physician sees the tympanic membrane to verify the presence of MEE by inspection.

The diagnosis AOM is fraught with uncertainty among physicians. In a French study involving 104 children 1–4 years of age, GPs were certain of the AOM diagnosis in only 54% of the pneumatic otoscopy examinations of 208 tympanic membranes. The GPs' AOM diagnosis was confirmed by an ENT specialist within 48 hours in 84% of cases. When the GPs assumed AOM, the confirmation rate was only 71%. Nearly every fourth (22%) diagnosis or assumption of AOM made by a GP was not corroborated by an ENT specialist (Legros et al. 2008). In a study from an international primary care network some years back, GPs reported that the

diagnostic certainty of AOM increases with the child's age: 58%, 66% and 73% in the age groups 0–12 months, 13–30 months and ≥31 months, respectively (Froom et al. 1990). In Denmark, a survey revealed that GPs were 67% certain of the presence of AOM in children ≤2 years (n=99) and 75% certain in older children (n=174). The main reasons for diagnostic uncertainty were poor visualization of the tympanic membrane (21%), differential diagnostic doubts (25%) and lack of knowledge (54%). This study concluded that diagnostic certainty could improve by removing cerumen and use of pneumatic otoscopy (Jensen and Lous 1999).

The challenging differential diagnosis of OME and AOM leads to overdiagnosis of AOM. Physicians also misdiagnose healthy ears as OME (Kuruvilla et al. 2013). ENT specialists correctly diagnosed AOM, OME and a retracted tympanic membrane (otherwise normal) in 73%, pediatricians in 36–54% and residents in 41% of nine high quality pneumatic otoscopy videos or still images. ENTs overdiagnosed AOM in 3–23% and pediatricians in 7–53% of the videos or still images. OME was most often misdiagnosed as AOM (Pichichero and Poole 2001, Pichichero 2002, Pichichero 2003).These results suggest that the proportion of misdiagnoses is even higher in regular office settings, where young children might resist cerumen removal and otoscopy examinations.

Overdiagnosing AOM leads to unnecessary prescriptions of antimicrobial agents and raises the prevalence of resistant bacteria (Pichichero and Poole 2001, Rosenfeld 2002). AOM is one of the primary indications for antibiotic prescriptions in children younger than 3 years of age (Lieberthal et al. 2013). Overdiagnoses lead to unnecessary surgical procedures, such as tympanostomy tube placements which is one of the most common ambulatory surgery performed on children in the USA (Kuruvilla et al. 2013, Rosenfeld et al. 2016).

Myringotomy or tympanocentesis have been used to accurately diagnose AOM. Myringotomy involves an incision which is made through the tympanic membrane to relieve ear pain due to pressure and to drain MEE. The term tympanocentesis is used when a needle is inserted through the tympanic membrane to obtain a sample of MEE. Both procedures are the golden standards to detect MEE. However, they cause pain and do not provide any extra benefit to the treatment when compared to a course of antibiotics (Engelhard et al. 1989, Kaleida et al. 1991). For this reason, these procedures are justified only if serious complications of OM (such as acute mastoiditis) are suspected, if the child has immunodeficiency and/or if a bacterial culture is needed to direct appropriate antibiotic treatment (Heikkinen et al. 2017).

Obstructive cerumen is one of the most frequent reasons for insufficient visibility of the tympanic membrane. Although nearly every other child has cerumen which impairs visibility and thus middle ear diagnostics (Schwartz et al. 1983, Marchisio

et al. 2016), less than 10% of the GPs and 30% of pediatricians removed cerumen when needed (Jensen and Lous 1999, Marchisio et al. 2016). Some physicians have only a 50% success rate in freeing visibility (Legros et al. 2008). Removing cerumen from the narrow ear canals of a young child requires practice – it is far from a simple task.

To enhance the diagnostic accuracy of AOM, physicians should be up-to-date and medical students and residents appropriately educated (Steinbach and Sectish 2002, Kaleida et al. 2009). Interactive courses with simulation techniques increase the physicians' diagnostic accuracy of AOM and the integration of new methods to everyday practice (Pichichero and Poole 2001, Kaleida et al. 2009, Samra et al. 2016). Rosenkranz et al. (2012) reported conflicting results. Despite interactive workshop training and increased confidence in pneumatic otoscopy and tympanometry, GPs were unlikely to integrate these methods into their practice (Rosenkranz et al. 2012). Currently, it is very easy and convenient to use the internet (*e.g.,* https://www.utmb.edu/pedi_ed/AOM-Otitis/) or mobile applications (*e.g.*, Buckingham Virtual Tympanum app for medical students (Samra et al. 2016)) for self-education. However, for a physician to overcome the barriers requiring manual skills such as cerumen removal and performance of pneumatic otoscopy, willingness, motivation and repeated examinations are key (Legros et al. 2008).

2.5.1 Symptoms of acute otitis media

The symptoms of AOM and a viral RTI are similar in young children in the otitis-prone age. AOM cannot be predicted based on the severity, duration or occurrence of symptoms reported by the parents of young children (Laine et al. 2010). Although reported ear pain is important for the diagnostic process of older children (Arola et al. 1990, Kontiokari et al. 1998), preverbal children cannot accurately describe pain and they present more often with a wide spectrum of nonspecific symptoms. Restless sleep of the child was among the most common reasons (30%) for a parent to suspect AOM. However, ear pain, irritability, fever, ear-rubbing, crying or prolonged cough do not predict AOM with a high level of specificity. Symptoms cannot be used to establish AOM in young children in the outpatient setting (Laine et al. 2010).

2.5.2 Otoscopy

Otoscopy is the core element of OM diagnostics, but is not free from challenges (Shaikh et al. 2010). To obtain a clear view of the tympanic membrane can be very

difficult if the patient is a struggling child. Otoscopy requires cooperation with the child and parents. The child must be held firmly to enable the physician to perform the otoscopic examination (**Figure 2**). Notably, otoscopy is not an objective tool and the diagnosis depends on the physicians' subjective interpretation of the middle ear findings. Not so long ago, in the 1980s, 165 pediatricians proposed 147 different combinations of signs and symptoms for the diagnosis of AOM (Hayden 1981).

Otoscopy, in general, allows the visualization of the ear canal, tympanic membrane and the middle ear aeriation. By simple otoscopy, physicians determine the middle ear diagnosis by visually and qualitatively assessing the physical characteristics (anatomy, transparency, color, light reflex, vascularity and position) of the tympanic membrane and presence of MEE. Otomicroscopy provides a better view of the tympanic membrane, but is usually not available for primary care physicians.

Video otoscopy (VO) uses traditional or endoscopic technology to visualize the tympanic membrane. Endoscopic technology means that a rigid endoscope is inserted into the ear canal. This requires particular cooperation to prevent trauma to the ear canal (Jones 2006). A feature of VO is that the image or the video can be projected onto a monitor for all to see in real time, and this increases markedly the educational value of VO. Magnification, clarification and further processing of the image or video is possible (Jones et al. 2004). The image is, however, only two-dimensional and this may affect the diagnostic accuracy (Pichichero and Poole 2005). On the other hand, a detailed analysis of the recorded tympanic membrane videos may enhance the diagnostic accuracy of middle ear examinations. These features suggest that VO could serve many purposes in the clinical assessment of the ear canal and middle ear.

VO was more sensitive (98%), specific (100%) and accurate (98%) than pneumatic otoscopy (91%, 77% and 89%) and tympanometry (89%, 82% and 89%) to detect MEE prior to myringotomy in 201 ears of 104 children less than 12 years of age (Shiao and Guo 2005). The diagnoses made by GPs with the use of asynchronous VO recordings obtained by a trained health care facilitator were more specific (98%) and had a higher PPV (89%) compared to on-site otoscopy performed by the same GPs (corresponding figures 93% and 71%). Otomicroscopy was the reference standard. Thus, the diagnostic accuracy of VO was similar or better compared to hands-on otoscopy examinations. Importantly, VO may be performed by persons with no medical education after a brief training and the images and videos can be interpreted either on-site or remotely (Lundberg et al. 2017).

Digital otoscopes provide high-definition still images or videos of the tympanic membrane. Trained experts viewed 210 digital tympanic membrane images with the reference diagnosis determined by otomicroscopy with adjunct audiometry

and/or tympanometry. They were 72% correct in identifying healthy tympanic membrane images. The correct diagnosis of MEE from a still image was more challenging (Moberly et al. 2017). Digital otoscopes have been integrated and adopted into the teaching of clinical ear assessment skills to medical students (Silverston 2016).

By pneumatic otoscopy, physicians may test and assess the tympanic membrane movement to help differentiate a healthy ear from OME and AOM. This is the reason that many guidelines recommend pneumatic otoscopy in everyday practice (Lieberthal et al. 2013, Heikkinen et al. 2017). However, the demanding nature of testing of the tympanic membrane movement is a well-known challenge (Cavanaugh 1989, Fisher and Pfleiderer 1992, Abbott et al. 2014).

In studies using myringotomy as the gold standard, pneumatic otoscopy has turned out to be a reliable method to detect MEE. In children ≤5 years old, preoperative pneumatic otoscopy before tympanostomy tube placement was 88% sensitive and 97% specific for detecting MEE, when the criteria for MEE were impaired mobility of the tympanic membrane and a suspicion of MEE (*i.e.,* uncertain) (Paradise et al. 1976). In similar study settings with patients aged 18 months to 12 years, the sensitivity and specificity of pneumatic otoscopy to detect MEE were 87–89%, and 93–58%, respectively (Toner and Mains 1990, Finitzo et al. 1992). In the study of Finitzo et al. (1992), the low specificity was explained by a high number of false positive diagnoses of OME (Finitzo et al. 1992).

Takata et al. (2003) pooled 52 full-length articles and found that pneumatic otoscopy has the best sensitivity (94%) and specificity (81%) to detect MEE when myringotomy was the golden standard (Takata et al. 2003). Furthermore, Rogers et al. (2010) demonstrated that the sensitivity to detect MEE increased with the level of experience of the physician in pneumatic otoscopy from 58% to 67% and the specificity from 78% to 81% (Rogers et al. 2010).

The importance of pneumatic otoscopy has been emphasized (Pelton 1998, Pichichero 2000, Takata et al. 2003) but physicians seem to use it to very inconsistently. Studies have shown low utilization rates of only 4% to 15% (Jensen and Lous 1999, MacClements et al. 2002, Marchisio et al. 2012). The main reasons for physicians not using pneumatic otoscopy or removing cerumen were of lack of time and practice, shortage in proper equipment (MacClements et al. 2002, Legros et al. 2008). Moreover, 30% of GPs used otoscopes with insufficient illumination (Berman 1995). This deficiency is hopefully overcome by new otoscopes with light bulbs with higher luminous intensity than the older ones.

Figure 2. Good position for otoscopic examination. When the child's head is rotated and the limbs held firmly together, the conditions for otoscopy are optimal for the physician. Photography by Aino Ruohola, with permission.

2.5.2.1 *Smartphone otoscopy*

The smartphone-enabled otoscope is designed for the inspection of the tympanic membrane under magnification with the smartphone as the external illumination source. Smartphone-enabled otoscopy is the result of the rapidly advancing field of telemedicine and mobile phone technology. The technology was introduced directly to consumers (www.cellscope.com), but the studies published to date are based on images obtained by professional users. Smartphone-enabled otoscopy **(Figure 3)** has been considered to offer a tool to enhance teaching of medical students and personnel, to allow cooperation between health care professionals and to open the avenues for remote consultations and follow-up (Sahyouni et al. 2016).

Richards et al. (2015) compared smartphone otoscopy to pneumatic otoscopy in a pediatric emergency department setting. Children (n=54, mean age 5.1 ± 3.7 years) presenting with otalgia, fever or symptoms of RTI were included and examined with pneumatic otoscopy followed by smartphone otoscopy, first by a resident, then by an attending physician. The physicians were not trained in the use of the smartphone otoscope and were blinded to each other's findings. The intrarater diagnostic agreement of residents and attending physicians was high in both ears (κ =

0.74−0.86), but the interrater agreement was modest for both otoscopes (κ = 0.40 and κ = 0.47). Although the initial pneumatic otoscopy may have influenced the interpretation of the smartphone otoscopy, physicians changed their original diagnosis in 12−16% of the middle ear examinations (to/from AOM). The study was limited by not accurately defining the diagnostic features of the middle ear findings (normal; abnormal and MEE; abnormal and tympanic membrane erythema; abnormal [other not listed]; cerumen impaction; and unable to visualize). The main messages of this study are that physicians agreed that the smartphone otoscope is easy to use, enables more precise diagnostics, enhances the view to the tympanic membrane and is a good educational tool (Richards et al. 2015).

Rappaport et al. (2016) examined 60 children (mean age 2.9 years, range 6 months to 18 years) who presented at the emergency department with RTI symptoms, otalgia or otorrhoea. Tympanic membrane videos were captured with a conventional Welch Allyn Digital MacroView Otoscope and with a smartphone otoscope. Four independent and blinded physicians found no differences in the diagnostic quality and confidence, diagnosis and likeliness to prescribe antimicrobials based on the tympanic membrane videos obtained with the digital or with the smartphone otoscope. The interphysician agreement to diagnose AOM was moderate (κ = 0.503) with the smartphone and substantial (κ = 0.664) with the digital otoscope (Rappaport et al. 2016).

A survey among pediatricians revealed their concerns about losing the hands-on examination and the direct patient contact. They emphasized that the physician should have an existing relationship with the family if he is to use remote possibilities of smartphone otoscopy satisfactorily, in other words, know the patient. Less than half (38%) agreed that they would have prescribed antibiotics based on a remote AOM diagnosis. Although the smartphone otoscope is targeted to the consumer market, more than half (63%) estimated that parents could not perform or obtain a video examination of their child's tympanic membrane and that the images would be of poor quality due to cerumen and lack of testing the tympanic membrane movement. However, they agreed on the potential value of the tympanic membrane images to educate families, and 66% considered that following the images over time could even reduce the use of antibiotics in the treatment of AOM (Rappaport et al. 2016).

The majority of the physicians in these two studies were satisfied with the smartphone otoscope, although some reported that it was awkward to hold and capture images simultaneously. Most of the parents were positive about seeing images of their child's tympanic membrane. Nearly all agreed that the images helped them to understand the child's condition and the chosen management. Although parents did not use the smartphone otoscope in these studies, more than

90% felt comfortable about using it and following the middle ear status at home over time. Two-thirds would have preferred sending images to their physician rather than making an office visit (Richards et al. 2015, Rappaport et al. 2016).

Moshtaghi et al. (2017) compared smartphone otoscopy to otomicroscopy (gold standard) in the detection and evaluation of tympanic membrane pathology in adult patients. An otologist blinded to the clinical data but who obtained a brief patient history was presented with a single tympanic membrane image obtained with the smartphone otoscope. In this setting 96% of the healthy tympanic membranes and 100% of the abnormal otomicroscopic findings were identified. The diagnostic accuracy compared to otomicroscopy was 82%. Smartphone otomicroscopy could serve as a screening tool for middle ear pathology, given its high specificity and low false positive rate (4%) (Moshtaghi et al. 2017).

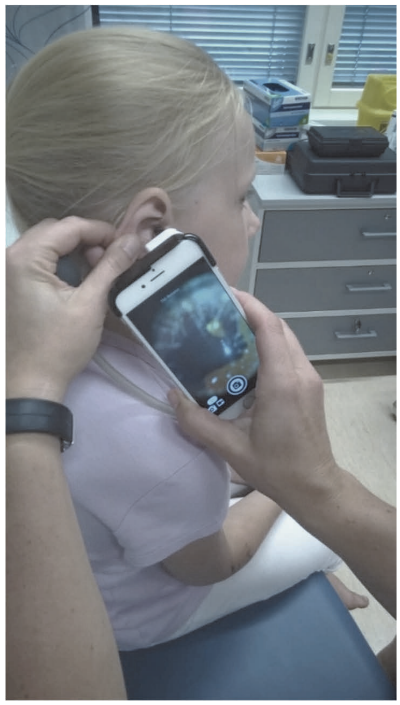


Figure 3. Smartphone otoscopy. Photography by Nora Erkkola-Anttinen, used with permission

The potential benefits of smartphone otoscopy for screening middle ear diseases has also been supported by a cross-sectional study on the validity of a Cupris® smartphone device (Mandavia et al. 2017). In this unselected study population (n= 52, mean age 41 years) the concordance in the context of primary diagnosis and decision to refer the patient to an ENT specialist between the smartphone and standard otoscopy were 95% and 100%, respectively. The rates of sensitivity, specificity, PPV and NPV of the Cupris® device to diagnose any middle ear disease

were 94%, 96%, 91% and 97%, respectively. The authors concluded that the device could also be used by non-professionals (Mandavia et al. 2017).

2.5.2.2 *New diagnostic methods*

To address the problems of subjective OM diagnostics and the two centuries old otoscope technique and to relate this to limited access to care, new tools for improving objective OM diagnostics are needed. New techniques could enable a more reliable assessment of the tympanic membrane with regard to OM and provide an accurate diagnosis, even from a distance.

Automatic tympanic membrane image classifiers have been developed to improve the diagnostic accuracy, to enable automated self-diagnosis and for the remote diagnostics of OM (Kuruvilla et al. 2013, Shie et al. 2014, Myburgh et al. 2016). Shie et al. (2014) segmented the tympanic membrane from the original output image and further processed the image by color, geometric structures and texture. Finally, the processed images were classified and diagnosed. There were 865 pre-diagnosed tympanic membrane images by ENT specialists which were analyzed with an 88% diagnostic accuracy (sensitivity 92%, specificity 80%) to detect OM. The authors envisioned that patients could take the tympanic membrane image at home, render it for the image processing and seek medical care if OM was detected. However, this classification was questioned because the authors strongly emphasized that a red color of the tympanic membrane indicates AOM (Shie et al. 2014). The 86% diagnostic accuracy of the classifier of Kuruvilla et al. (2013) surpassed that of physicians (80%) in diagnosing healthy ears, OME or AOM. The classifier of Myburgh et al. (2016) was tested with high quality pre-assessed tympanic membrane images captured by video-otoscopy. The image analysis took approximately 3.5 seconds and the images were classified with the use of a trained decision tree. The average objective diagnostic OM accuracy was 81% (findings classified as obstruction, normal, AOM, OME and CSOM with perforation). The sensitivity, specificity, PPV and NPV of the system to detect AOM was 81%, 92%, 75% and 95%, respectively (Myburgh et al. 2016).

The optical coherence tomograph (OCT) is a hand-held device for the examination of the structures and dynamics of the middle ear. OCT determines the thickness of the tympanic membrane and the presence of biofilm behind the tympanic membrane noninvasively and quantitatively. A study in a pediatric population showed that the overall thickness of the tympanic membrane and any associated biofilm were dissimilar in normal, acute and chronic middle ear conditions. A biofilm was present in nearly all of the scans of chronic disease. An important role for OCT could be in identifying middle-ear biofilms and in aiding the differential

diagnostics of OM. The next step in use of OCT is 3-dimensional imaging of the entire middle ear cavity (Monroy et al. 2015).

Shortwave infrared light (SWIR) enables the visualization of biological structures undetectable with visible light. Unlike normal optical imaging with visible light, SWIR (1,000–2,000 nm) reduces normal light scattering and provides greater light transmission through biological tissues. Carr et al. (2016) introduced a SWIR otoscope to improve transtympanic middle ear diagnostics. In the middle ear, SWIR enables optical penetration through the tympanic membrane into the deeper tissues of the middle ear cavity. This visualizes anatomical features that are normally undetectable (ossicular chain, cochlear promontory, round window's niche and chorda tympani). The SWIR otoscope could enhance the detection of MEE which absorbs light strongly between 1,400 and 1,550 nm because the SWIR increases the number of wavelengths, which improves the endogenous contrast of MEE compared to normal light. This allows determination of the presence or absence of MEE objectively. The advantages of integrating SWIR into otoscopy are that the device operates and resembles ergonomically and visually the usual otoscope and requires minimal additional training of the user (Carr et al. 2016). Adoption of the SWIR technology has been hampered by high costs.

2.5.3 Otoscopic findings

When determining a diagnosis of OM, physicians should pay attention to the position of the tympanic membrane as well as its light reflex, opacification, predominant color and mobility, and to the presence of MEE. **Figure 4** and **Figure 5** show some examples of the tympanic membrane view by video-otoscopy and smartphone otoscopy.

Bulging of the tympanic membrane is strongly indicative of AOM. A Finnish study demonstrated that when the tympanic membrane is cloudy, bulging or has decreased mobility, AOM is present in 80–95% of symptomatic young outpatient children (Karma et al. 1989). These results were supported by a primary care study of 783 children 6 to 24 months of age who were examined for RTI symptoms with pneumatic otoscopy by four experienced otoscopists who also obtained still images of the tympanic membrane. Bulging of the tympanic membrane was present in 96%, opacification in 100%, white or yellow color in 90%, marked redness in 20% and decreased mobility in 99% of the ears with AOM (Shaikh et al. 2011a).

Bulging as pathognomonic for AOM was further supported by seven expert otoscopists who reviewed 135 randomly selected tympanic membrane still images from the previous set of 783 children. They were blinded to patient, symptom and

tympanic membrane mobility data. In a total of 945 image evaluations bulging was present in 93%, opacification in 100%, predominant color was white or yellow in 64% and marked redness in 58%. Notably, even without data on the mobility of the tympanic membrane, the experts agreed with the four experienced otoscopists in 89% of the diagnoses (Shaikh et al. 2011a).

Redness of the tympanic membrane as diagnostic criterion for AOM is a major reason for antibiotic overuse. Since crying or cerumen removal may cause redness of the tympanic membrane through vasodilatation, redness should not be considered as indicative of AOM (Karma et al. 1989). However, one study showed that GPs considered redness of the tympanic membrane diagnostic for AOM, especially in children aged 13–30 months (Froom et al. 1990). Furthermore, in 90% of cases misdiagnosed as AOM most of the errors were related to a red tympanic membrane (Rosenfeld 2002). When redness was present together with other tympanic membrane abnormalities without bulging, OME or no effusion was diagnosed in 87% of the image evaluations (Shaikh et al. 2011a).

In OME, the tympanic membrane was never reported to be bulging (Shaikh et al. 2011a), but opacification was present in 98% and a white or yellow color in 63% of the images, and decreased mobility in 69% (Shaikh et al. 2011a). Again, these results were in accordance with those of Karma et al. (1989).

Taken together, physicians should use bulging of the tympanic membrane as the most important characteristic finding to distinguish AOM from OME.

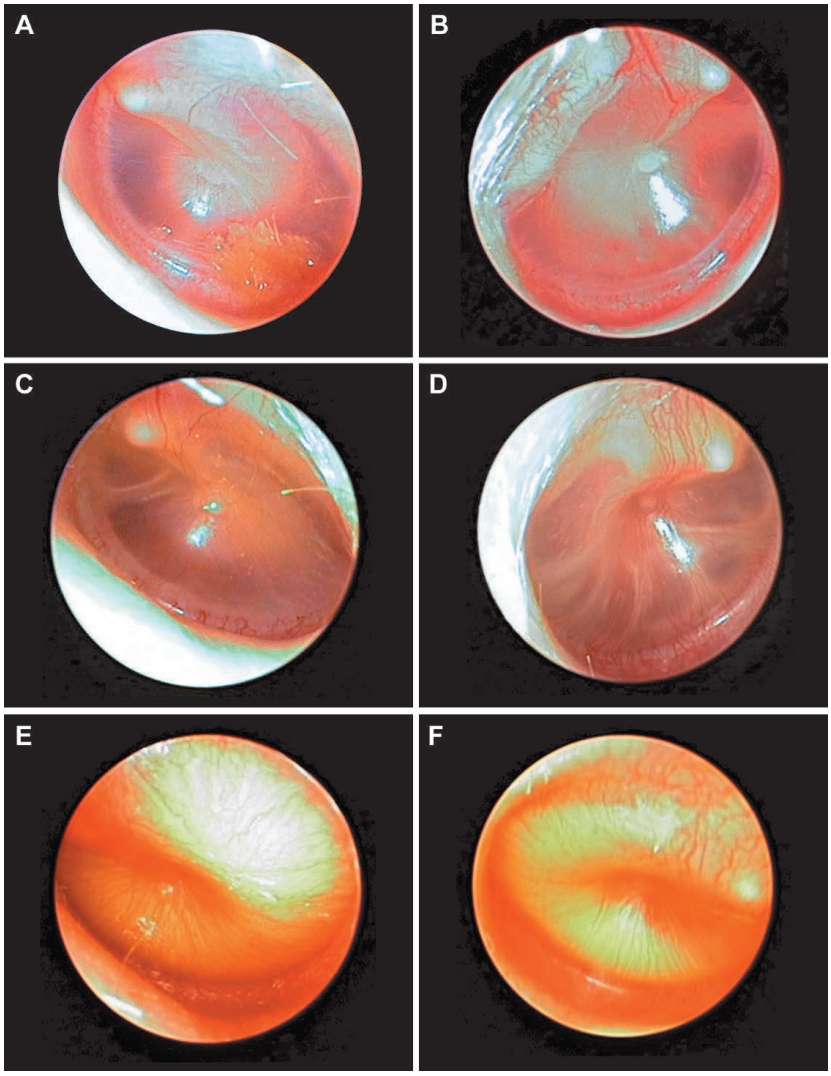


Figure 4. Otoscopic findings at video-otoscopy. Images in the left column show a healthy ear (A), otitis media with effusion (C) and acute otitis media (E) in the left ear. The right column shows the respective images from the right ear (B), (D), (F). Photographs by Miia Laine, Aino Ruohola and Paula Tähtinen, used with permission.

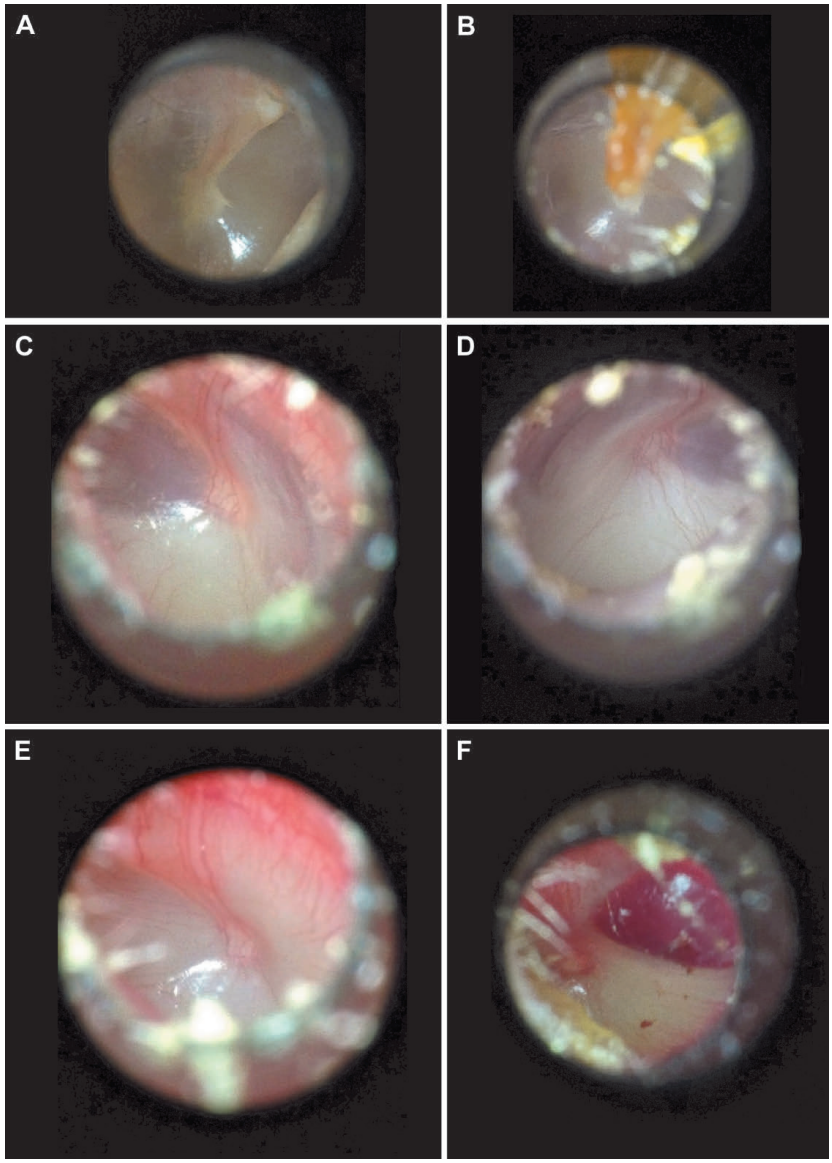


Figure 5. Otoscopic findings obtained with a smartphone otoscope. Image (A) shows a healthy middle ear from the right ear. Image (B) shows how a minor cerumen fragment impairs the visibility to the tympanic membrane. The images in the left column show otitis media with effusion (C) and acute otitis media (E) in the left ear. The corresponding images from the right ear are shown in the right column (D), (F). Photographs by Nora Erkkola-Anttinen and Paula Tähtinen, used with permission.

2.5.4 Tympanometry

The tympanometer is a handheld, portable or desktop device (**Figure 6**) which measures the ease with which acoustic energy is transmitted from one medium of the ear canal to another in the middle ear cavity (air-air or air-MEE), *i.e.,* acoustic admittance (Brookhouser 1998). The acoustic admittance is the movement of acoustic energy between two media and it is optimal when the two media are similar. Tympanometry is used to determine the absence or presence of MEE, examine the middle ear pressure and the patency of tympanostomy tubes (Brookhouser 1998, Margolis et al. 1994, Onusko 2004).

The tympanometric examination is noninvasive and rather easy to perform. However, several factors, including the experience of the performer, influence the diagnostic accuracy. It requires an air-tight seal between the probe and the ear canal. Generally, the younger, the sicker and the less cooperating the patient is, the poorer the diagnostic accuracy. Up to 50% of the tympanometric examinations may fail in uncooperating children (Sassen et al. 1994, Koivunen et al. 1997, Palmu et al. 1999, Engel et al. 2000). Also, because very young children have elastic ear canals, the results of tympanometry do not seem to be reliable in children younger than 7 months (Paradise et al. 1976), but the findings regarding this question are conflicting. Among children younger than 7 months the success rate of tympanometric examinations was high (97%), as were the PPV (90%) and NPV (89%) values for the detection of MEE. The study concluded that tympanometry is reliable also for examining young children (Palmu et al. 1999).

The diagnostic accuracy of pneumatic otoscopy and tympanometry for detecting MEE are comparable and tympanometry enhances the diagnostic accuracy of middle ear examinations (Johansen et al. 2000, Lous et al. 2012). The value of tympanometry as a supplement to pneumatic otoscopy has been corroborated in a primary care study demonstrating a significant 30% reduction in AOM diagnoses (Blomgren et al. 2004). GPs reported that a 1-day course of tympanometry improved their practical skills (88%) and increased the acumen of the benefits of the data provided by tympanometry (91%). Approximately 80% of the GPs had changed their management plan of middle ear conditions after they had adapted tympanometry into their clinical repertoire (Lous et al. 2012). Cerumen does not influence the diagnostic accuracy unless it obstructs more than half of the ear canal diameter (Block et al. 1998). Results are affected by the tympanometer used (Patricoski and Ferguson 2006) and by the diagnostic criteria of MEE. For this reason, the results of different studies are not directly comparable.

Figure 6. Tympanometer.

2.5.4.1 *Principles of tympanometry*

The tympanometer emits a sound stimulus (acoustic signal) to the middle ear and a simultaneous vacuum pump introduces a sweep of positive and negative pressures (+200 daPa to -400 daPa) to change the pressure in the ear canal. At both ends of the pressure sweep, acoustic admittance is inhibited because the tympanic membrane is stretched. When the sound stimulus hits the tympanic membrane, the tympanic membrane starts to vibrate and the internal microphone in the probe of the tympanometer measures the reflected sound energy (static acoustic admittance). When the middle ear is healthy, *i.e*., the middle ear is filled with air, the tympanic membrane vibrates readily and the reflected acoustic signal does not lose excess sound energy to the tympanic membrane or to the middle ear cavity behind it. In contrast, when MEE is present, the vibration of the tympanic membrane is impaired and this causes the reflected acoustic signal to lose admittance (Brookhouser 1998).

The results of the tympanometric examinations are provided in the form of a two-dimensional graph **(Figure 7)** where the x-axis displays the pressure and y-axis the static admittance. The following four definitions are crucial for the understanding of the principals of tympanometry.

1. Static acoustic admittance (SAA, mmho) reflects the greatest amount of acoustic energy absorbed by the middle ear and is depicted as the height of the peak of the tympanogram. A SAA value of 0.2 mmhos has been considered as a threshold for the presence of MEE (Margolis et al. 1994). Palmu et al. (2005) also suggested

that ear-specific SAA values could be used, where the values are compared when there is MEE (sick visit) and when the ear is healthy (healthy visit). They calculated that a SAA ratio < 0.35 (*i.e.,* a 2/3 decrease in SAA) between a healthy and a sick visit could be indicative of MEE (Palmu and Syrjänen 2005).

2. Tympanometric peak pressure (TPP, daPa) is determined as the position of the peak at the pressure axis (x-axis). This is the point of maximum SAA, and it occurs when the air pressure is identical on both sides of the intact tympanic membrane. It provides a clinically useful, although indirect, measure of the middle ear pressure (Brookhouser 1998). The middle ear pressure is expressed in decaPascals (daPa) or pressure equal to cubic millimeters of water (mmH_2O). These two parameters have almost identical numeric values (1daPa = 1.02 mmH_2O) (Palmu et al. 2001). Although TPP is not an effective predictor of MEE (Margolis et al. 1994), it may be used, in addition to otoscopy, to determine the retraction of the tympanic membrane and the resolution of MEE (Brookhouser 1998).

A negative TPP value (< -100 daPa) has been considered to express a negative middle ear pressure (nMEP) without MEE (Palmu et al. 2001). However, nMEP is a sign of ET dysfunction preceding the accumulation of MEE (Bluestone and Klein 2007). The appearance of nMEP (< -100 daPa) predicted OM within 3 weeks during RTI symptoms in 40% of children with an initially healthy ear (Palmu et al. 2002). Additionally, a negative TPP (< -100 daPa) together with low SAA (≤ 0.2 mmho) and a wide (≥ 300 daPa) curve is usually associated with the presence of MEE (Paradise et al. 1976, Palmu et al. 2001).

3. The tympanometric width (also called gradient, daPa) is determined as the width of the tympanometric peak pressure at half of the static admittance (*i.e.,* the height of the tympanogram) (Margolis et al. 1994). A wide tympanogram (>300 daPa) combined with a low SAA (< 0.2 mmH_20) is related to the presence of MEE (Nozza et al. 1994, Smith et al. 2006). The tympanometer used in Study I (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA) calculates the width automatically.

4. Equivalent ear canal volume (Vea, cm^3) expresses the volume of air in front of the tympanometer probe. The reference volume depends on the age of the subject. It may be affected by cerumen, which reduces the volume. On the other hand, in case of a perforation or a patent tympanostomy tube, the volume exceeds the reference value (Margolis and Heller 1987, Onusko 2004).

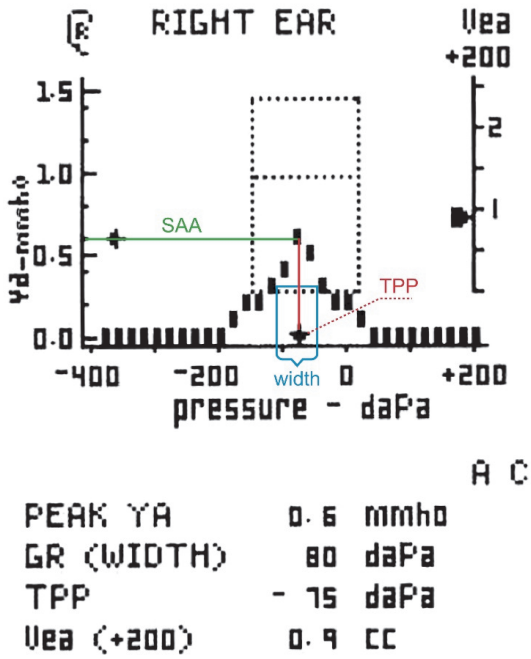


Figure 7. Example of a tympanogram displaying acoustic admittance as a function of air pressure. Abbreviations: SAA, static acoustic admittance; TPP, tympanometric peak pressure. Reprinted with permission from the thesis by Miia Laine (Laine 2015).

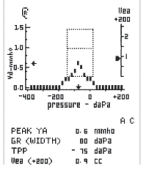
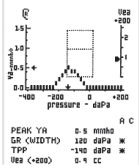
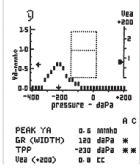
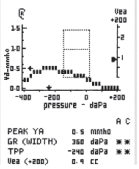
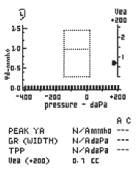
2.5.4.2 *Classification of tympanograms*

Jerger (1970) presented the first classification of tympanograms into types A, B and C. Type A was the peaked tympanogram related to a healthy ear, type B the flat tympanogram related to the presence of MEE and type C the peaked tympanogram related to negative middle ear pressure without MEE (Jerger 1970). Later, the Jerger classification has been modified.

Paradise et al. (1976) presented that tympanographic curve steepness, or the sharpness of the curve gradient, is a diagnostic marker. They suggested that shallow curves (neither peaked nor flat) are related to MEE (Paradise et al. 1976).

Orchik et al. (1978) introduced the definition of wide tympanograms (type As and type Cs) which were shallow but presented an observable TPP. Types As and Cs were not, however, pathognomonic for the presence of MEE (Orchik et al. 1978). Tympanogram type As (SAA ≤ 0.2 mmho and TPP > 100 daPa) is considered to exclude MEE. However, MEE has been detected in 22.5% of the middle ears of young children (2–11 months) with an As type tympanogram (Palmu et al. 1999). The type C tympanogram was later categorized as type C1 (TPP -100 to -199 mmH_2O) and type C2 (TPP ≤ -200 mmH_2O) to reflect negative TPP (Fiellau-

Nikolajsen and Lous 1979). **Figure 8** presents the classification of the tympanogram types.

	Type of tympanogram					
	A	As	C1	C2	Cs	B
Static admittance (mmho)	≥ 0.2	< 0.2; or ≥ 0.2 if width > 300 daPa	≥ 0.2	≥ 0.2	< 0.2; or ≥ 0.2 if width > 300 daPa	< 0.2
Tympanometric peak pressure (daPa)	> –100	> –100	–100 to –199	≤ –200	≤ –100	No peak
Width (daPa)	≤ 300	> 300	≤ 300	≤ 300	> 300	No peak
Middle ear status interpretation (Smith et al. 2006)	normal, no MEE	normal, no MEE	nMEP MEE unlikely	nMEP MEE unlikely	nMEP MEE likely	MEE most likely
						

Abbreviations: nMEP, negative middle ear pressure; MEE, middle ear effusion

Figure 8. Classification of tympanograms by Jerger (1970), Orchik et al. (1978) and Smith et al. (2006). Modified from the thesis of Miia Laine (Laine 2015).

2.5.4.3 *Diagnostic accuracy of tympanometry*

The diagnostic accuracy of tympanometry to detect MEE has been studied widely. Smith et al. (2006) examined the tympanometric findings and the probability of MEE in 3686 children less than 3 years old and showed that with a flat tympanogram, MEE was present in 80% of otoscopic examinations, whereas with a tympanometric height ≥0.6mmHo the rate was only 3% (Smith et al. 2006).

This thesis concentrates on pediatric outpatient studies with 1) the reference diagnosis provided by pneumatic otoscopy, or 2) tympanometric examinations performed by parapersonnel or parents or 3) MicroTymp2 (Welch Allyn, Skaneateles Falls, NY, USA) used for tympanometry (same as used in Study I). These studies illustrate the primary care perspective, where myringotomy is not used and where middle ear diagnoses relies on pneumatic otoscopy and tympanometry. **Table 1** presents the diagnostic accuracy of tympanometry to detect MEE.

Table 1. Diagnostic accuracy of tympanometry to detect middle ear effusion. These studies have met at least one of three selection criteria: 1) reference diagnosis was obtained by pneumatic otoscopy, or 2) the examiner was parapersonnel, or 3) a WelchAllyn tympanometer was used.

Study	Number of children (n)	Age (range)	Tympano-meter model	Number of tympanometric examinations (n)	Performer of tympano-metry	Success rate	Definition of abnormal tympano-gram	Sensitivity/ Specificity	PPV/NPV
Studies with myringotomy as the reference standard for the detection of middle ear effusion									
Babonis, 1991	120	6mo-10y	MT1	220	Phy	95%	B	78% / 82%	84% / 76%
van Balen, 1994	142	6mo-12y	MT1	233	Phy	92%	B, C2	94% / 48%	NR
Koivunen, 1997	162	7mo-8y	MT1	314	Nur	87%	B	Cooperat: 79% /93% Uncooperat:71% /38%	NR NR
Blomgren, 2007	199	6mo-18y	GS	392	Nur	90%	Flat[1]	54% / 82%	NR
Rogers, 2010	102	5mo-5y	MT2	201	Phy	100%	B	84% /48%	67% / 80%
Outpatient studies with pneumatic otoscopy as the reference standard for the detection of middle ear effusion									
Palmu, 1999	58	2-11mo	GS	242	Phy	Overall: 94% Sick: 93% Control: 97%	B	70% / 98% 67% / 98% 82% /99%	93% / 94% 90% / 94% 87% / 97%
Palmu, 2005	630	7-10mo	GS	906 ears	Phy	NR	B	Symp: 61% /99%	96% / 92%
Chianese, 2007	597	6-24mo	GS	2854	Phy	74%	B	NR	NR
Helenius, 2012	515	6-35mo	MT2	Total: 4246 Symp: 2206 Asymp: 1006	Phy	44% - 79%	B	Symp: 62% / 96% Asymp: 71% / 93%	95% / 67% 73% / 90%
Puhakka, 2014	600	6mo-14y	MT2	2152	Phy	NR	B	56% / 96%	60% / 95%
Laine, 2015	156	6-35mo	MT2	373	Nur	60% - 81%	B, Cs, C2	84% / 87%	66% / 95%

Abbreviations: MT1, MicroTymp, Welch Allyn; MT2, MicroTymp2, Welch Allyn; GS, Grason-Stadler GSI 33; Phy, Physician; Nur, Nurse; NR, Not reported
[1] Age >1 years: Flat or TPP <0.1; Age >1 years: Flat or TPP <0.2

Tympanometry to detect MEE

Tympanometry vs myringotomy. Studies comparing the diagnostic accuracy of the type B tympanogram (Microtymp, Welch Allyn) with myringotomy in the detection of MEE have reported sensitivity and specificity ranges of 78–84% and 48–93% in cooperating children (Babonis et al. 1991, Koivunen et al. 1997, Rogers et al. 2010). In uncooperating children, the same figures were 71% and 38%, respectively (Koivunen et al. 1997). The youngest children in these studies were 6 to 7 months, the oldest 8 to 10 years. A pooled analysis of 16 studies using the type B tympanogram to diagnose MEE in children with OME (prevalence of MEE 74%) summarized that the sensitivity of the type B tympanogram to detect MEE compared to myringotomy was 81% and the specificity 75% (Takata et al. 2003).

When tympanogram types B and C2 were combined, the sensitivity to detect MEE increased (94%), while the specificity decreased (48%) (*i.e.*, the number of false positives increased) (van Balen and de Melker 1994). The same pattern was reported when type B and C2 tympanograms were used to detect MEE in children with OME. A clear increase in sensitivity (94%) but a decrease in specificity (62%) occurred when compared only to type B tympanograms (Takata et al. 2003).

Tympanometry vs pneumatic otoscopy. Outpatient studies in children less than 2 years of age have shown that the type B tympanogram relates to MEE in approximately 94% of pneumatic otoscopy examinations (Palmu et al. 1999, Chianese et al. 2007). The sensitivity of the type B tympanogram to detect MEE differs between sick and health visits from 61% to 82%, while specificity is high, 98% (Palmu et al. 1999, Palmu and Syrjänen 2005). In an outpatient study, the type B tympanogram was associated with MEE in 95% of otoscopic examinations at symptomatic visits and AOM was diagnosed in 53% of these examinations. When the type B tympanogram was obtained at asymptomatic visits, 87% of otoscopic examinations were related to MEE, all of which were diagnosed as OME. From an important practical point of view, this study demonstrated that the type B tympanogram cannot be used to diagnose AOM in symptomatic nor in asymptomatic children. In such cases, pneumatic otoscopy is required to determine the specific middle ear diagnosis (Helenius et al. 2012). It should be noted that a false type B tympanogram may be obtained in a resisting child and if the probe is directed towards the ear canal wall. To prevent these false positive results, tympanometry should be repeated (Koivunen et al. 1997).

The type Cs tympanogram has been associated with MEE in 15–22% of otoscopic examinations (Palmu et al. 1999, Palmu and Syrjänen 2005). On the other hand, the type Cs tympanogram has been obtained in 53% of healthy ears in asymptomatic children (Helenius et al. 2012). This means that the type Cs tympanogram cannot be used to detect MEE reliably. Furthermore, the type C tympanogram may be related to MEE in only 5% of middle ear examinations, regardless of symptoms (Palmu et al. 1999) and is not useful to detect MEE.

While most studies have examined tympanometry to detect MEE, Helenius et al. (2012) evaluated the proportions of type A, C1, C2, Cs and B type tympanograms in relation to specific otoscopic diagnoses in 515 outpatient children (age 6–35 months) in primary care. Tympanometry was not able to determine specific middle ear diagnoses but it could distinguish middle ears with and without MEE (Helenius et al. 2012).

Tympanometry to exclude MEE

Tympanometry vs pneumatic otoscopy**.** The type A tympanogram relates to a healthy ear in 78% of symptomatic and in 92% of asymptomatic children (Helenius et al. 2012). In outpatient studies, the type A tympanogram is highly specific (87–98%) and has a high NPV (type A tympanogram and no MEE) of 94–95% to exclude MEE (Palmu et al. 1999, Puhakka et al. 2014, Laine et al. 2015). From another point of view, when the middle ear was healthy by pneumatic otoscopy at symptomatic visits, any peaked tympanogram (A, C1, C2, Cs) was obtained in 96% of tympanometric examinations (Helenius et al. 2012, Puhakka et al. 2014).

Conversely, AOM was diagnosed in 6–13% of middle ear examinations with the type A tympanogram in children less than 24 months of age (Palmu et al. 1999, Revai et al. 2008). This is a good reminder that tympanometry complements pneumatic otoscopy. However, taken together, the type A tympanogram is suitable for most symptomatic children for exclusion of MEE.

Combining tympanograms of type A and type C1 associates with a healthy ear in 83% of symptomatic and in 89% of asymptomatic visits (Helenius et al. 2012). For routine practice, types A and C1 could be grouped together to indicate a healthy, aerated middle ear (Koivunen et al. 1997).

To summarize, tympanometry does not determine specific middle ear diagnoses but can differentiate middle ears with MEE from those without MEE. Helenius et al. (2012) showed that at symptomatic and asymptomatic visits any peaked tympanogram (A, C1, C2, Cs) related to a healthy middle ear in 67% and in 87% of otoscopic examinations, respectively. Importantly, regardless of symptoms, a peaked tympanogram is usually associated with a healthy ear (Helenius et al. 2012).

2.5.4.4 *Nurse studies*

The rationale of nurse-performed tympanometry studies has been the possibility to reorganize primary care resources. If nurses would perform tympanometry to detect or exclude MEE when AOM is suspected, physician resources could be directed to other duties. The success rate in performing tympanometry varies from 60% to 91% and improves with the nurses' examination experience (Blomgren et al. 2007, Laine et al. 2015).

A trained nurse obtained a sensitivity of 79% and specificity of 93% to detect MEE using a minitympanometry to examine young cooperating children (median age 35 months). In uncooperating young children (median age 19 months), the corresponding figures were 71% and 38% (Koivunen et al. 1997). By contrast, nurses who considered a single training session of tympanometry to be adequate obtained markedly worse results. Under ideal examination conditions (cerumen removed) the sensitivity to detect MEE was only 54% and the specificity 82%. Structured training programs were recommended (Blomgren et al. 2007).

The previous Finnish AOM guideline recommended follow-up of the resolution of MEE after an episode of AOM (Heikkinen et al. 2010). Laine et al. (2015) studied the clinical usefulness, *i.e.,* the proportion of visits where a nurse could exclude MEE in both middle ears of an asymptomatic child. Nurses excluded MEE reliably

with type A and C1 tympanograms, the NPV was 95%. However, the proportion of visits where nurses could reliably exclude MEE was moderate, 41%. From a practical point of view, this study showed that nurses could use the device reliably (Laine et al. 2015). Nurse-performed tympanometric examinations merit further studies.

2.5.4.5 *Parent-performed tympanometry*

Already in 1976, Paradise et al. envisioned that tympanometry could be used by paraprofessionals after a teaching session (Paradise et al. 1976). Only three studies have examined tympanometry in the use of parents (Moody et al. 1998, Antonio et al. 2002, Doyle et al. 2009). In addition, two studies have incorporated parental examinations to assess the resolution of MEE after an episode of AOM (Renko et al. 2006, Tapiainen et al. 2014). These studies show that parents are capable and compliant to perform successful tympanometric examinations at home after they have been taught how to use the device. However, none of these studies examined the reliability of the parental examination results, an extremely important factor from an implementation point of view.

Table 2 presents the five studies that have been published on tympanometry performed by the parents. Three of these studies investigated parental compliance in performing tympanometry daily. The aim was to objectively measure middle ear function in relation to RTI and OM for 6 months during the cold season of the year (Moody et al. 1998, Antonio et al. 2002, Doyle et al. 2009). During symptoms of RTI, a negative middle ear pressure preceded the development of MEE. Some children were especially likely to have a negative middle ear pressure, perhaps because of ET dysfunction, and to develop MEE. In these children, the middle ear pressure remained abnormal (negative) for a longer time also during healthy days than in the children who did not develop MEE. An interesting finding was that tympanometry might provide information about the pathogenesis of OM also before the onset of RTI symptoms (Antonio et al. 2002).

In two Finnish studies in primary care the parents monitored at home the resolution of MEE with a tympanometer after their child had had an episode of AOM. In the first study, the diagnostic criteria of AOM included the presence of MEE, acute symptoms of the child (3 months to 7 years of age) and inflammatory signs on the tympanic membrane. The AOM diagnosis was determined by pneumatic otoscopy. The resolution of MEE was defined as the conversion of tympanogram type B to type A or C for at least two consecutive days (Renko et al. 2006). The second study was a randomized, double-blinded, placebo controlled clinical trial. Parents conducted daily tympanometric examinations at home for 14 days or until the

study physician diagnosed a healthy middle ear by pneumatic otoscopy or otomicroscopy (Tapiainen et al. 2014). The success rates of parental tympanometry examinations in these studies were 80% and 87%, respectively. The findings of both studies might not be generalized to the young, otitis-prone population because the mean age of children was >3 years in the study by Renko et al. (2006) and only 20% of the children were less than 2 years in the study by Tapiainen et al. (2014).

Table 2. Parent-performed tympanometry.

	Number of children (n) [families]	Age (range)	Number of obtained Tympanograms (n)	Success rate	Main outcome	Compliance for daily tympanometry
Racecar tympanometry						
Moody 1998	20 [10]	2-7y	160	97%	Parental feasibility to perform daily tympanometry	Average 90%
Antonio 2002	40 [20]	2-6y	NR	97%	The temporal relationship between parental-identified cold and the diagnosis of OM	Median 92%
Doyle 2008	249 [123]	1.1-8y	79902	97% (range 0-83%)	To objectively measure the middle ear function correlation to RTI and OM	67% of the families were 80% compliant; 51% were 90% compliant
MicroTymp, Welch Allyn tympanometry						
Renko 2006	90	3mo-9y	NR	80%	Time to the resolution of MEE after an episode AOM.	Average 83%
Tapiainen 2014	84	6mo-15y	NR	87%	Time to the resolution of MEE after an episode AOM	Mean number of tympanograms per child treatment group: 18, placebo group 20

Abbreviations: MEE, middle ear effusion; RTI, respiratory tract infection; OM, otitis media; AOM, acute otitis media; NR, not reported

2.5.4.6 *Tympanometry and hearing*

MEE may produce a fluctuating conductive hearing loss of 20–30 dB but it can be as great as 50 dB (Paradise 1981, Koivunen et al. 2000). If persistent, MEE may pose a risk for normal communicational development especially for children at risk (Rosenfeld et al. 2013).

Type A and C tympanograms exclude hearing impairment ≥ 25 dB with a 98% accuracy. This result was obtained by Dempster et al. (1991) who examined the ability of tympanometry to detect significant conductive hearing impairment ≥ 25 dB caused by OME in 285 children. In addition, the type B tympanogram was 93% sensitive, but only 76% specific to detect hearing impairment. Approximately half of the children with the type B tympanogram still had normal hearing thresholds (Dempster and MacKenzie 1991).

Tympanometry could provide important information about the hearing of the child. Koivunen et al. 2000 showed that the amount of MEE could indirectly correspond

to the level of hearing loss in children with chronic MEE or recurrent AOM. In their study, tympanometry was performed after the child's premedication and transient evoked otoacoustic emissions (TEOAE) were measured prior to myringotomy with the child under general anesthesia. Reduced or absent TEOAEs, type B (SAA <0.2 mmho) and type C2 (SAA ≥0.2 mmho and TPP -300 to -400 daPa) tympanograms were significantly associated with the weight and type (mucoid, non-mucoid) of MEE obtained in myringotomy (Koivunen et al. 2000).

2.5.5 Spectral gradient acoustic reflectometry (SG-AR)

Spectral gradient acoustic reflectometry (SG-AR) is a handheld adjunctive tool designed both for health care professionals and consumers to provide objective and immediate information about the presence or absence of MEE (Kimball 1998) **(Figure 9)**. Spectral gradient analysis improved the capability of the first acoustic reflectometry device (Teele and Teele 1984) to detect MEE (Kimball 1998, Block et al. 1998).

Figure 9. Consumer model of a spectral gradient acoustic reflectometer (EarCheck™ Middle Ear Monitor).

2.5.5.1 *Principles of SG-AR*

The SG-AR device emits a sweeping sound wave within a range of 1.8 to 4.4 kHz to the ear canal. A microprocessor analyzes the sum of the sound waves emitted to and reflected from the tympanic membrane. The result of the SG-AR examination is called a spectral gradient; it reflects the maximum cancellation of these two sound waves (Kimball 1998).

When the middle ear is healthy and the tympanic membrane is mobile, a greater proportion of the emitted sound waves are reflected from the tympanic membrane as a broad frequency spectrum with a high spectral gradient value. When MEE is present, as in AOM, the mobility of the tympanic membrane is reduced. Thus, the reflected sound wave is louder with a narrower frequency spectrum and lower spectral gradient value (Combs 1988, Kimball 1998, Babb et al. 2004).

2.5.5.2 *Classification of SG-AR results*

The result of the SG-AR examination is classified either as an angle value or as a numerical value, depending on the model of the SG-AR. The professional SG-AR model presents the obtained data as a spectral gradient angle, whereas the consumer model presents it as a numerical scale from one to five. Both interpretations are used to determine the probability of the presence of MEE (Kimball 1998) **(Table 3)**.

Table 3. SG-AR result classifications for consumer and professional SG-AR models.

SG-AR	Consumer Model EarCheck™		Professional Model EarCheck PRO®	Both models
	Color	Recommendation	Angle value range	Probability of MEE
Level 1	Green	"Fluid unlikely"	≥95°	Low
Level 2	Yellow	"Monitor"	70–95°	Moderately low
Level 3	Red	"Consult doctor"	60–69°	Moderate
Level 4	Red	"Consult doctor"	49–59°	Moderately high
Level 5	Red	"Consult doctor"	<49°	High

Abbreviations: MEE, middle ear effusion

2.5.5.3 *Diagnostic accuracy of SG-AR*

The diagnostic accuracy of SG-AR has been studied. However, comparing the study results is not straightforward. Studies use different SG-AR cut-off levels to

detect or to exclude MEE. The study populations are different, some children were referred for surgical treatment of chronic MEE, while others were acutely ill with AOM or had only mild symptoms of RTI. The prevalence of MEE varies by the type of visit. MEE was present in 50% of the sick visits, in 20% of the follow-up (3–5 weeks after an episode of AOM) and in 5% of the visits at 24 months (Teppo et al. 2006). Most of the children in these studies are ≥ 3 years old and this affects the generalizability of these results to the young otitis prone age group. Studies examining the diagnostic accuracy of SG-AR are presented in **Table 4**.

Studies have reported several practical findings. Small ear canals produce more SG-AR error signals. This should be kept in mind when examining young children with constant error signals (Babb et al. 2004). As a technical observation, SG-AR angle values were higher when OME and AOM were diagnosed with air-middle ear effusion interfaces than with middle ears filled with effusion (Laine et al. 2012). It seems that middle ear pressure, the position of the tympanic membrane and the amount of MEE may all affect the SG-AR angle value. A supine position (Teppo and Revonta 2007) and anesthesia by relaxing the ET (Barnett et al. 1998) influence the diagnostic accuracy of SG-AR.

Table 4. Diagnostic accuracy of SG-AR (EarCheckPro and EarCheck) to detect middle ear effusion.

	Number of children (n)	Age	Number of SG-AR examinations (n)	SG-AR performer	SG-AR Success rate	SG-AR definition of MEE	Sensitivity/ Specificity	PPV/NPV
Studies with myringotomy as the reference standard for the detection of middle ear effusion								
Teppo, 2007	50	10mo-6y	100	Phy	83%	≤69° Levels 3-5	83% / 84% 77% / 85%	NR
Teppo, 2009	78	10-76mo	148	Par	82%	Levels 2-5 Levels 3-5	94% / 51% 72% / 85%	60% / 92% 79% / 79%
Linden, 2007	199	7mo-15y	398	Phy	94%	<50° >100°	27% /95% 89% / 44%	78% / 67% 51% / 86%
Muderris, 2013	84	3-14y	168	Phy	100%	Levels 3-5	80% / 73%	83% / 68%
Studies with pneumatic otoscopy as the reference standard for the detection of middle ear effusion								
Barnett, 1998	150	6mo-14y	274	Per	NR	Levels 2-5 (≤95°) Level 5 (<49°)	94% / 30% 36% / 94%	77% / 67% 93% / 37%
Block, 1998	528	6mo-18y	874	Per	99%	Levels 3-5 (≤69°)	67% / 87%	57% / 91%
Block, 1999	102	6mo-12y	160	Per	79%	Levels 3-5 (≤69)	86% / NR	NR
Barnett, 2000	17	9mo-6y	NR	Par: Ped/Nur	80%	NR	NR	NR
Babb, 2004	33	1-12y	43	Phy	92%	Levels 3-5 (≤69°) Levels 4-5 (≤59°)	77% / 96% 59% / 100%	87% / 91%
Teppo, 2006	271	1,5-2y	739	Nur	79%	Acute: ≤59°	42% / 95%	94% / 58%
Chianese, 2007	647	6-24mo	3096	Phy	NR	Levels 3-5 (≤69°)	47%	90%
Laine, 2012	515	6-35mo	Total: 4246 Symp: 2802 Asymp: 1240	Phy	95%	Levels 2-5(≤95°) Levels 4-5 (≤59°)	Symp: 87% / 44% Asymp: 92%/53% Symp: 45% / 78% Asymp: 32%/95%	62% / 76% 63% / 87% 69% / 59% 72% / 77%
Puhakka, 2014	600	6mo-14y	2152	Phy	NR	Levels 3-5 (≤69°)	53% / 93%	48% / 94%
Laine, 2015	156	6-35mo	380	Nur	87%	Levels 2-5(≤95°)	79% / 87%	66% / 95%

Abbreviations: MEE, middle ear effusion; PPV, positive predictive value; NPV, negative predictive value; Phy, physician; Par, parents; Ped, pediatrician; Nur, nurse; Acute, acute sick visit; Symp, symptomatic; Asymp, asymptomatic; NR, not reported

With surgery as the reference standard, extreme SG-AR angle values are relatively reliable indicators of the presence or absence of MEE. With a SG-AR angle value <49º, the PPV (likelihood of presence for MEE in surgery) was 88%. In contrast,

with a SG-AR angle value >95°, the NPV (likelihood of no MEE in surgery) was 83% (Barnett et al. 1998). Linden et al (2007) reported similar findings. The PPV for the SG-AR angle value <50º to detect MEE was 78% and the NPV for a SG-AR angle value >100º to rule out MEE was 86% (Linden et al. 2007). However, there is a wide grey area of diagnostic uncertainty between SG-AR degrees <50° and >100° (Linden et al. 2007). SG-AR levels 2–3–4 are associated with MEE in 40–70% of middle ears (Barnett et al. 1998). These SG-AR recordings are not feasible for determining the presence or absence of MEE prior to surgical treatment of OM.

The diagnostic accuracy of SG-AR compared to tympanometry has been reported to be equal with regard to detection of MEE, and this has been verified at surgery. The sensitivity of SG-AR level 5 (<49º) to detect MEE was 38% and the PPV 88%. The corresponding figures for tympanometric peak compliance <0.1 were 54% and 82% and for peak compliance <0.2, 63% and 78% (Barnett et al. 1998). In children with AOM and with different cut-off levels (type A tympanogram and SG-AR levels 1−2 to exclude MEE, SG-AR levels 3−5 and type C and B tympanograms to indicate MEE), the sensitivity of SG-AR and tympanometry and to correctly detect MEE was 86% and 83%, respectively. The corresponding PPVs were 84% and 76% (Block et al. 1999).

Only a few studies have focused on the diagnostic accuracy of SG-AR in young outpatient children with signs and symptoms of AOM (Chianese et al. 2007, Laine et al. 2012, Puhakka et al. 2014).

With pneumatic otoscopy as the reference standard, Laine et al. (2012) studied SG-AR to discriminate specific otoscopic diagnoses. At symptomatic visits, the middle ear was diagnosed healthy in 76% of the otoscopic examinations which related to SG-AR level 1. Conversely, OME with an air-middle ear effusion interface was diagnosed in 12% of the otoscopic examinations which related to SG-AR level 2. Taken together, 88% of middle ears were considered nearly healthy with SG-AR levels 1–2 when the child was symptomatic. With SG-AR levels 4–5, MEE was diagnosed in 84% and in 96% of otoscopic examinations, respectively. At asymptomatic visits, SG-AR level 1 was associated with a healthy middle ear in 87% of otoscopic examinations. The corresponding figures for SG-AR levels 4–5 to detect MEE were 63% and 83%, respectively (Laine et al. 2012).

Chianese et al. (2007) and Laine et al. (2012) used a receiver operating characteristic curve to describe the overall diagnostic accuracy of SG-AR and tympanometry to differentiate middle ears with MEE from healthy ears. Chianese et al. (2007) reported that the area under the curve for tympanometry and SG-AR to detect MEE were 0.83 and 0.78. The diagnostic accuracy of tympanometry to detect MEE exceeded that of SG-AR. The results may not, however, be

generalized to children with minor RTI symptoms, since these children had AOM and the prevalence of MEE was high, 58% (Chianese et al. 2007). The results were supported by Laine et al. (2012). At symptomatic visits, their analysis gave SG-AR an area under the curve value of 0.81 *i.e.,* good diagnostic accuracy to detect any MEE (OME or AOM). At asymptomatic visits, the area under the curve was 0.76 which associates with a fair diagnostic accuracy for SG-AR to detect MEE (Laine et al. 2012).

Puhakka et al. (2014) assessed the correlation between SG-AR and tympanometry to detect MEE. They included outpatient children with RTI symptoms without exclusion criteria. The overall prevalence of MEE was rather low, only 11%, apparently due to diverse RTI symptoms and a wide age range of the children. Approximately 30% of the children were < 3 years old. SG-AR levels 3–5 and a type B tympanogram were used to indicate MEE. Conversely, SG-AR levels 1–2 (angle ≥70º) and type A/As, C, Cs tympanograms were used to exclude MEE. When a type A/As tympanogram was obtained, the SG-AR level was 1–2 in 96% of examinations. However, with SG-AR levels 1–2, type B tympanograms were obtained in 58% of examinations. With SG-AR values 4–5, a type B tympanogram was obtained in 41% and 68% of examinations, respectively. The overall agreement between SG-AR and tympanometry to detect or exclude MEE was 86%; it was slightly lower (81%) in children <3 years old. The authors found that the NPV was 94% to detect MEE with SG-AR levels 3–5. This means that with SG-AR levels 1–2, MEE would have been present in only 6% of otoscopic examinations (Puhakka et al. 2014). They concluded that these results support the concept of parental home screening with the SG-AR (Block et al. 1998, Barnett et al. 2000).

To summarize, SG-AR level 1 is associated with a healthy ear in symptomatic children, but it cannot exclude MEE (Chianese et al. 2007, Laine et al. 2012). With SG-AR level 1 (n=708), MEE was present in 24% (168/708) of otoscopic examinations (Laine et al. 2012). In asymptomatic children, however, a SG-AR level 1 was obtained in 87% of otoscopic examinations (Laine et al. 2012) and the NPV of SG-AR angle ≥ 100° to exclude MEE was 98% (Teppo et al. 2006). From a primary care perspective, SG-AR level 1 could be used to follow the resolution of MEE after an episode of AOM.

Unfortunately, SG-AR levels 2–3 cannot be used to any extent to predict the presence or absence of MEE (Barnett et al. 1998, Laine et al. 2012). At symptomatic visits, SG-AR levels 2–3 were obtained in 31% (862/2802) and in 12% (339/2802) of examinations. MEE was present in 45% and in 65% of these otoscopic examinations, respectively (Laine et al. 2012). Conversely, at asymptomatic visits, SG-AR level 2–3 were obtained in 35% (428/1240) and in

10% (124/1240) of SG-AR examinations. They related to MEE in 29% (125/428) and in 46% (57/124) of otoscopic examinations, respectively (Laine et al. 2012).

SG-AR levels 4–5 relate to the presence of MEE in symptomatic children (Barnett et al. 1998, Linden et al. 2007, Chianese et al. 2007) and the child should be referred to a physician for further middle ear examinations.

Finally, there is an understanding that the extreme SG-AR levels (1 and 5) relate to a healthy middle ear and to MEE, respectively (Block et al. 1998, Chianese et al. 2007, Laine et al. 2012). However, at symptomatic visits, SG-AR level 1 was present in only 25% (708/2802) and SG-AR level 5 in 16% (452/2802) of all SG-AR examinations. (Laine et al. 2012). This shows that the extreme levels 1 and 5 are obtained relatively rarely, and that most SG-AR results are in the "gray area", levels 2–4, which reduces the diagnostic value of SG-AR. Importantly, the comparison of SG-AR and tympanometry tends to suggest that tympanometry is slightly more accurate for the detection of MEE.

2.5.5.4 *Nurse studies*

The basis for studying nurse-performed SG-AR examinations for detection or exclusion of MEE are similar to those for tympanometry. If nurses would detect or exclude MEE in symptomatic children when parents suspect AOM, SG-AR could be used to guide referral to a physician.

In two studies, the success rate of SG-AR examinations was 79% and 87% and related to the level of the nurses' experience in doing SG-AR examinations (Teppo et al. 2006, Laine et al. 2015).

At sick visits, SG-AR degrees <50º and <60º had a high PPV of 94% and 89% to detect MEE. Among healthy children, the NPV of an SG-AR angle of 100º to exclude MEE was excellent, 98% (Teppo et al. 2006).

Laine et al. (2015) evaluated the clinical usefulness of SG-AR examinations performed by nurses in terms of the proportion of visits where a nurse could exclude MEE in both middle ears of an asymptomatic child. Nurses obtained successful bilateral SG-AR examinations in 81% of the asymptomatic study visits. With SG-AR level 1, the exclusion of MEE was possible only in 15% of visits. This might reflect that SG-AR level 1 is obtained rather rarely (25%) at asymptomatic visits (Laine et al. 2012). These results imply that nurse-performed SG-AR examinations to control the resolution of MEE after an episode of AOM might not be clinically feasible (Laine et al. 2015).

2.5.5.5 *Parent-performed SG-AR*

The question of parents' ability to use the SG-AR in the domestic setting was raised already in the 1990s (Block et al. 1998). However, only three studies have addressed the matter (Barnett et al. 2000, Cullen and Darke 2003, Teppo and Revonta 2009).

Barnett et al. (2000) conducted the first study concerning the home use of the SG-AR. Parents recorded the SG-AR angle readings during RTI and good health with an 80% success rate. However, in this study the parents were either pediatricians or nurse practitioners, *i.e.,* health care professionals. No predictive values were presented for the detection of MEE (Barnett et al. 2000).

Cullen et al. (2003) followed two cohorts of children for one year to evaluate whether the home use of SG-AR impacts the occurrence of unnecessary physician visits related to OM. Most children (nearly 85%) were less than 3 years old. Families in the SG-AR cohort were provided with the SG-AR and parents were asked to monitor their child whenever they suspected OM. No statistically significant difference was found in the total number (mean 3.5) of physician visits between these two study groups. Most parents (70%) were satisfied with using the SG-AR at home and were comfortable when making decisions concerning their child's middle ear status. However, parents stated that despite using the SG-AR, they wanted their physician to examine their child because of comorbid symptoms (Cullen and Darke 2003).

Teppo et al. (2007) showed that when parents examined their child before tympanostomy tube placement, the success rate was 82% and they interpreted the SG-AR results correctly. With SG-AR levels 3–5 as test positive (MEE present), the specificity to detect MEE was 85% and the PPV 79%. When levels 2–5 were representative of MEE, the corresponding figures were reduced to 51% and 60%, respectively. In this study, the prevalence of MEE was high (39%), as expected (Teppo and Revonta 2007).

These studies show that parents perform the SG-AR examinations with a high success rate (80–82%) reaching that of physicians (83%) (Teppo and Revonta 2007). Others have reported much higher success rates for physicians, 94% and of 95% (Linden et al. 2007, Laine et al. 2012).

2.5.5.6 *SG-AR and hearing*

Lee et al. (2013) investigated the applicability of SG-AR to screen for hearing loss in children 1–14 years of age. SG-AR, tympanometry and pure tone audiometry were performed and speech reception thresholds established before surgical treatment of chronic OME. When age-appropriate hearing tests are not available, this study suggested that SG-AR levels ≥3 could be used as an adjunctive tool for making decisions on surgical treatments, because it correlated with pure tone audiometry and speech reception thresholds. However, these results are not applicable to regular outpatients, because of the chronic characteristics of OM, and the high prevalence (87%) of MEE. The potential value of SG-AR in identifying hearing loss with higher SG-AR levels was brought up already by Barnett et al. (2000), but data on this question is very limited.

2.6 Management

2.6.1 Symptomatic treatment

Symptomatic treatment is important to relieve ear pain, fever and rhinitis, all of which are symptoms of both viral RTI and its sequelae AOM (Lieberthal et al. 2013). Paracetamol, ibuprofen or naproxen may be used orally at age-adjusted doses (Bertin et al. 1996, Heikkinen et al. 2017). When AOM is diagnosed, anesthetic ear drops may provide additional relief of otalgia (Foxlee et al. 2006). Antihistamines might prolong the duration of MEE. Antihistamines or corticosteroids are not beneficial with respect to AOM outcomes and are not thus recommended (Chonmaitree et al. 2003). Myringotomy or tympanocentesis are no longer recommended unless complications are suspected because they are painful and non-effective treatment modalities (Van Buchem et al. 1981, Engelhard et al. 1989, Shaikh et al. 2011b).

2.6.2 Antimicrobial drug treatment

In this era of emergence of multiresistant pathogens, reducing unnecessary antibiotic use is important. One of the important questions in the treatment of AOM is: Which children will benefit from antibiotics? In 2006, a meta-analysis of six randomized clinical trials concluded that children ≤2 years old with bilateral AOM, or with otorrhoea benefit from antibiotic treatment (Rovers et al. 2006). At the moment, the US guideline recommends that children of any age with otorrhoea or

severe symptoms (severe or moderate otalgia, otalgia ≥48 hours or fever ≥ 39°C) should be treated with antibiotics (Lieberthal et al. 2013).

A review of 157 AOM treatment trials (years 1965–2005) involving 36,710 children reported that the study designs varied by outcome measures and timing, and most importantly, by diagnostic criteria of AOM. The review concluded that the clinical diagnosis of AOM should be clarified to aid physicians to diagnose, treat and compare the results of different AOM trials (Pichichero and Casey 2008a).

In 2011 two randomized placebo-controlled trials proved that antibiotic treatment is beneficial in young outpatient children (6–35 months) with stringently diagnosed AOM (Hoberman et al. 2011, Tähtinen et al. 2011). Children in the first study received amoxicillin-clavulanate for 10 days and in the second study for 7 days. Tähtinen et al. (2011) reported that treatment failed in 19% of the children on antibiotics and in 45% of the children on placebo. Overall, in the amoxicillin-clavulanate treated group the need for rescue treatment was reduced by 81% and the resolution of symptoms was faster compared to the group on placebo. Hoberman et al. (2011) reported clinical failure at the end-of-treatment (day 10–12) in 16% and in 51% of children on treatment and placebo, respectively. Very importantly, both studies had the same diagnostic criteria of AOM (acute onset of symptoms, detection of MEE, signs of acute inflammation and bulging tympanic membrane by pneumatic otoscopy) and used improvement of clinical symptoms and otoscopic signs to assess treatment failure or success. Treatment failure was defined as no improvement or worsening of the child's overall condition, no improvement of the otoscopic signs at end-of-treatment, severe infection necessitating open-label antibiotic or any reason for discontinuing the study drug. In both studies, diarrhea and eczema were the most common adverse events in the amoxicillin-clavulanate group.

A secondary analysis from the study of Tähtinen et al. (2011) recently showed that children with AOM and severe bulging of the tympanic membrane seem to benefit most from antimicrobial treatment when compared to placebo (Tähtinen et al. 2017). The proportion of treatment failures in the antimicrobial treatment and placebo groups were 11% and 64%, respectively. From another point of view, a peaked tympanogram (type A, C1 and C2 tympanograms) and age 24–35 months at the time of AOM diagnosis decreased the risk for treatment failure. Physicians could use these findings to guide their AOM treatment strategies and to avoid unnecessary antibiotic prescriptions (Tähtinen et al. 2017).

Delayed versus immediate antimicrobial treatment of AOM has been studied. Tähtinen et al (2012) found no significant differences in the improvement of AOM between the delayed (48 hours) and immediate treatment groups in young children

6–35 months of age. However, the time to the resolution of symptoms, such as fever (48 hours vs 6 hours), and to a normal otoscopic finding at study day 16 (50% vs 36%), was longer in the delayed treatment group. Furthermore, child absenteeism from day care (3 days vs 2 days) and parental absenteeism from work (2 days vs 1 day), were longer in the delayed treatment group (Tähtinen et al. 2012). In another study, parents reported that immediate antibiotic prescription usually relieved symptoms (*e.g.*, fever, disturbed sleep, need for analgesia) after the first 24 hours. On the other hand, parents filled in the prescription for only 23% of the children in the delayed group (72 hours) (Little et al. 2001). Spiro et al. (2006) showed that a delayed antibiotic prescription was filled in for 38% of all children (median age 3.6 years) and for 53% of children younger than ≤2 years. The most important reasons for parents to get the delayed prescription were fever and otalgia (Spiro et al. 2006). Thus, the management strategy affects the child, the parents and the society.

Amoxicillin or amoxicillin-clavulanate are the drugs of choice for the treatment of AOM (Heikkinen et al. 2017). The duration of the antimicrobial treatment varies between 5 and 10 days (Lieberthal et al. 2013, Hoberman et al. 2016, Heikkinen et al. 2017). The amoxicillin dosage of 80–90 mg/kg/day is recommended in countries with a high prevalence of penicillin-resistant pneumococci, or when the child does not respond to the 40mg/kg/day dosage (Lieberthal et al. 2013).

Physicians should keep track of the microbiologic reports on the occurrence of resistance of the main pathogens of AOM so the proper antibiotics are used. In Finland, the proportion of amoxicillin resistant *S. pneumoniae* in pus samples of children less than 5 years old was approximately 1% and of *H. influenzae* 24% in 2015 (Jalava 2016). Amoxicillin had limited efficacy on about 9% of the *S. pneumoniae* cultures. Approximately 25% of *H. influenzae* and nearly all strains of *M. catarrhalis* produced beta-lactamase and were resistant to penicillin and amoxicillin. However, these bacteria could have been eradicated with amoxicillin-clavulanate.

Macrolides, such as azithromycin, have no effect on *H. influenzae* and nearly 30% of *S. pneumoniae* strains were reported to be resistant to macrolides (Jalava 2016). The recent US AOM guideline suggests that macrolides are not justified as an initial choice of antibiotic treatment unless the child is allergic to penicillin (Lieberthal et al. 2013). Sulfa-trimethoprim is recommended only for children allergic to penicillin (Heikkinen et al. 2017). In children with tympanostomy tubes, topical antibiotic treatment of AOM is recommended (van Dongen et al. 2014).

2.6.3 Watchful waiting

The rationale for watchful waiting *i.e*., initial observation and antibiotic prescription only when the child's symptoms deteriorate within a few days, is based on the overall benign course of AOM. The discussion of watchful waiting started after a meta-analysis summarized that AOM had a spontaneous resolution rate of approximately 80% and that the benefit from antibiotic treatment was only 14% over placebo (Rosenfeld et al. 1994).

Two reviews raised concerns about the watchful waiting strategy (Pichichero and Casey 2008a, Pichichero and Casey 2008b). The reviews consisted of observational and natural history studies (from the years 1958–2006) in which children had not received antibiotics to treat AOM. Most of the studies were not qualified for the diagnostic criteria of AOM; bulging of the tympanic membrane was only required in roughly 50% and MEE in only 30% of studies. Moreover, the children were often older than 2 years and children with a severe AOM (*i.e.,* perforation of the tympanic membrane), or who needed antibiotics, were excluded. Children who were treated with antibiotics were treated with sub-optimal dosing or antibiotics with limited efficacy (Pichichero and Casey 2008a, Pichichero and Casey 2008b).

The main aim of watchful waiting is to reduce the use of antimicrobials (Lieberthal et al. 2013). At the moment, AOM guidelines allow for watchful waiting for children aged 6–23 months with unilateral AOM without severe symptoms; the possibility for close follow-up is emphasized (Lieberthal et al. 2013, Heikkinen et al. 2017). Uitti et al. (2016), however, questioned the necessity of close follow-up of young outpatient children with strictly diagnosed AOM who were initially managed without antibiotics. When parents assessed that the overall condition of their child had improved in 48 to 72 hours of the AOM diagnosis, only 3% of children developed worse signs or tympanic membrane perforation at one week compared to 30% of the children whose parents assessed that the child's overall condition had deteriorated. If only those children with symptomatic failure were reexamined, it could relieve the family and primary care burden by reducing the unnecessary follow-up visits (Uitti et al. 2016).

Parental satisfaction with watchful waiting and acceptance of this strategy is associated with higher parental education and involvement with the decision making with the physician. Parental concerns of watchful waiting have often related to prolonged symptoms or to a risk of a more serious condition of the child (Finkelstein et al. 2005). Parents familiar with the problems of antibiotic resistance were most likely willing to accept the watchful waiting strategy (Broides et al. 2016). Furthermore, parents who were told about the self-limited nature of AOM

and the controversy of antibiotic treatment, filled antibiotic prescriptions in for their child less often (Pshetizky et al. 2003).

2.6.4 Resolution of middle ear effusion

The natural course of the spontaneous resolution of MEE after an episode of AOM is favorable. Resolution of MEE occurred in 59% and in 74% children with untreated AOM at 1 and 3 months, respectively. When the initial timing of the appearance of MEE was unknown, 28% resolved by 3 months. However, from 3 months onward, only 25% of MEE resolved by 6 months, and 33% by one year (Rosenfeld and Kay 2003).

An epidemiological study among children under 3 years of age demonstrated that when children were treated with antibiotics for AOM, MEE resolved in 30% of ears within 14 days, in 60% within one month, in 80% within 2 months and in 90% within 3 months in children less than 3 years of age (Teele et al. 1980).

It is not easy to determine the effect of antibiotic treatment with regard to the resolution of MEE. These young children often present with new symptoms of viral RTI, perhaps even AOM, in the time frames discussed above. Renko et al. (2006) reported that the median time to the resolution of MEE after an episode of AOM was 14 days in 69% of children treated with antibiotics (Renko et al. 2006). Tapiainen et al. (2014) conducted a randomized, double-blind, placebo controlled clinical trial to assess the time to disappearance of MEE after an episode of AOM. In this study, parents performed daily tympanometric examinations at home for 14 days or until the study physician diagnosed a healthy ear by pneumatic otoscopy or otomicroscopy. The definition of a healthy ear was a type A tympanogram from both ears on two consecutive measurement days. The mean time to the resolution of MEE was significantly shorter (19 days vs. 33 days) in the group treated with amoxicillin-clavulanate than with placebo. After 14 days, a normal otoscopic status and a type A tympanogram were present in 45% and 69% of the children treated with antimicrobials and in 19% and 38% of the children on placebo, respectively. The corresponding figures for persistent MEE at 60 days were 5% and 24%. The generalizability of these results is reduced by the fact that only 20% of the children were less than 2 years old (Tapiainen et al. 2014). Still, this study raised the question about preferring antibiotics as an initial treatment of AOM, especially for children at risk for cognitive developmental disorders.

Ruohola et al. (2017) reported that the most important predictors of prolonged resolution of MEE after an episode of AOM were recurrent AOM, viral RTI and nasopharyngeal bacterial colonization. In contrast to the findings of Tapiainen et

al. (2014), they found that antibiotic treatment did not hasten statistically significantly the time to resolution of MEE (a median of 20 days in the amoxicillin-clavulanate treated group vs 29 days in the group on placebo). A new observation was that with one recurrent AOM, the median time to the resolution of MEE was 67 days compared to 15 days for those children with no recurrent AOM. A peaked tympanogram at entry and a unilateral AOM related to a faster resolution of MEE (Ruohola et al. 2017). This study was conducted in young outpatient children under age 3 years with strict AOM criteria; thus, these results are applicable to the otitis prone population in general.

2.6.5 Follow-up visits after an episode of acute otitis media

In Scandinavia, the resolution of MEE after an episode of AOM is followed by different protocols. The US AOM guideline, however, does not recommend routine follow-up but emphasizes the importance of accurately diagnosing OME, a self-limiting condition (Lieberthal et al. 2013). Overdiagnosis and overtreatment of OME impact on the child and the health care system by unnecessary surgical and antibiotic treatments (Pichichero 2000, Rosenfeld et al. 2016).

In Finland, the previous AOM guideline recommended a follow-up visit for every child every 3–4 weeks until 3 months (Heikkinen et al. 2010). The recent update, however, states that data on the appropriate necessity and/or timing of these follow-up visits are lacking. Currently, the need for follow-up visits should be assessed individually (Heikkinen et al. 2017).

In Norway, a follow-up visit is recommended once 6–12 weeks after the diagnosis, especially for children not treated with an antibiotic (Norsk forening for otorhinolaryngologi, hode- og halskirurgi 2012). In Sweden, the child is checked at three months only of the AOM/OME was bilateral or if the tympanic membrane was perforated (Läkemedelsverket 2010).

Are these scheduled follow-up visits needed? The optimal timing of these visits is a challenge, since the natural time to the resolution of MEE or the time to resolution after antibiotic treatment after an episode of AOM varies (Teele et al. 1980, Rosenfeld and Kay 2003). Could the burden on families and primary care by repeated follow-up visits be eased by examining only children in risk for prolonged MEE? The study by Ruohola et al. (2017) importantly found that recurrent AOM and viral RTI are the most important predictors of prolonged resolution of MEE (Ruohola et al. 2017). Since these results were obtained from the young outpatient population, the need for a systematic follow-up protocol after an episode of AOM may be questioned.

2.6.6 Surgical treatments

After three months, the probability of spontaneous resolution of MEE decreases. Patients at risk are characterized by young age, day care and older siblings. All of these risk factors cause an increased risk for recurrent viral RTI and AOM. Children at greatest risk for complications, such as conductive hearing loss, delayed speech and cognitive developmental difficulties due to persistent MEE, should be treated with tympanostomy tube placement (Rosenfeld et al. 2016). In otherwise healthy children aged < 3 years with persistent MEE, prompt *vs.* delayed tympanostomy tube placement did not improve the developmental outcomes at age 9−11 years (Paradise et al. 2007). The expected benefits and potential risks of surgical intervention must be weighed case-by-case. Adenoidectomy together with tympanostomy tube placement is recommended for children < 4 years old only if they have nasal obstruction or chronic adenoiditis (Rosenfeld et al. 2016).

2.6.7 Physician adherence to treatment guidelines

Recent studies have demonstrated that physicians adhere rather variably to AOM treatment guidelines (Forrest et al. 2013, Lieberthal et al. 2013).

Overdiagnosis of AOM is an acknowledged problem and the detection of MEE might be difficult even in cooperating children. Rosenfeld (2002) concluded that if primary care physicians would diagnose AOM according to guidelines, antibiotic prescriptions would diminish by 29% (Rosenfeld 2002).

One reason for overdiagnosis might be that physicians do not have readily access to adequate diagnostic tools or do not use them if they have access. Pneumatic otoscopy, which is needed to differentiate a healthy ear from OME and AOM, was available only for 36% of the physicians in one study and only 11% used it (Jensen and Lous 1999). In addition, pneumatic otoscopy performance rates vary between 3.5% and 66% (MacClements et al. 2002, Marchisio et al. 2012). Alarmingly, one study even showed that physicians might consider AOM as a minor trouble and may thus be reluctant to invest in diagnostics (Kontiokari et al. 2000).

Guidelines recommend tympanometry as an adjunct to pneumatic otoscopy to detect or exclude MEE (Lieberthal et al. 2013, Rosenfeld et al. 2016, Heikkinen et al. 2017). Although the use of tympanometry improves the diagnostic accuracy of AOM (Johansen et al. 2000, Blomgren and Pitkäranta 2003), physicians perform it only seldom (Jensen and Lous 1999, Honkanen et al. 2002, Rosenkranz et al. 2012). The number of AOM diagnoses decreased by 56% in children with recurrent AOM when pneumatic otoscopy and the type B-tympanogram were used

to diagnose AOM (Blomgren et al. 2004). It is disconcerting that the use of tympanometry did not reduce antibiotic prescriptions among GPs (Johansen et al. 2000) and that despite focused training in the art of tympanometry, physicians diagnosed and prescribed antibiotics to treat AOM with type A and C tympanograms (in 14–40% of cases) (Spiro et al. 2004).

Watchful waiting does not seem to be favored, and when antibiotics are prescribed, the dosage or duration of treatment does not follow recommendations (Célind et al. 2014, Palma et al. 2015, Marom et al. 2017). Antibiotics may be prescribed even on demand of the parents (Bauchner et al. 1999).

Cerumen impairs the view of the tympanic membrane and challenges diagnostics. The removal of cerumen is not always a simple feat, especially in a resisting child (Legros et al. 2008, Marchisio et al. 2016). This might be one of the reasons for physicians to neglect the importance of removing obstructive cerumen, something recommended by several AOM guidelines (Marchisio et al. 2010, Heikkinen et al. 2017).

The way physicians diagnose and treat AOM affects the child, the family and public health services with immediate and far-reaching consequences. Guidelines are evidence-based summaries, recommendations, which aim to standardize patient care efficiently and safely. It seems, however, that the implementation of guidelines into practice is not simple and is fraught with many challenges (Carlsen and Norheim 2008, Haggard 2011, Carthey et al. 2011).

2.7 Burden of AOM

AOM is one of the most common reasons for a child to visit a primary care physician (Arguedas et al. 2010). An internet questionnaire sent to 17,354 European parents revealed that parents consulted a physician in 47–87% of the times when their child (1−5 years) had symptoms of any illness and in 72−99% of cases when symptoms of AOM were present. Depending on the country, families consulted a GP in 3−87%, a pediatrician in 4−90% and the emergency department in 2−34% of physician confirmed AOM episodes. Per one episode of AOM, the mean number of visits to a GP and to the emergency department was approximately 2 (range 1−6 and 1–10, respectively) (Wolleswinkel-van den Bosch, et al. 2010, Speets et al. 2011a, Speets et al. 2011b).

Office visits constitute the largest proportion of the total AOM costs (5 billion US$) which are highest in children aged 1–2 years (Bondy et al. 2000). The cost differences between regular office and emergency department visits are

substantial. A large cross-sectional analysis of incremental costs related to the diagnosis and treatment of AOM concluded that AOM accounted for nearly 3 billion US$ in added health care expenses when compared to children without AOM (Ahmed et al. 2014). Complex episodes of AOM, relapses, are more costly than single episodes of AOM (Capra et al. 2000).

AOM places a considerable burden on health care systems, families and children (Greenberg et al. 2003, Wolleswinkel-van den Bosch, et al. 2010, Dube et al. 2011, Marchisio et al. 2012, Barber et al. 2014). It is one of the main indications for antibiotic prescriptions in children younger than 3 years of age (Lieberthal et al. 2013). OME is the most common cause for pediatric surgery (Rosenfeld et al. 2016). Emphasis should be put on measures to prevent AOM, especially in young children. Accurate AOM diagnostics and reduction of unnecessary physician visits are of major importance (Bondy et al. 2000, Arguedas et al. 2010).

2.8 Pediatric telemedicine

The American Telemedicine Association defines telemedicine as “the remote delivery of health care services and clinical information using telecommunications technology. This includes a wide array of clinical services using internet, wireless, satellite and telephone media”. The term telehealth is wider and it includes clinical and non-clinical services. The terms telemedicine and telehealth are viewed as synonymous and interchangeable terms (American Telemedicine Association 2016). Telemedicine includes telepractice, teleconsultations, tele-education and teleresearch (Burke and Hall 2015). The possibilities to provide access to care, enhance quality of patient care, improve efficiency and reduce costs are among the goals of the technological development of telemedicine. The expected benefits include: aid with visual diagnosis; identification of high-stake events with low frequency; allowance of second opinions also to reassure parents; assessment of the level of illness especially in infants; and avoidance of unnecessary transfers (Kim et al. 2017).

The first pediatric telemedicine studies were conducted in the 1970s (Cunningham et al. 1978). Since then, the internet and the explosive development of mobile technology have contributed to the rapid expansion of telemedicine. The policy statements of the American Academy of Pediatrics have emphasized the importance of implementing telemedicine methods into pediatric care (Committee on Pediatric Emergency Medicine 2007, Marcin et al. 2015).

Store-and-forward technology is used when it is unnecessary to examine the patient person-to-person. In this form of telemedicine, the patient’s medical history

and information about the present illness are first recorded in an electronic database. The data includes laboratory results, images (*e.g.,* radiographs, computed tomography, magnetic resonance imaging), tracings (electrocardiograph, electroencephalogram) or videos (*e.g.,* ultrasound). These data are accessible to a physician for further evaluation, analysis and clinical decision making in an offsite location. This technology is used in tele-radiology (Zennaro et al. 2014, Rowell et al. 2014, Westberg et al. 2017), tele-dermatology (Heffner et al. 2009, Fogel and Teng 2015) and tele-cardiology (Satou et al. 2017).

A prospective 1-year study from the Electronic Children's hospital of the Pacific showed that expeditious store-and-forward consultations improved the quality of patient care, diagnosis and management in 15−24% of cases, and reduced the need for patient transport (12%) and, ultimately, costs (Callahan et al. 2005). Later, a retrospective review by the Pacific Asynchronous Telehealth system showed that the consultation questions were solved in 60% of all 1000 teleconsultations; to this extent, the need for an in-person office visit was obviated. Although this pediatric population was under military healthcare, the Pacific Asynchronous Telehealth was considered to work as a model for civilian pediatric population, as well (Mahnke et al. 2011).

Remote monitoring telemedicine includes the patient's continuous monitoring in real-time from a distant location. Monitored data consists of physiological variables, electrocardiography (telemetry) and electroencephalography or pulse oximetry. This technology may be used in tele-neurology (Velasquez et al. 2016) and in hospital surroundings for critically ill patients (Marcin et al. 2004a). The quality of telemedicine can meet high standards even in acute intensive-care units. Despite the severity of the child's condition, health care professionals and parents have been satisfied with the use of telemedicine (Marcin et al. 2004b). When remote monitoring is combined with audio visual monitoring, it is called telemonitoring (Gattu et al. 2016).

Real time interactive audio-videoconferencing technology allows live discussions and visual communication with one or more counterparts. The high technology of audio-video streams and the examination equipment have increased the accuracy of the assessment of the patient's clinical condition (Gattu et al. 2016). The provision of real-time pediatrician consultations to primary care physicians during an RTI season led to an 83% reduction in transfers to a next-level hospital of children ≤ 5 years old. This shortened waiting times, improved primary care and reduced costs (Cifuentes et al. 2017).

Nurses and child care center staff with no prior health care education were trained to work as telemedicine assistants and performed 940 telemedicine visits at the day care center. They obtained high-quality diagnostic images (*e.g.,* of the tympanic

membrane), removed cerumen, conducted electronic stethoscope examinations, measured vital signs, made rapid streptococcal tests and administered nebulized medications. This combination of store-and-forward information and the real-time interaction with a physician resulted in only 3% of the telemedicine visits requiring an in-person physician visit. In other words, 97 % of the telemedicine visits led to decision making without the physical presence of a physician (McConnochie et al. 2005).

In another study setting, 520 pediatric primary care acute visits were randomized to telemedicine or in-person visits to assess the effectiveness of three telemedicine models to replace usual care. Children with a condition known on beforehand to require an in-person visit (*e.g.,* limb injury, abdominal pain) where excluded. Approximately half of the visits were related to RTI symptoms. All children (mean age 5.6 years) visited their regular physician. They also visited the telemedicine physician and the in-person physician, both unable to conduct hands-on clinical examinations. The base model included only the patient's history and physical examination via telemedicine. The simple model included also a few laboratory tests (urine testing, rapid streptococcal test) and administration of nebulized medication. The extended model included unrestricted laboratory testing. For analysis, the proportions of visits completed by the regular care physician, telemedicine physician and in-person physician with these three models were calculated. In the base model, the proportions of visit completion were 76%, 74% and 77% for the regular physician, telemedicine physician and in-person physician, respectively. For the simple model, the figures were 85%, 85% and 87%, respectively, and for the extended model, 100%, 97% and 97%. In conclusion, 85% of the visits to primary care pediatric physician could be completed by a telemedicine model including a few simple laboratory tests (McConnochie et al. 2006).

mHealth, also known as mobile health, is a form of telemedicine using wireless devices and mobile phone/smartphone technologies (American Telemedicine Association 2016). Since smartphones and internet are accessible to most families and adolescents (St. George et al. 2016), mHealth is a rapidly growing field of telemedicine.

mHealth has been introduced into the care and symptom follow-up of chronic pediatric diseases, such as type 1 diabetes and asthma (Carroll et al. 2011, Johnson et al. 2016). For asthma, studies have shown improved self-reported medication adherence, quality of life and self-efficacy compared to the children in the control groups who only received conventional asthma care (Jan et al. 2007, Mosnaim et al. 2015, Farooqui et al. 2015, Johnson et al. 2016). Telemedicine visits were non-inferior to in-person visits when asthma outcomes were compared after a six-

month period (Portnoy et al. 2016). Parents consider that care provided by mHealth relieve their burden of worrying (Carroll et al. 2011, Prakasam et al. 2017). These studies provide important feasibility information and urge further studies on the use of mHealth in the care of chronic pediatric diseases.

mHealth has been investigated in triage settings. Children (mean age 4.9 years) with asthma exacerbation were recruited to evaluate the feasibility and clinical value of parentally obtained mobile phone videos in the triage assessment of the child's respiratory status. Most of the parents (75%) succeeded to take a video and send it by text message or email to the study personnel. Nearly 70% of the videos were considered to be of sufficient quality for evaluation (Freeman et al. 2017). An observational study found an excellent interrater agreement between the simultaneous assessments of young febrile children (median age 15 months) by bedside pediatrician and a pediatrician using iPad and Face-Time-technology. A separate cohort of children 2 months to 18 years of age presenting with respiratory symptoms were also recruited in the same study. All assessed components were visual signs suitable for telemedicine evaluations. It was concluded that clinical impressions or "gestalt" was not lost with telemedicine (Siew et al. 2016).

2.8.1 Implementation of pediatric telemedicine

Telemedicine studies conducted so far have demonstrated several benefits **(Table 5)** related to the implementation of pediatric telemedicine, a relatively new and emerging concept of care.

Parents appreciate telemedicine because of convenient access to care. It was the most important reason (96%) for parents to choose telemedicine as their child's acute care. Without this option, 30% of the parents would have taken their school-aged child to the emergency department and 50% would have sought care elsewhere (McIntosh et al. 2014). After the parents had been familiarized with telemedicine, 50% requested for such a visit when available, and 94% would have chosen a daycare center with telemedicine services over one without (McConnochie et al. 2005). All of the parents (98%) were very satisfied with the care their child received, 83% were interested in future telemedicine visits for their child and 95% for themselves (McIntosh et al. 2014).

Parents value the time and cost saving effect of telemedicine visits (Dick et al. 1999, Wood et al. 2016, Russo et al. 2017). Nearly 50% of the favorable comments of 800 parents, who were interviewed before and after their child's (mean age 6.3 years, range 7 months to 13 years) first telemedicine visits, related to the parental time/work time saved (McConnochie et al. 2010a). One telemedicine visit saved

approximately 4.5 hours of working time (McConnochie et al. 2005). Other positive comments related to quicker diagnosis and treatment (5%), avoidance of emergency department visits and to lesser exposure to children with contagious diseases. Only 3% of the negative comments concerned the reliability of the diagnosis. Others addressed communication issues, limitations of the scope of problems that telemedicine could address, and preference of in-person care (McConnochie et al. 2010a). The family concerns related to privacy have been controversial (Utidjian and Abramson 2016, Russo et al. 2017).

Parents expect the health issue to be solved at the telemedicine visit, otherwise they will seek care elsewhere (McConnochie et al. 2005, McIntosh et al. 2014). The term "visit completion" is used for the ability of the clinician to evaluate the child and feel confident that the information obtained is adequate to make accurate diagnostic decisions and treatment plans. "A telemedicine service without this possibility would be nothing more than an expensive telephone-triage system" (McConnochie et al. 2005).

Physicians completed 97% of the 2,554 attempted telemedicine visits during the 24−month Primary Care Phase in the development of Health-e-Access Telemedicine program. Physicians were able to provide their services with high efficiency and achieved an 83% continuity in care, *i.e.*, the child's care was provided by the physician who worked at the patient's primary care practice. The reasons for incomplete visits (3%) were a need for hands-on examination (30%), insufficient treatment possibilities at the patient site (30%), a need for further testing or imaging (14%) and technical issues (*e.g.,* poor image or sound data) (18%). Overall, 46% of the physicians were confident in making diagnoses via telemedicine, but among physicians who completed more than 50 telemedicine visits, the figure was 83% (McConnochie et al. 2010b). However, these results were obtained in a carefully organized program, and are not universally generalizable.

Telemedicine improves care by optimizing treatment and medications. The diagnosis or treatment plan was changed in 74% of teleconsultations (Mahnke et al. 2011), and antibiotic prescription suspended or formulated in 17% of teleconsultations related to children with respiratory symptoms (Cifuentes et al. 2017). Telemedicine has also reduced physician-related medication errors (Dharmar et al. 2013).

Telemedicine equalizes the socioeconomic differences restricting children's access to care. Children with a higher socioeconomic status had 75% more overall acute visits than impoverished children before access to telemedicine. After the implementation of telemedicine, the overall number of acute illness visits of the impoverished children reached that of the affluent ones (Ronis et al. 2017).

Table 5. Benefits of pediatric telemedicine. (McConnochie 2006, Burke and Hall 2015, Marcin et al. 2015, Utidjian and Abramson 2016).

Benefit	Specific description
Access to care	Reduces missed appointment rates
	Diversity of appointment schedules
	Possibility to better continuity to care
	Eliminates geography as a barrier to access
Physician	Education
	Higher quality care
	More services to offer
	Enhance subspecialist consultations
	Support and guidance from tertiary locations
Patient/Family	Education
	Time-saving
	Enhance self-management
	Increased adherence to care
	Increased disease awareness
	Reduce parental work absence
Primary care resource utilization	Reduce emergency room visits
	Avoid redundant diagnostic testing
	Reduce unnecessary patient transports
	Reduce unnecessary referrals by prescreening
	Better use of limited resources by enhancing communication between providers

The adoption of telemedicine must overcome several obstacles **(Table 6).** Pediatricians have expressed needs for specific methods to optimize and design effective telemedicine treatment strategies (Ray et al. 2015, Ray et al. 2016). Health service acceptance of pediatric telemedicine depends on factors of organizational, technological, resource, cultural, financial, legal and individual character (Ray et al. 2016).

The initialization of telemedicine might require significant up-front costs affecting the speed with which telemedicine is implemented − despite expected cost savings. Concomitantly with a nearly 25% increase in illness-related telemedicine utilization rates, the number of emergency department visits were reduced by approximately 22% compared to children without telemedicine access. The overall illness-related expenditures decreased because telemedicine visits were less expensive than emergency department visits (McConnochie et al. 2009). The American Association of Pediatrics recommends stable funding mechanisms to support continuous development, expansion and maintenance of telemedicine, as well as financial incentives to health care providers who have successfully integrated telemedicine into practice (Marcin et al. 2015).

Table 6. Barriers to implementation of pediatric telemedicine. (Burke and Hall 2015, Utidjian and Abramson 2016, Ray et al. 2016, Russo et al. 2017, Kim et al. 2017).

Type of barrier	Specific description
Physician	Loss of personal contact
	Perceived technical difficulties
	Lack of education and familiarity
	Perceived usefulness and ease of use
	Implementation to normal work-flow and especially in time-sensitive situations
Patient/Family	Lack of education
	Loss of personal contact
	Privacy and security concerns
	Perceived technical difficulties
	Trustfulness towards the telemedicine tools
	Burden the family by excessive responsibilities
Technological	Lack of infrastructure
	Lack of high quality equipment
Financial	Lack of return on investment
	Lack of clear reimbursement policy
	Need of ongoing technical support/maintenance
	Requires significant up-front costs, personnel, education and training
Administrative	Bureaucracy
	Credentialing and licensing process
Legal	Technology failure
	Medicolegal liability issues

Telemedicine possess an enormous resource as a provider of the core elements of primary care: it is accessible, continuously available, family-centered, comprehensive, compassionate, coordinated and effective (American Academy of Pediatrics Medical Home Initiatives for Children With Special Needs Project Advisory Committee 2004, Marcin et al. 2015). High quality studies are warranted to examine the efficacy, cost-effectiveness and impact of telemedicine interventions on pediatric outcomes. Telemedicine will undoubtedly have a major role in the future of health care delivery.

2.8.2 Telemedicine in pediatric otorhinolaryngology

Telemedicine could be useful for easing the burden of AOM. The pioneering 12-year Health-e-Access Telemedicine program (2001−2013) provided 13,812 telemedicine visits for children in daycare, elementary schools, neighbor after-hours sites and medical homes (McConnochie et al. 2016). Of these children (mean age 5.3 years), one-fourth were younger than 2 years of age. A huge majority (98%) of all these visits were completed, indicating that the telemedicine visit resulted in diagnosis, management decisions and treatment similarly as they would

have been completed under an in-person visit. More than one-third (39%) of the diagnoses were related to RTI and middle ear conditions. The top diagnoses included AOM (20%), followed by RTI (10%), OME (4%), ear pain (4%) and cerumen impaction (1%) (McConnochie et al. 2016).

Video-otoscopy

The validity of VO was assessed in a study involving 66 aboriginal children (age range 9 months to 16 years) living 1000 kilometers from the nearest major city. A pediatric otolaryngologist determined a middle ear diagnosis after examining these children by otoscopy, tympanometry and pure-tone audiometry following pre-defined criteria. Then the ears were imaged by VO. A month later the same physician assessed the images using an internet-browser. The importance of cerumen removal to improve image quality was pointed out; cerumen was present in 20% and 53% of field and tele-otology examinations, respectively. The overall image quality was good, and tended to be better in older children. There was significant agreement for the diagnoses of AOM, OME and ET dysfunction. With high quality images combined to tympanometry and clinical patient data, middle ear diagnoses and recommendations of management can be determined with confidence (Eikelboom et al. 2005). Smith et al. (2008) similarly reported a high agreement for diagnosis (99%) and management plans (93%) between real-time telemedicine and face-to-face assessments in 152 otolaryngology consultations of 97 children (age range 14 months to 15 years) (Smith et al. 2008). Although promising, these results are not generalizable to children with AOM, because the diagnoses were preferentially related to chronic conditions of OM.

In Sweden, 64 children (age 2−16 years) with otalgia where examined in an attempt to identify the significant features of a good quality tympanic membrane image (Lundberg et al. 2008). Approximately one-third of the children were 2−4 years old. A specially trained nurse performed the VO and a primary care GP examined and treated the children. All the obtained images were remotely reviewed by an ENT-specialist, GP and a GP registrar. The overall grading scale for image quality was assessed (excellent, acceptable and not acceptable) and the image-related variables (focus, light, obscuring objects, composition) and anatomical features (surface structure, thickness, color and position of the tympanic membrane) were evaluated. Of the images, 82% were graded as qualitatively acceptable or excellent. The image quality improved over time, which shows that learning and experience affect image quality. Cerumen related often to impaired image quality. While thickness and position of the tympanic membrane had the lowest values of the interrater agreement, identification of the anatomical components of the tympanic membrane were most important for a good image quality (Lundberg et al. 2008). Based on this study, a validated AOM grading scale

OMGRADE was published to provide standardized methods to diagnose and follow-up the course of an AOM episode (Lundberg et al. 2013).

The validity and reliability of the OMGRADE scale has been assessed for remote diagnostics. Tympanic membrane videos were obtained from children (2−16 years) at primary care services in South Africa and then after remotely assessed in Sweden by an ENT and GP. The agreement of the classification of the tympanic membrane between the asynchronous assessments (4 and 8 weeks) and the field otomicroscopy was substantial and the intrarater and interrater agreements were almost perfect ($\kappa = 0.68−0.72$ and $\kappa = 0.87−0.85$). The diagnoses determined by otomicroscopy related most often to healthy ears (85%), which is not surprising for an unselected study population (Lundberg et al. 2014).

Patricoski et al. (2003) found that post-surgical follow up of the patency of the tympanostomy tubes via telemedicine by high quality still images is possible. Overall inter-observer agreement was 84% for all and 89% for the high-quality telemedicine images. VO images were comparable to an in-person otomicroscopic examinations. If the patency of tympanostomy tubes would be followed by telemedicine, ENT-visits could be allocated to children in the need of a specialist consultation (Patricoski et al. 2003). Xu et al. (2008) calculated that ENT-telemedicine is cost-effective if more than 100 consultations are made per year (Xu et al. 2008).

Screening

Screening of AOM is not needed because symptoms of acute infection are among the three diagnostic criteria (Lieberthal et al. 2013). From another point of view, integration of an mHealth-enabled ear screening system to provide remote specialist consultations at the unserved areas of Australia was found to be feasible (Elliott et al. 2010). As the proportion of screened children increased, waiting times and the referrals to tertiary hospital were reduced (Smith et al. 2015). Ear disease screening was cost effective in this population of indigenous Australian children who are at high risk for chronic middle ear diseases (Nguyen et al. 2015).

The validity of a smartphone-based hearing screening (hearScreen™) was comparable to conventional pure-tone audiometry in a study with 1070 South African school children (age 8±1.1 years). For developing countries, this inexpensive, easily available hearing screening method was considered to provide a feasible tool for detecting unidentified hearing loss (Mahomed-Asmail et al. 2016).

3 AIMS OF THE STUDY

The aims of the studies for this thesis were to investigate whether parental tympanometry, SG-AR or smartphone otoscopy examinations could be utilized in the diagnostic chain of AOM. The hypothesis was that parental examinations are feasible.

The specific study aims were:

1. To investigate whether parents can use tympanometry reliably (I)

2. To examine whether parents can use spectral gradient acoustic reflectometry reliably (II)

3. To investigate if changes in parentally obtained acoustic reflectometry measurements predict the middle ear status (III)

4. To examine the diagnostic quality of parentally obtained smartphone otoscopy videos and images in the diagnostics of otitis media (IV)

4 MATERIALS AND METHODS

The thesis consists of four original publications that include the detailed methods of Studies I-IV. Written informed consent was obtained from a parent of each child before any study procedure was performed. Medical history, demographic and clinical characteristics of all children were recorded. All study visits were free of charge, and no compensation for participation was given. Previously unpublished data of the incidence of AOM in Turku area is provided in Chapter **5.4.**

The Ethical Committee of the Hospital District of Southwest Finland approved the study protocols of the research project Baby Elephant (I-III) and the study MobiiliKorva (IV). Both entities were registered clinical trials (www.clinicaltrials.gov identifier NCT00299455) and (www.clinicaltrials.gov identifier NCT02452164). The National Authority for Welfare and Health (Valvira) approved the use of the smartphone otoscope in Study IV.

4.1 Studies I-III

The study Baby Elephant was a research project examining the optimal diagnostics and management of AOM. It was conducted at primary care level in years 2006−2009 in Turku, Finland.

The project information was shared as handouts to families through health care centers, well-baby clinics, day care centers, and via other study projects in the Department of Paediatrics and Adolescent Medicine at Turku University Hospital. Families with children less than three years of age living in the city of Turku were sent letters containing the study information.

Children aged 6 to 35 months who were initially brought for an outpatient visit due to parental suspicion of AOM were enrolled. The children were followed in two cohorts. In the first cohort, children diagnosed with AOM (n=322) participated in the AOM treatment trial, and were examined regularly in scheduled visits (Tähtinen et al. 2011). The second cohort included children who were not diagnosed with AOM at the enrollment visit (n=247). These children were then followed for signs and symptoms and re-examined at one prescheduled visit after approximately 12 days. For both cohorts, acute visits were arranged whenever needed. Children in both cohorts were examined at scheduled visits with SG-AR, tympanometry and pneumatic otoscopy.

The exclusion criteria for the research project were: systemic or nasal steroid or antihistamine or oseltamivir therapy within the preceding 3 days and use of any

investigational drugs during the preceding 4 weeks; allergy to penicillin or amoxicillin; spontaneous perforation of the tympanic membrane and drainage; present tympanostomy tube (whether patent or occluded); clinical evidence of infection requiring systemic antimicrobial treatment (*e.g.,* pneumonia, meningitis, septicemia, urinary tract infection); documented Epstein-Barr virus infection within the preceding 7 days; Down syndrome or other condition affecting middle ear infections; known immunodeficiency; vomiting or other symptom to violate per oral dosage; and poor parental co-operation due to language or other reasons.

In Study I, children with persistent MEE at a pre-scheduled study visit after the study drug period were included. At the teaching visit parents were taught the use of the tympanometer. Families were provided with the tympanometer if parents were willing to use the device at home; the child was cooperating during tympanometric examinations; and parents learned technically the use of the tympanometer. The parental tympanometric examinations conducted at the teaching visit and at home on a study visit day or one day earlier were included; in addition, tympanometric examination performed by a study physician was required. To minimize the repetition of the same result, home examinations less than 3 days apart were excluded. If a child had more than 6 home examinations only the first six ones were included. During the follow-up period, parents of 78 children performed 432 tympanometric home examinations daily.

In Studies II and III, families were provided with the SG-AR device if the child was cooperating; parents were willing to use the device at home; and the parents learned how to use the device technically at the teaching visit.

In Study II, children were included if the parental home SG-AR examination was performed successfully on the same day as a study physician had performed the same examination and pneumatic otoscopy at the study clinic. To minimize the repetition of the same result, parental SG-AR examinations conducted at home on the teaching visit day and on study visit days less than 3 days apart from the previous visit. Furthermore, study visits exceeding 6 per child were excluded. During the follow-up period, parents of 359 children performed 10, 332 SG-AR home examinations.

In Study III, children diagnosed with a healthy middle ear at the initial study visit were included. The different SG-AR level changes, which were associated with the change in the middle ear status from healthy to AOM, or when the middle ear remained healthy at the subsequent study visit within 1−16 study days, were investigated. To comprise a measurement pair of parental SG-AR results within which a SG-AR level change could occur, one parental home SG-AR examination result conducted within ± 1 day to the initial and another conducted within ± 1 day to the subsequent study visit were included.

4.1.1 Diagnostic procedures by study physicians

In Studies I-III, the children were always examined in an upright position. The study physician first performed SG-AR (EarCheck PRO Otitis Media Detector, Innovia Medical LLC, Omaha, NE, USA), then tympanometry (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA), and finally pneumatic otoscopy (Macroview otoscope model 23810, Welch Allyn, Skaneateles Falls, NY, USA). Cerumen was removed before pneumatic otoscopy.

Pneumatic otoscopy was the diagnostic standard, and otoscopic findings were categorized as follows. The diagnosis of AOM required three criteria. First, MEE had to be detected (with at least two of the following tympanic membrane findings: bulging position, decreased or absent mobility, abnormal color, or opacity not due to scarring). Second, acute inflammatory signs had to be present in the tympanic membrane (with at least one of the following: distinct erythematous patches or streaks or increased vascularity over full, bulging or yellow tympanic membrane). Third, the child had to present the signs and symptoms of acute infection.

The diagnosis of OME was based on the following three criteria: first, MEE had to be shown by reduced mobility of the tympanic membrane; or by visible air-fluid interface; second, a retracted or normal (*i.e.,* slightly concave) position of the tympanic membrane; and third, the absence of acute inflammatory signs in the tympanic membrane (*i.e.,* distinct erythematous patches or streaks). The middle ear was diagnosed as healthy when pathologic otoscopic findings and/or MEE were not detected.

In Study I, OME and AOM were categorized as MEE because tympanometry is not able to distinguish between different diagnostic categories (Helenius et al. 2012). In Study II, any OME and/or any AOM were categorized as MEE because SG-AR is not able to differentiate between different otoscopic diagnoses (Laine et al. 2012).

4.1.2 Diagnostic procedures by parents

Study I. Parental tympanometry. At the teaching visit (20−30 min), the study physician taught the parents verbally and graphically the principles of tympanometry (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA). Then parents were taught to use the tympanometric device independently. At the end of the study visit, parents performed tympanometric examination on their child **(Figure 10)**.

At home, parents were asked to perform daily bilateral tympanometry on their child, at approximately the same time each day, and to print out the tympanograms. In case of a flat tympanogram, they were asked to repeat the examination three times when possible. Parents brought the printed tympanograms to the next scheduled visit.

Figure 10. Parental tympanometry examination. Photography Nora Erkkola-Anttinen, used with permission.

Studies II-III. Parental SG-AR. At the teaching visit (10−20min), the study physician taught parents the operational principles and technical use of the SG-AR device. Parents were taught how to perform examinations with a consumer model (EarCheck™ Middle Ear Monitor; Innovia Medical LLC, Lenexa, KS, USA) and then parents independently performed SG-AR on their child and the study physician helped when needed.

At home, parents were asked to perform daily bilateral SG-AR on their child and record the results in the symptom diary **(Figure 11)**. Families were instructed to contact the study physician if the SG-AR value changed by two levels over two consecutive days. Parents returned the SG-AR devices and the symptom diaries at the end of the study follow-up.

Figure 11. Parental SG-AR examination. Photography Nora Erkkola-Anttinen, used with permission.

4.1.3 Classification of the diagnostic results

Study I. Tympanometry was performed using a MicroTymp 2 tympanometer with a printer. The device uses a probe tone of 266 Hz and a sweep range of +200 to -400 daPa, from positive to negative pressure with a speed of 400 ± 40 daPa/s.

Tympanograms were classified according to the original classification by Jerger, modified by Orchik et al. and Zielhuis et al. (Jerger 1970, Orchik et al. 1978, Zielhuis et al. 1989). Peaked tympanograms were classified to be type A when tympanometric peak pressure was over -100 daPa, type C1 when pressure was between -100 and -200 daPa, C2 when pressure was lower than -200 daPa, and Cs when the tympanogram was low-peaked or wide (peak compliance less than 0.2 mmho, width over 300 daPa). A flat tympanogram was classified to be type B. If a flat tympanogram was obtained, tympanometry was repeated three times when possible. In other cases, tympanometry was repeated twice.

Three study physicians independently interpreted and classified the tympanograms blinded to the otoscopic diagnoses (Erkkola-Anttinen, Laine and Ruohola), and when disagreeing, Ruohola made the final decision. Only clearly interpretable tympanograms without artifacts were classified. Parents did not interpret any tympanograms.

Study II and III. The classification of the SG-AR results is provided in **Table 3**. Physicians and parents performed the SG-AR examination only once if the screen immediately showed a successful angle value (49º−120º) or a SG-AR level (1−5). Otherwise it was repeated, depending on the child's co-operation. The examination was considered failed if the angle value was seen only momentarily or the instrument displayed an error symbol.

4.1.4 Statistical analyses

In Study I, the results of parental and physician tympanometric examinations were compared to each other and to the study physician's pneumatic otoscopy that served as a diagnostic standard. The agreement of parental and physician tympanometric examinations were analyzed by calculating the kappa value. Absolute rate differences were calculated between the parental success rate of tympanometric examinations at home and at the study visit; between the success rate of parental and physician tympanometric examinations; and between parental and physician tympanometric examinations and the pneumatic otoscopy done by a study physician. Statistical analyses were performed using SPSS® Statistics 21.0 (IBM Software, USA).

In Study II, the parental and study physician SG-AR examination results were compared to the study physician's pneumatic otoscopy. Sensitivity, specificity, PPV and NPV to detect MEE were analyzed with their respective 95% confidence intervals (95% CI) for the diagnostic test result. In the analysis, SG-AR level 1 was tested as an indicator of a healthy ear and absence of MEE. Further, SG-AR levels 2–5 and levels 4–5 were tested as indicators of MEE. Statistical analyses were performed using SPSS® Statistics 21.0 (IBM Software, USA).

In Study III, the association of parentally obtained increasing SG-AR level between two study visits were analyzed to indicate the appearance of AOM detected in pneumatic otoscopy. The SG-AR level was defined as increasing when it changed ≥2 levels from a lower to a higher level (*e.g.*, from level 1 to 3) suggesting the appearance of AOM. The SG-AR level was defined as decreasing when it changed ≥ 2 levels from a higher to a lower level (*e.g.*, from level 5 to 3) suggesting the resolution of MEE. When the SG-AR level change was ≤1, it was defined as no level change.

In an initially healthy ear with an increasing SG-AR level, the hypothesis was that the middle ear status would deteriorate from healthy to AOM. When the SG-AR level was unchanging, the hypothesis was that the middle ear diagnosis remained healthy.

Increasing SG-AR level was tested as an indicator of the middle ear status to deteriorate from healthy to AOM. Additionally, unchanging SG-AR level was tested as an indicator for the middle ear to remain healthy. The sensitivity, specificity, PPV and NPV with their respective 95% confidence intervals (95% CI) for the diagnostic test result were analyzed.

4.2 Study IV

The MobiiliKorva Study was an investigator-initiated open clinical study. Participants were randomly assigned into two parallel study groups for the first study week. The study was conducted at primary care between September 1, 2015 and April 10, 2016 in Turku, Finland.

Various recruitment methods were used in Turku area to enroll families. In addition to study information handouts and posters, a study website (www.korvatulehdustutkimus.fi) and a Facebook account (www.facebook.com/MobiiliKorva) were created to share study information. The study was endorsed on twitter by Department of Paediatrics and Adolescent Medicine, Turku University Hospital (https://twitter.com/TyksLnk).

Inclusion criteria were: children 6 to 35 months of age attending daycare with at least one AOM diagnosed within 90 days of the study entry. Additionally, parents had to possess iPhone 5, 5s or 6, because the CellScope Oto was designed only for these smart-phone models. No specific middle ear findings were required at the time of enrollment. Exclusion criteria were disorders or craniofacial malformations that affected the anatomical structures of the ear canal and/ or the middle ear; patent ventilation tubes or chronically perforated TM at least in one ear; and poor parental co-operation due to language or other reasons.

This study was conducted independently of any commercial entities. The smartphone otoscopes were bought with personal research funding (Erkkola-Anttinen). At the time of the planning and the clinical phase of the study, it was not possible to acquire the smartphone otoscope online in Finland as it had a sales permit for the US market only. Therefore, we collected the devices ourselves from the US and paid import duty in Finland.

CellScope Oto is a smartphone-enabled otoscope designed for the inspection of the tympanic membrane under magnification using iPhone as external illumination source (www.cellscope.com). The system consists of a specially designed optical otoscope with an insufflation bulb port. The optical otoscope can be attached to iPhone 5/5s with a compatible case and to iPhone 6 with a connector. The

insufflation port is compatible with an insufflation bulb (WelchAllyn Macroview Otoscope Insufflation Bulb 23804, WelchAllyn, Inc. Skaneateles Falls, NY, USA) enabling pneumatic otoscopy. The package includes 2 reusable pediatric-sized (2.5 mm diameter) and 2 adult-sized (4.25 mm diameter) speculums and a storage container. The iPhone must operate with iOS version 7.11 or later. At the moment, the CellScope Oto does not bare the CE-marking (Communitas Europae) but has an U.S. Food and Drug Administration (FDA) 1 – 510k approval.

We decided not to use the manufacturer's smartphone application for two reasons. First, it would have required entering personal participant data. Second, all the obtained image data would have been in the possession of the device manufacturer. Therefore, Purefox Ltd., Turku, Finland designed TM-Rotator software, an independent smartphone application to take images and videos with a smartphone otoscope and to save them into the iPhone Camera Roll. Parents downloaded the free (to the participants) TM-Rotator from the Apple App Store for iPhone (https://itunes.apple.com /us/ app/tm-rotator/id997871414?mt=8).

At the first study visit, the research flow was explained to the parents. **Figure 12** demonstrates the study flowchart. For the first study week, children were randomly assigned to the immediate or to the delayed teaching group. The Department of Biostatistics, University of Turku, performed the randomization in blocks of variable sizes. The study physician was blinded to this information.

If the child was allocated to the immediate teaching group, the study visit continued with a teaching intervention. If the child was allocated to the delayed teaching group, parents were provided with a smartphone otoscope without any further advice, as if they had bought it online. A teaching intervention was scheduled to study days 8−11.

Study physician called the parents in both groups one week after the teaching intervention and sent SMS messages on study days 24±2, 38±2 and 52±2 to encourage parents to continue with the examinations. Families were instructed to contact the study physician whenever needed.

No additional pre-planned study visits were arranged. Parents were instructed to take their child to their own physician when needed. However, if obstructive cerumen developed into a child's ear canal during the study, it was possible to make an appointment for its removal. The study physician did not participate to the care of the children and did not give feedback on the smartphone otoscopy videos or images. The study website (www.korvatulehdustutkimus.fi) provided information containing symptoms, pain relieving medication and images of different middle ear findings under the theme of AOM. Families returned the otoscopes at the final visit.

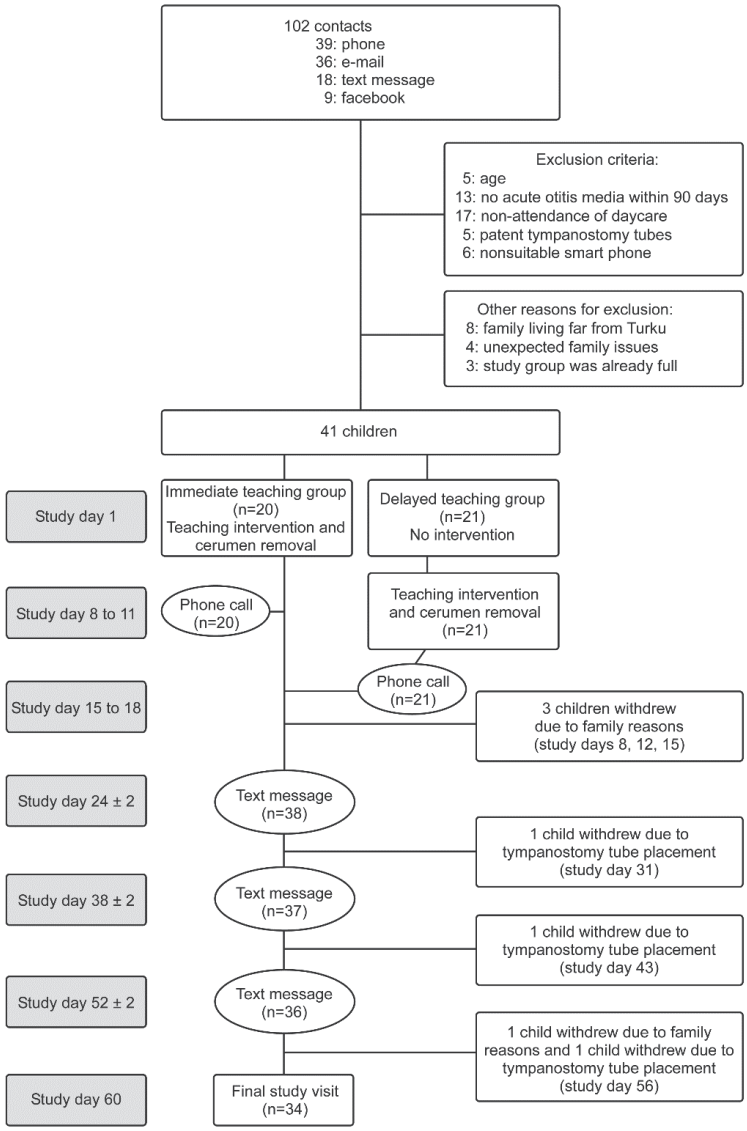


Figure 12. Flowchart of Study IV.

4.2.1 Diagnostic procedures by study physicians

The child's clinical examination included pneumatic otoscopy (Macroview otoscope model 23810, Welch Allyn, Skaneateles Falls, NY, USA). Otoscopy was performed mainly to inspect that the child met the inclusion criteria and possible cerumen was removed from the ear canal.

4.2.2 Diagnostic procedures by parents

During the 60−minute teaching intervention, parents were given an introductory presentation of the basic anatomy of the ear canal, tympanic membrane and middle ear. Key point anatomical structures of the tympanic membrane and middle ear (umbo, manubrium of malleolus, cone of light, and the four different quadrants) were highlighted for the best possible diagnostic value of the video. The principals of the development and diagnostic criteria of AOM were discussed. Parents were showed examples of smartphone otoscopy videos from a healthy ear, OME and AOM, and still images of tympanic membrane from our previous study (Tähtinen et al. 2011).

Parents were taught how to use the smartphone otoscope and the TM-Rotator. Parents practiced performing the smartphone otoscopy examination first on each other and then on their child. A right size ear speculum was chosen for the child. A small or medium sized rubber soft seal (SoftSeal™, WelchAllyn, Inc., Skaneateles Falls, NY, USA) was provided to increase the airtightness between the ear canal and the ear speculum. Parents were instructed how to use the pneumatic bulb to test the movement of the tympanic membrane and were provided with the insufflation bulb for home-use. They were also instructed to use over-the-counter oily ear drops to prevent cerumen formation if needed.

During the first study week, parents in both groups were instructed to perform bilateral smartphone otoscopy on at least five days. Parents in the delayed teaching group were asked to perform the smartphone otoscopy correspondingly also within a week after the teaching intervention.

During the rest of the 60 days study period, parents were asked to perform bilateral smartphone otoscopy **(Figure 13)**

1) once a week when the child was healthy;
2) daily when parents considered their child to have symptoms of RTI (*i.e.,* cold, runny nose, sneezing, rhinitis, fever, cough, sore throat, ear pain, hoarseness, wheezing, obstruction or conjunctivitis);
3) daily for one week after an AOM diagnosis;
4) whenever parents suspected their child to have ear pain; and
5) on days that parents took their child to see a physician.

Parents sent their videos to the study physician using iMessage, WhatsApp or e-mail. One message included one unilateral tympanic membrane video or image with the following information; the ear in question and the child's symptoms.

Figure 13. Parental smartphone otoscopy examination. Photography Aino Ruohola, used with permission.

4.2.3 Classification of the diagnostic results

One tympanic membrane video or still image from each ear per examination day after the first study visit was included in the study. All obtained video and still image data were used in the analyses, including the videos of children who withdrew during the study period. Virtually all smartphone otoscopy examinations were videos, and are hereafter referred to as videos.

First, the technical quality of the video, based on the view of the tympanic membrane and clarity of the video, was assessed **(Table 7)**. Second, from the videos of sufficient technical quality, a healthy ear, OME or AOM diagnosis was determined using pre-defined diagnostic criteria **(Table 8)**. This two-step outcome analysis was used because there were no previous data allowing us to make any pre-estimations concerning the quality of parent-performed smartphone otoscopy examinations. In addition, to illustrate the real-life study setting, *i.e.,* the parents' independent online purchase of the smartphone otoscope, cerumen was not removed from the ear canals of the delayed teaching group children in the at the first study visit.

If none of these diagnoses could be determined, the reasons for the failure were analyzed. Furthermore, regardless of the technical quality of the videos, we always assessed whether it was possible to detect or exclude AOM.

All parentally obtained videos were analyzed in random order by three independent evaluators, an ENT-specialist (Irjala), a GP (Erkkola-Anttinen) and

an otitis media expert (Laine) (Tähtinen et al. 2011). During the analysis process, the evaluators were blinded to all patient characteristics, group assignment and symptoms. The final diagnosis was based on consensus reached when two of the three evaluators agreed on the diagnosis. If all evaluators disagreed on the diagnosis, the video was determined as non-diagnostic.

Table 7. The systematic technical quality analysis of the parent-performed smartphone otoscopy videos.

Anatomical overall view of the videos	**Rating method**
TM cannot be identified	0
Less than half of the TM can be identified	1
At least half of the TM can be identified and umbo and the manubrium of the malleus can be identified nearly completely or completely	2
The whole TM can be identified	3
Clarity of the videos	
Out of focus	0
Fairly unclear, but the anatomy of the TM can be identified	1
Almost clear, the anatomy of the TM can be identified	2
Perfect focus	3
Video Quality score	overall view x clarity of the video
Insufficient technical video quality	0-3
Sufficient technical video quality	4-9
Is the video clinically of sufficient quality to either detect or to exclude AOM?	yes/no
Does cerumen interfere further middle ear diagnostics?	yes/no

Abbreviation: TM, tympanic membrane

The diagnosis of a healthy ear was based on the following criteria: no MEE was detected behind a normally, *i.e.,* slightly concave, positioned transparent tympanic membrane; no acute inflammatory signs were detected on the tympanic membrane; if movement of the tympanic membrane was detected, it had to be normal.

The diagnosis of OME was based on the following criteria: presence of MEE shown by a cloudy tympanic membrane or by a visible air-fluid interface; the position of the tympanic membrane had to be retracted or normal, *i.e.,* slightly concave; absence of acute inflammatory signs on tympanic membrane (*i.e.,* distinct erythematous patches or streaks). If the movement of the tympanic membrane was detected, it had to be reduced.

The diagnosis of AOM required the following criteria: presence of MEE (at least two of the following tympanic membrane findings: bulging position, abnormal color, or opacity not due to scarring); acute inflammatory signs had to be present on the tympanic membrane (at least one of the following: distinct erythematous patches or streaks or increased vascularity over full, bulging or yellow tympanic

membrane); if the movement of the tympanic membrane was detected, it had to be decreased or absent.

Table 8. Characteristics of the middle ear findings systematically evaluated to determine a middle ear diagnosis.

TM transparency	**TM color/redness**
Transparent	No redness
Poorly transparent	Vascularity identified
Opaque/non-transparent	Strongly increased vascularity
Non-diagnostic	Mild/small distinct erythematous patches or streaks
	Strong/extensive distinct erythematous patches or streaks
	Non-diagnostic
The position of the TM	**Movement of the TM**
Retracted	Absent mobility (includes if movement was not detected)
Slightly concave	Decreased mobility
Normal	Normal mobility
Bulging	Non-diagnostic
Non-diagnostic	
Presence and amount of MEE	**Quality of MEE**
No effusion	Clear
Visible air-fluid interface	Serous
Full	Cloudy
Non-diagnostic	Purulent
	Non-diagnostic

Abbreviations: TM, tympanic membrane; MEE, middle ear effusion

4.2.4 Statistical analyses

No sample size calculation was performed while no corresponding data was available for calculations. Instead, it was estimated that with 40 children and the planned otoscopy examination frequency, approximately 1700 videos would be received. Because of early withdrawals, one more family was randomized to the study group in aim to attain the pre-estimated number of videos.

The outcomes between the immediate and delayed teaching groups during the first week's intervention were compared with Fisher's Exact Test (with significance level of 0.05 (two-tailed)). The kappa value (Fleiss et al. 1979) among multiple raters was calculated to illustrate the interrater agreement to detect or exclude AOM. The data analysis was generated using SAS software, Version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

5 RESULTS

The results consist of the original Studies I-IV. Additional unpublished data on the incidence of AOM in Turku area is presented in Chapter **5.4**.

5.1 Parent-performed tympanometry (I)

Parents of 69 children conducted independent tympanometry examinations on set days. Of these examinations, 94 were performed at the study clinic during the teaching and 338 independently at home. Parents succeeded to obtain an interpretable tympanogram (*i.e.,* type A, C1, C2, Cs or B) in 91% (86/94) and in 81% (273/338) of the examinations conducted at the teaching visit and at home, respectively. All the 432 examinations were analyzed together because the reliability of the examinations either to predict a healthy middle ear with the peaked tympanogram or MEE with the flat tympanogram was similar at the teaching visit and at home.

For these 432 examinations, the success rate of parentally and physician obtained interpretable tympanograms was 83% (359/432) and 91% (393/432) (absolute rate difference 8%, 95% CI 3–12%). In 75% (326/432) of the examinations, both parents and physicians succeeded to obtain an interpretable tympanogram from the same ear. Furthermore, parents and physicians agreed with either a peaked (*i.e.,* A, C1, C2, Cs) or a flat (*i.e.,* type B) tympanogram in 88% of examinations (288/326) (kappa value 0.77). From another perspective, parents and physicians agreed on the same type tympanogram (*i.e*., A, C1, C2, Cs or B) in 71% (233/326) of these 326 interpretable tympanometric examinations **(Table 9)**.

Table 9. Results of parental and study physicians' tympanometric examinations. Modified from Original Publication I.

	Parental tympanometric examinations							
Physician tympanometric examinations	**Type of tympanogram**	**A**	**C1**	**C2**	**Cs**	**B**	**Not interpretable**	**Not succeeded**	**Total (n)**
	A	**60**	28	6	0	11	12	0	117
	C1	8	**16**	5	1	9	14	1	54
	C2	2	3	**13**	1	6	15	1	41
	Cs	0	0	1	**1**	1	2	0	5
	B	4	4	2	1	**143**	20	2	176
	Not interpretable	4	3	3	3	20	6	0	39
	Not succeeded	0	0	0	0	0	0	0	0
	Total (n)	78	54	30	7	190	69	4	432

Peaked tympanograms were classified to be type A when tympanometric peak pressure was over > -100 daPa, type C1 when pressure was between -100 and -200 daPa, C2 when pressure was lower than -200 daPa, and Cs when the tympanogram was low-peaked and wide (peak compliance less than 0.2 mmho, width over 300 daPa). A flat tympanogram was classified to be type B.

Figure 14 shows that when any peaked tympanogram was obtained, pneumatic otoscopy indicated healthy middle ear in 72% (122/169) and in 69% (149/217) of parental and physician tympanometric examinations, respectively (absolute rate difference 4%, 95% CI -6% to 13%). When a flat tympanogram was obtained, pneumatic otoscopy indicated any MEE in 92% (174/190) and in 96% (169/176) of parental and physicians' tympanometric examinations, respectively (absolute rate difference 4%, 95% CI -9% to 1%).

Otoscopic findings were categorized as follows: Healthy middle ear: No middle ear effusion (MEE) detected in otoscopy. a-MEE: Visible air-effusion interface and/or air-bubble(s) detected in otoscopy. c-MEE: Otoscopy showing a middle ear completely filled with effusion. We categorized otitis media with effusion (OME) and acute otitis media (AOM) as MEE, because our study group has previously showed that tympanometry is not able to distinguish between different diagnostic categories (Helenius et al. 2012).

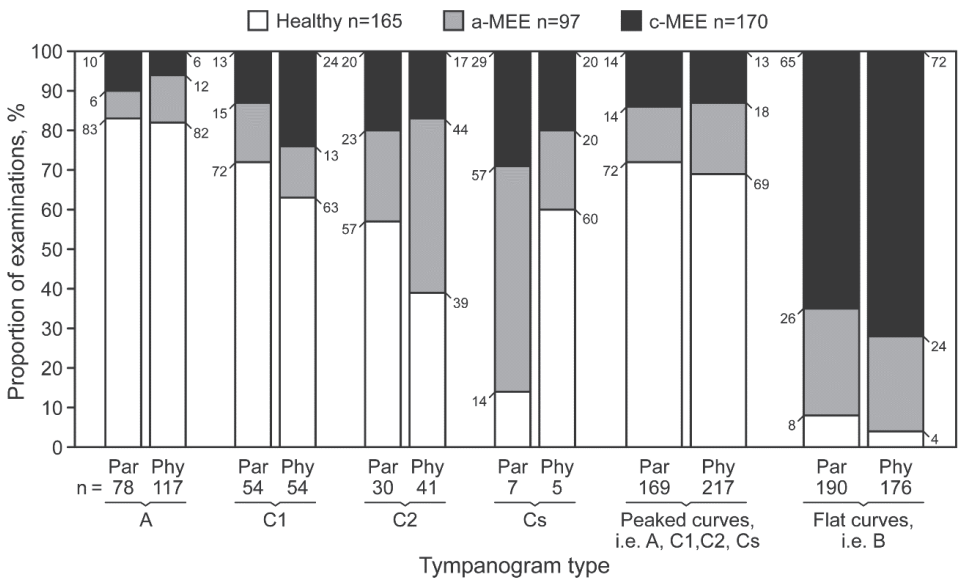


Figure 14. Proportions of the three otoscopic findings in relation to successful parental (Par) and physician (Phy) tympanograms (percentages may not total 100% due to rounding). Modified from Original Publication I.

5.2 Parent-performed SG-AR (II, III)

In Study II voluntary parents of 359 children were provided with a SG-AR device for home use and parents of 88% (316/359) children succeeded to conduct SG-AR home examinations. Altogether, a total of 10332 parental home SG-AR examinations were performed. After exclusion, to meet the set SG-AR examination day, 614 parental SG-AR home examinations of 201 children were analyzed.

Parents succeeded in 97% (593/614) of SG-AR home examinations with no difference regarding age. The success rate for physician SG-AR examinations conducted on the same day as the study visit was similarly 97% (588/608). Moreover, to meet the inclusion criteria of a successful parental home SG-AR examination with a correspondent successful physician SG-AR and pneumatic otoscopy examination from the same ear conducted at the study visit, 571 SG-AR examination results of 192 children comprised the final study data and population. The study flowchart is provided in the Original publication II. The overall prevalence of MEE diagnosed by pneumatic otoscopy was 55% (223/406) at symptomatic and 22% (45/208) at asymptomatic visits.

At symptomatic visits (**Figure 15**), when parents and physicians obtained SG-AR level 1, otoscopy showed a healthy middle ear in 64% (69/107) and 76% (65/85)

of SG-AR examinations, respectively. When the obtained SG-AR level was 1 and otoscopy showed any MEE, diagnosis of OME related to 82% (31/38) and 100% (20/20) of parental and physician SG-AR examinations, respectively. Therefore, 18% (7/ 38) of parental level 1 SG-AR ex-aminations were related to AOM.

When parents and physicians obtained SG-AR levels 4–5, otoscopy showed MEE in 88% (83/94) and 94% (111/118) of SG-AR examinations, respectively. When the obtained SG-AR levels were 4–5 and otoscopy showed any MEE, diagnosis of AOM related to 52% (43/83) and 55% (61/111) of parental and physician SG-AR examinations, respectively.

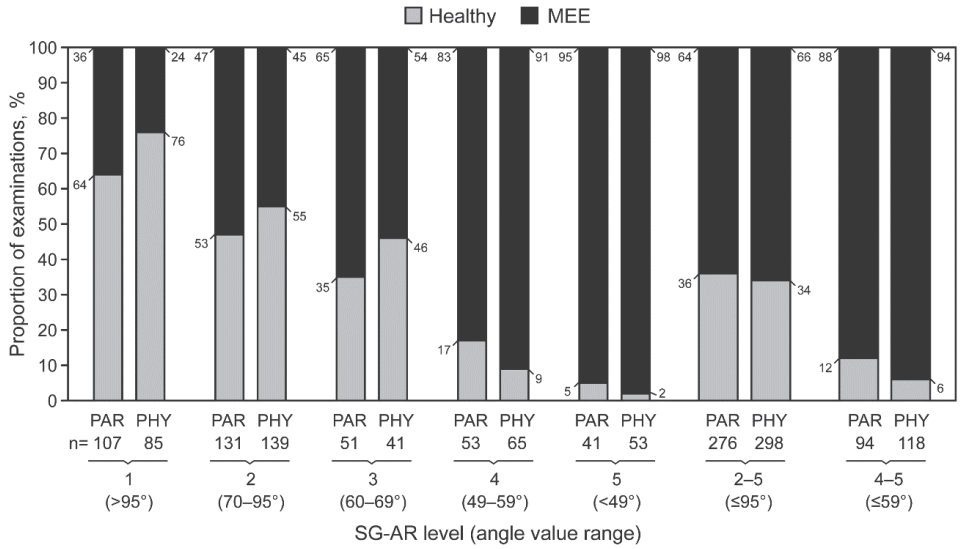


Figure 15. Parental and physician SG-AR results in relation to the physician otoscopy at symptomatic visits. Modified from Original Publication II.

At asymptomatic visits (**Figure 16**), when parents and physicians obtained SG-AR level 1, otoscopy showed a healthy middle ear in 83% (81/98) and 96% (70/73) of SG-AR examinations, respectively. When the obtained SG-AR level was 1 and otoscopy showed any MEE, diagnosis of OME related to 100% (17/17) and 100% (3/3) of parental and physician SG-AR examinations, respectively.

When parents and physicians obtained SG-AR levels 4–5, otoscopy showed MEE in 43% (6/14) and 48% (10/21) of SG-AR examinations, respectively. When the obtained SG-AR levels were 4–5 and otoscopy showed any MEE, diagnosis of OME related to 83% (5/6) and 80% (8/10) of parental and physician SG-AR examinations, respectively.

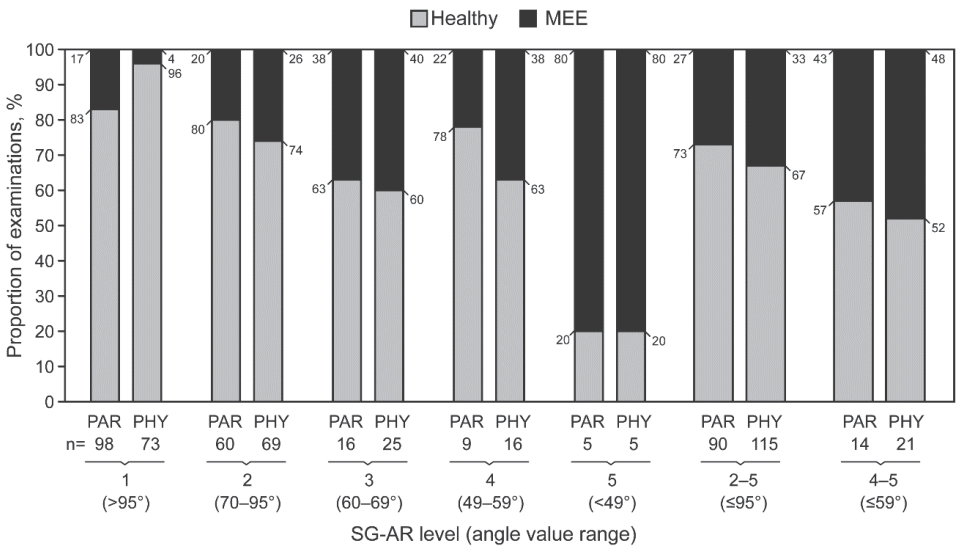


Figure 16. Parental and physician SG-AR results in relation to the physician otoscopy at asymptomatic visits. Modified from Original Publication II.

Sensitivities, specificities, and the positive and negative predictive values (and 95% CIs) of parental and physician SG-AR examinations to detect MEE with different SG-AR level combinations are presented in **Table 10**.

Table 10. Sensitivity, specificity, and the positive and negative predictive values (and 95% CIs) of parental and physician SG-AR examinations to detect MEE with different SG-AR level combinations. Modified from Original publication II.

Visit type	SG-AR level		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Symptomatic visit	level 1 (>95°) vs. level 2-5 (≤95°)	Parents	82% (77% to 87%)	41% (34% to 49%)	64% (59% to 70%)	64% (55% to 74%)
		Physicians	91% (86% to 94%)	39% (31% to 47%)	66% (60% to 71%)	76% (66% to 85%)
	level 4-5 (≤59°) vs. level 1-3 (≥60°)	Parents	38% (32% to 45%)	93% (89% to 97%)	88% (80% to 94%)	54% (48% to 60%)
		Physicians	51% (45% to 58%)	96% (92% to 98%)	94% (88% to 98%)	60% (54% to 66%)
Asymptomatic visit	level 1 (>95°) vs. level 2-5 (≤95°)	Parents	59% (42% to 74%)	55% (47% to 63%)	27% (18% to 37%)	83% (74% to 90%)
		Physicians	93% (80% to 98%)	48% (39% to 56%)	33% (25% to 42%)	96% (88% to 99%)
	level 4-5 (≤59°) vs. level 1-3 (≥60°)	Parents	15% (6% to 29%)	95% (90% to 98%)	43% (18% to 71%)	80% (73% to 86%)
		Physicians	24% (12% to 40%)	93% (87% to 96%)	48% (26% to 70%)	81% (75% to 87%)

In Study III, parents of 185 children performed 361 paired SG-AR home measurements. The median age of the children was 12 months (range 6–35 months). The first measurement of these pairs was the reference measurement performed at a time when a study physician had determined the middle ear as healthy by pneumatic otoscopy.

Figure 17 illustrates the association of SG-AR level differences and the condition of middle ears determined by pneumatic otoscopy. In 16% (59/361) of the SG-AR measurement pairs, SG-AR levels were increasing. Of these measurement pairs, AOM was diagnosed in 71% (42/59) while 29% (17/59) were healthy. There was no difference in the SG-AR levels in 78% (280/361) of the SG-AR measurement pairs during the follow-up and 93% (259/280) of these middle ears were healthy at the subsequent visit.

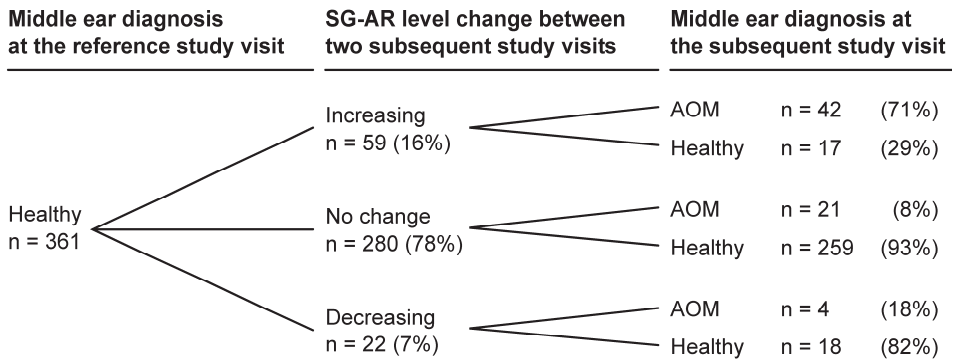


Figure 17. The association of SG-AR level differences and the condition of middle ears determined by pneumatic otoscopy. Modified from Original Publication III.

The sensitivity and specificity for increasing SG-AR level to predict the deterioration of a healthy middle ear to AOM and for an unchanging SG-AR level to predict a healthy middle ear are presented in **(Table 11)**.

Table 11. Sensitivity, specificity and the positive (PPV) and negative (NPV) predictive values (and 95% CIs) for increasing and unchanging SG-AR levels to detect the middle ear status change.

Middle ear status change	SG-AR level	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Healthy-AOM	*Increasing*	63% (50%-74%)	94% (91%-97%)	71% (58%-82%)	92% (88%-95%)
Healthy- Healthy	*Unchanging*	88% (84%-92%)	69% (56%-79%)	93% (89%-95%)	57% (45%-68%)

5.3 Parent-performed smartphone otoscopy (IV)

All study visits occurred according to the protocol, additional visits for cerumen removal were arranged for 15 children. The characteristics of 41 children (median age 21 months) are provided in the table 1 of Original article IV.

Parents performed 1,500 smartphone otoscopy examinations (on average 36 per child, range 0−94) without any adverse events. Only one family was unable to perform any examinations due to the child's resistance. A video (n=1442) or a still image (n=30) was obtained in 98% (1472/1500) of all examinations and only 2% (28/1500) of parental examinations were unsuccessful. The median video length was 18 seconds (range 1−62 seconds). Although still images were included in the analyses, they were virtually useless due to poor anatomical view. **Figure 18** shows the study results.

Parents produced 1,293 videos after the teaching intervention. Of these videos 67% (867/1293) were of sufficient and 33% (426/1293) of insufficient technical quality, respectively. We were able to determine one of the three diagnoses (healthy ear, OME or AOM) in 56% (486/867) and in 8% (35/426) of the videos with sufficient and insufficient technical quality, respectively. Consequently, 38% (486/1293) of all videos were of sufficient technical quality enabling the determination of diagnosis.

Of all the obtained videos, 60% (772/1293) did not allow us to determine any of the three diagnoses. The reasons were inadequate view of the tympanic membrane in 46% (356/772), unsatisfactory clarity in 33% (258/772), interfering cerumen in 22% (171/772), and lack of the tympanic membrane movement testing of the in 97% (752/772) of the videos.

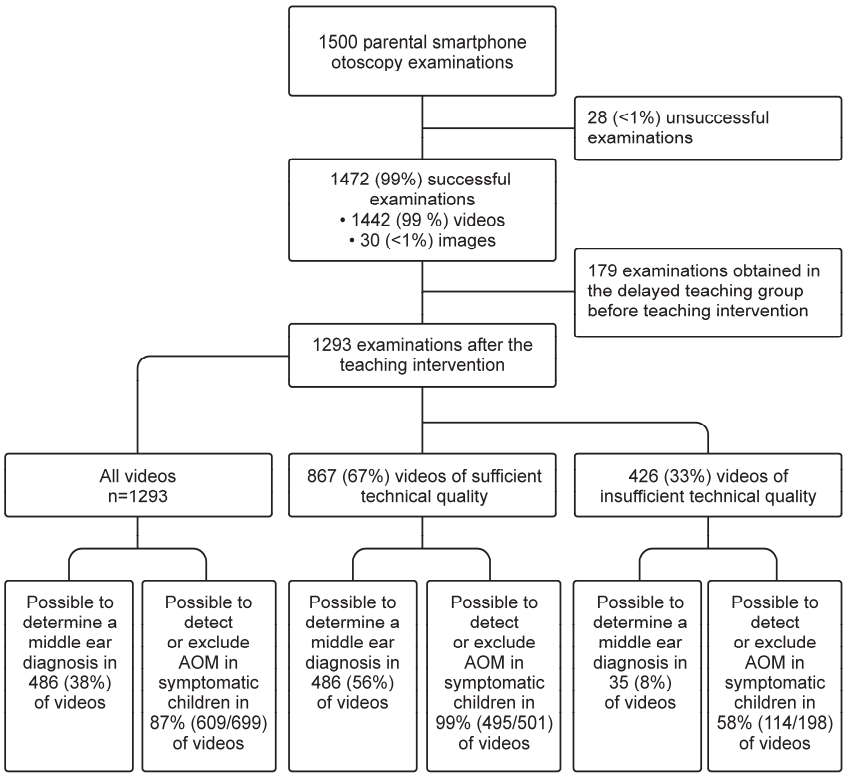


Figure 18. Technical and diagnostic quality of parental smartphone otoscopy videos and images after the teaching intervention.

Parents reported that 54% (699/1293) of the video examinations were performed when their child had symptoms of RTI. Of these 699 videos, AOM could be detected or excluded in 87% (609/699). In videos with sufficient and insufficient technical quality, we could detect or exclude AOM in 99% (495/501) and in 58% (114/198) of the videos, respectively **(Figure 18)**. Typically, when only a small area of the tympanic membrane was visualized in the video, middle ear effusion could not be excluded but AOM could. The three evaluators had a substantial degree of agreement to detect or exclude AOM (kappa value 0.69).

Teaching intervention improved significantly the technical quality of the videos, thus increasing the possibility to determine one of the three diagnoses.

Table 12 shows the comparison of the results between the immediate and delayed teaching groups during the first week's intervention. During the first week's intervention period, 62% (95/153) and 22% (39/179) of the videos were of sufficient technical quality in the immediate and delayed teaching group, respectively (P<0.001). Cerumen was present in 18% (27/153) compared to 47% (84/179) of the videos in the immediate and delayed teaching group, respectively. Consequently, the diagnosis could be determined in 33% (50/153) and in 12%

(22/179) of the videos in the immediate and delayed teaching groups, respectively (P<0.001). Furthermore, AOM could be detected or excluded in 78% (31/40) and in 30% (23/76) of the videos regardless of their technical quality (P<0.001).

Table 12. Video quality comparison between the immediate and delayed teaching groups during the first week's intervention. Modified from Study IV.

	All Videos During the First Week´s Intervention		
	Immediate Teaching Group	Delayed Teaching Group	P Value[b]
Number of Videos (%)	153	179	
Possible to Determine the Middle Ear Diagnosis	50/153 (33)	22/179 (12)	<0.001
Healthy Middle Ear	16/50 (32)	17/22 (77)	
Otitis Media with Effusion	29/50 (58)	2/22 (9)	
Acute Otitis Media	5/50 (10)	3/22 (14)	
Possible to Either Detect or to Exclude Acute Otitis Media in a Symptomatic Child – no. (%)[a]	31/40 (78)	23/76 (30)	<0.001

[a] One child in both groups with missing symptom data.
[b] P value illustrates the diagnostic comparison of the videos between the immediate and delayed teaching groups

After the teaching intervention, the technical and diagnostic video quality improved markedly in the delayed teaching group. One week after the delayed teaching group's teaching intervention, 65% (86/133) of the videos were of sufficient technical quality, and the diagnosis could be determined in 34% (45/133); and AOM could be detected or excluded in 80% (106/133) of the videos. Regardless of the child's symptoms, it was possible to either detect or exclude AOM in 80% (106/133) of the videos **(Table 13)**.

Table 13. Comparison of the diagnostic quality of videos in the delayed teaching group before and one week after the teaching intervention. Modified from Study IV.

	Technical Video Quality					
	Insufficient Quality		Sufficient Quality		All videos	
Teaching intervention	Before	After	Before	After	Before	After
Number of videos (%)	140/179 (78)	47/133 (35)	39/179 (22)	86/133 (65)	179	133
Possible to determine the middle ear diagnosis	3/140 (2)	4/133 (3)	19/39 (49)	41/133 (31)	22/179 (12)	45/133 (34)
Healthy middle ear	2/3 (67)	2/4 (50)	15/39 (38)	31/41 (76)	17/22 (77)	33/45 (73)
OME	0	2/4 (50)	2/39 (5)	8/41 (20)	2/22 (9)	10/45 (22)
AOM	1/3 (33)	0	2/39 (5)	2/41 (5)	3/22 (14)	2/45 (4)
Possible to either detect or to rule out AOM in a symptomatic child	17/70 (24)	9/17 (53)	6/6 (100)	41/41 (100)	23/76 (30)	50/58 (86)

5.4 Incidence of AOM in Turku area

To investigate the number of AOM diagnoses in children aged 6−35 months in Turku area, Turku University Hospital and Turku Region Joint Emergency Services, The Welfare Division of Turku City and three largest private medical centers in Turku (Terveystalo, Mehiläinen and Neo) provided statistical data of AOM and RTI diagnoses covering the years 2014, 2015 and 2016. The data included the total number of sick visits (n), RTI (J06.9) and AOM diagnoses (H66, H66.0. H66.1, H66.2, H66.3, H66.4, H66.9). The diagnoses were classified according to the International Statistical Classification of Diseases and Related Health Problems. Since parents took their child to a physician with nonspecific overlapping symptoms of AOM and RTI, and approximately half of the children had AOM when parents suspected (Laine et al. 2010) the data included both these diagnoses.

In the statistical analyses the proportion of AOM and RTI diagnoses of all sick visits in children aged 6−35 months in Turku area were analyzed from the numerical data.

During 2014−2016, children 6−35 months of age had annually 31, 000 sick visits to the primary care units (The Welfare Division of Turku City and Tyks and Turku Region Joint Emergency Services) and private physician centers in Turku. Of these visits, the annual proportion of primary care visits varied between 30% and 40% **(Table 14)**.

Table 14 shows that of all visits during the years 2014, 2015 and 2016, RTI and AOM diagnoses were determined in 23% (7362/31944), in 27% (8699/32340), and in 32% (9823/31170) of all physician sick visits. Altogether, during the three-year period, RTI and AOM diagnoses were determined in 27% (25 844/95 454) of all physician sick visits.

In 2014, 2015 and 2016, AOM diagnoses were determined in 12% (3709/31944), in 13% (4344/32340) and in 15% (4645/31170) of all physician sick visits. During the three years, AOM was diagnosed in 13% (12689/95454) of all physician sick visits in young children aged 6−35 months in Turku area.

Table 14. The total number of sick visits and of RTI and AOM diagnoses in children aged 6−35 months in Turku area during 2014−2016.

	Year 2014	Year 2015	Year 2016	Total
Number of RTI diagnoses of all physician visits (%)	3653 (11)	4355 (13)	5178 (17)	13186 (14)
Number of AOM diagnoses of all physician visits (%)	3709 (12)	4344 (13)	4645 (15)	12698 (14)
Number of all physician visits	31944	32340	31170	95454

6 DISCUSSION

The rationale of studying the use of parental examinations in the diagnostic chain of AOM in primary care is based on the immense amount of annual AOM diagnoses and physician visits worldwide.

Approximately 350 million annual episodes of AOM occur in children under the age of five worldwide (Monasta et al. 2012). In the US, the annual number of children (<18 years) with AOM was estimated at 8.7 million in 2009 (Ahmed et al. 2014). In the late 1990s in Finland, the estimated number of annual OM episodes in children of day care age was approximately 500,000 (Niemelä et al. 1999). Primary care physicians worldwide have agreed that OM is the most prevalent childhood infectious disease (Arguedas et al. 2010). In 2014, the annual number of OM related physician visits at health care centers for Finnish children was over 130,000 (Saukkonen and Vuorio 2016).

What is the diagnostic chain of AOM? Currently, there is no such chain. The diagnostic chain of AOM could include parental examinations to help parents to assess the need for a physician visit. At the moment, parents take their child with symptoms and signs of overlapping RTI and AOM to a physician because parents have no tools to assess whether their child needs to see a physician particularly because of AOM. These visits take place all around the clock, repeatedly and even to be on the safe side. During the years 2014–2016, children aged 6–35 months in the Turku area made annually 31,000 – 32,000 sick visits to primary care units and private physicians. In approximately 30% of these visits, the diagnosis was either RTI or AOM. Notably, AOM was the diagnosis in nearly 15% of all sick visits. The socioeconomic impact of AOM arises from direct and indirect costs. Direct medical costs arise mainly from physician visits (Wolleswinkel-van den Bosch, et al. 2010). Most of the direct non-medical costs arise from traveling costs and of the indirect costs from parental work absence (Bondy et al. 2000, Rovers et al. 2004, Speets et al. 2011a).

The tympanometer and the SG-AR are traditional tools which physicians can use to detect MEE. Both have been studied for parental use, but implementation to everyday life has not been achieved (Moody et al. 1998, Barnett et al. 2000). The explosion of health and mobile technology and telemedicine continues to change the field of health care, and the role of patients is shifting towards more active participation in their own care. Smartphone otoscopy is a novel tool for enhancing remote diagnostics and it may have potential to decrease the burden of the family and health care of repeated physician visits.

OM in its all forms is one of the leading causes for pediatric outpatient health care visits. This thesis claims that parents could have a role in in the diagnostic chain of AOM using tympanometry, SG-AR or smartphone otoscopy at home.

6.1 Parent-performed tympanometry (I)

The rationale of investigating parental tympanometry examinations was based on previous studies showing that tympanometry is an easy-to-use, objective and reliable tool to detect MEE (Smith et al. 2006, Chianese et al. 2007, Helenius et al. 2012). Only a few studies had examined tympanometry in parental use and usually from a feasibility point of view (Moody et al. 1998, Antonio et al. 2002, Doyle et al. 2009). Prior to this study, no studies had been published about the reliability of parental tympanometry examinations.

After parents had been taught how to use the device, the overall success rate of parental home examinations (83%) can be regarded as excellent, since it exceeded even the success rate of physicians based on previous studies (Chianese et al. 2007, Helenius et al. 2012). The success rate of home examinations was comparable to the 80% reported for examinations of children of a mean age of approximately 3 years (Renko et al. 2006). Other studies have reported even higher parental success rates (87–97%), probably due to an older age of the study populations (Moody et al. 1998, Antonio et al. 2002, Tapiainen et al. 2014) and do not reflect the reality in children in otitis prone age.

In this study, with pneumatic otoscopy as the diagnostic standard, the otoscopic diagnoses were categorized as healthy (no MEE), air-interface MEE and complete MEE. Because Helenius et al. (2012) showed that tympanometry cannot distinguish between different middle ear diagnoses, OME and AOM were categorized as any MEE (Helenius et al. 2012). Since MEE is a prerequisite of AOM, children without MEE during RTI symptoms could be followed at home and would not need to be taken for a physician visit to check for AOM.

When parents obtained a flat tympanogram, it was as reliable to detect MEE as that obtained by physicians. In addition, parentally obtained peaked tympanograms excluded MEE equally well as tympanograms obtained by physicians. The diagnostic reliability of parental flat tympanograms was higher than of peaked tympanograms. In other words, parental examinations were especially reliable in detecting MEE. This finding is consistent with previous studies showing that flat tympanograms, obtained by physicians, indicate MEE in 80–95% of otoscopic examinations (Smith et al. 2006, Chianese et al. 2007, Helenius et al. 2012). The

concordance ($\kappa = 0.77$) between a peaked or a flat tympanogram obtained by parents and physicians was high.

Parental tympanometry could be incorporated into primary care in two settings: first, for examination of symptomatic ears at acute visits and, second, for follow-up of the resolution of MEE after an episode of AOM at non-acute visits.

If parents obtained a peaked tympanogram of their symptomatic child, they could safely monitor the child's middle ear status because MEE and thus AOM would be unlikely. Conversely, with a flat tympanogram, the child should be referred to a physician for further examinations to either confirm or exclude AOM, as the presence of MEE would be most likely. With this setting, acute unnecessary visits due to parental suspicion of AOM ought to be avoided.

The recent update of the Finnish AOM guidelines recommends that the need for a follow-up visit after an episode of AOM should be assessed individually (Heikkinen et al. 2017), although the necessity for such follow-ups has been questioned (Laine et al. 2015, Ruohola et al. 2017). Moreover, the guideline suggest that the follow-up could be carried out by tympanometry – if normal, otoscopy is not required (Heikkinen et al. 2017). Our results demonstrate that parents could perform tympanometry for follow-up of the resolution of MEE. Although a parentally obtained peaked tympanogram was a slightly less accurate predictor of a healthy middle ear, it has been previously reported that in the rare cases of a peaked tympanogram and MEE, the amount of MEE is unsubstantial to affect hearing (Koivunen et al. 1997, Koivunen et al. 2000).

The result of this study is that parents do learn to use tympanometry with a good success rate. Most importantly, parental tympanometric examinations are as reliable as those obtained by physicians of young children in the outpatient setting.

6.2 Parent-performed SG-AR (II, III)

The main purpose of parental SG-AR use at home would be to reliably observe the appearance of MEE in a child presenting with symptoms of RTI, because MEE is a prerequisite for AOM (Lieberthal et al. 2013). Considering ear-related visits to physicians only, the use of SG-AR should provide parents with a method to evaluate whether the child needs further middle ear examinations.

The rationale in Study II was to investigate parental use of the SG-AR, because both families and primary care units are strained and ear-related visits are very frequent among young children. Since SG-AR has been considered to be a handy adjunct tool in the diagnostics of AOM (Kimball 1998), the question of parental

ability to use the SG-AR in the home setting was brought up already twenty years ago and has since then been endorsed by more recent studies (Block et al. 1998, Teppo and Revonta 2009). To complement the previous studies which indicate that only the extreme levels of SG-AR are reliable to detect either a healthy ear or one with MEE (Block et al. 1998, Chianese et al. 2007, Laine et al. 2012), the main aim of Study III was to investigate whether the use of SG-AR level changes are more reliable to detect the changes in the middle ear status than single SG-AR levels.

The parental success rate in performing SG-AR examinations was excellent (97%) and surpassed even that of parents who were health care professionals (80%) (Barnett et al. 1998) and of physicians (Teppo and Revonta 2007, Linden et al. 2007, Laine et al. 2012). This reflects the ease of use of the SG-AR device.

When comparing results between different SG-AR studies, the study setting is important, because it is associated with the likelihood of MEE. In Study II, the prevalence of MEE was high during both symptomatic (55%) and asymptomatic (22%) visits. In other studies the prevalence of MEE has varied, depending on the study population (11–58%) (Block et al. 1998, Chianese et al. 2007, Puhakka et al. 2014) and the visit type (5% to 50%) (Teppo et al. 2006).

In symptomatic children, SG-AR levels 4–5 obtained by both parents and physicians indicated reliably the presence of MEE. Parents attained a similar diagnostic accuracy to detect MEE as physicians in other studies (Chianese et al. 2007, Laine et al. 2012). However, the reliability of the parental SG-AR level 1 to exclude MEE was only moderate, since MEE was detected in approximately every third of the otoscopic examinations. This occurrence was the same for parents and physicians. These findings are supported by the NPV reported in previous studies – 68% and 76% to exclude MEE at SG-AR level 1 and at the same cut-off values as in the present study (Chianese et al. 2007, Laine et al. 2012). From another point of view Teppo et al. (2009) also reported a high NPV (92%) for SG-AR level 1 to exclude MEE, but the children were undergoing tympanostomy tube placement (Teppo and Revonta 2009). Conversely, Puhakka et al. (2014) reported a higher NPV (93%) to exclude MEE with SG-AR levels 1–2 (Puhakka et al. 2014). The high NPV to exclude MEE in the last study is probably due to that fact the children were slightly older and had had milder RTI symptoms, which yielded a low prevalence of MEE (11%).

In asymptomatic children, SG-AR level 1 obtained both by parents and physicians excluded MEE rather reliably, although the parental NPV (83%) for level 1 to exclude MEE was lower than that of physicians (96%). From another point of view, with SG-AR level 1 and MEE, no AOM were diagnosed by pneumatic otoscopy. Again, with SG-AR levels 4−5, MEE was present in half of otoscopic

examinations, indicating that these levels are not reliable for detection of MEE in asymptomatic children.

Study III examined the association of the SG-AR level differences between two separate SG-AR measurements instead of a single SG-AR measurement. Monitoring of SG-AR level changes showed that it is unlikely that AOM develops in an initially healthy ear with unchanging SG-AR levels. The PPV for unchanging SG-AR levels to predict a healthy ear was much higher (93%) than that of an individual SG-AR level 1 finding (76%) in the study of Laine et al. (2012). This difference is most likely due to methodological variations, since the physicians and diagnostic standards were the same in both studies. The findings imply that the use of paired SG-AR measurements, for example during RTI symptoms, is more informative of the middle ear status than an individual SG-AR measurement.

When the SG-AR level increased between two separate measurements, the PPV to detect AOM was 71%. Although it appears that increasing SG-AR levels could be more informative compared to an individual SG-AR level 5 (PPV of 64% to predict AOM) (Laine et al. 2012), the current SG-AR technology may have insufficient sensitivity to provide further aid in the diagnostics of AOM.

As for tympanometry, parental SG-AR examinations could be implemented to the triage practice of children with RTI symptoms and to the follow-up of asymptomatic children after an episode of AOM.

Symptomatic children with parentally obtained SG-AR levels 4–5 should be referred for examination by a physician. With SG-AR levels 4−5, the presence of MEE is most probable and accurate pneumatic otoscopy is needed to distinguish between OME and AOM, and to institute treatment. The modest sensitivity of increasing SG-AR levels to detect the deterioration of the middle ear status from healthy to AOM – which obviously would be most important – does, not however, add to the current diagnostics of AOM.

Unfortunately, an isolated measurement result of SG-AR level 1 of symptomatic children seems to be clinically inadequate to exclude MEE and cannot be used for screening. However, unchanging SG-AR levels might be used to obviate the need for a visit to a physician only because of parental suspicion of AOM. If the SG-AR level in the child's ear remains unchanged during RTI symptoms, parents could monitor their child with the SG-AR at home unless other/comorbid symptoms of the child would emerge and necessitate a visit to a physician. This easy way of implementation would reduce unnecessary visits of families to health care centers, and release physician resources.

Asymptomatic children might require several visits to a physician follow-up for the resolution of MEE after an episode of AOM (Heikkinen et al. 2010). The present study shows that a parentally obtained SG-AR level 1 examination indicates that the ear is probably healthy (83%). The result is somewhat disappointing, because MEE would still be present in nearly 20% of otoscopic examinations. Taken together, SG-AR level 1 implies that the child's middle ear is healthy, but this result cannot be unconditionally recommended as an exclusive test of MEE.

To summarize, one of the purposes of Studies II and III was to find ways to most advantageously and expediently use primary care resources, since ear-related visits are very frequent in young children. From a practical perspective, these studies showed that parents do learn to use the SG-AR device technically successfully and reliably. From the perspective of primary care resources and diagnostic accuracy, further improvement of the SG-AR technology is needed before SG-AR can be considered as an adjunctive tool in the diagnostic chain of AOM.

6.3 Parent-performed smartphone otoscopy (IV)

The most important reason to examine parental smartphone otoscopy was the new diagnostic tool targeted to family use. Second, the implementation of telemedicine to pediatric care has been emphasized (Marcin et al. 2015).

Telemedicine improves access to care and might provide rapid answers to questions regarding health and diagnostic. Telemedicine might help the everyday life of families with children. Parents have been willing and able to use mobile devices to share clinical information with health care professionals (Freeman et al. 2017). The pioneering 12-year Health-e-Access Telemedicine program showed that a large proportion of the diagnoses determined at pediatric telemedicine visits (40%) related to the diagnoses OM and RTI (McConnochie et al. 2016). In this study, we examined the diagnostics of AOM from a modern aspect. We taught parents how to perform a smartphone-enabled otoscopy examination and used a device commercially available online. This is the first study to examine the diagnostic quality of parentally obtained tympanic membrane videos.

The most important finding of the present study is that it is possible to detect or exclude AOM by inspection in most parent-performed smartphone otoscopy videos regardless of their technical quality and in virtually all videos with sufficient technical quality. Parent-performed smartphone otoscopy could eliminate unnecessary primary care appointments or, on the other hand, expedite a timely diagnosis and initiation of therapy. A reduction in the number of visits to

physicians might even reduce overdiagnosis of AOM (Jensen and Lous 1999, Pichichero and Poole 2001, Pichichero 2002, Pichichero 2003).

Although the possibility to detect or exclude AOM is good, parent-performed smartphone otoscopy videos provide only a moderate possibility to establish one of the three specified diagnoses (healthy, OME, AOM). In this respect, our study hypothesis was not supported. It was particularly difficult to differentiate a healthy ear from OME, since parents succeeded to test the tympanic membrane movement in only a minority of smartphone otoscopy videos. The testing of the tympanic membrane movement is challenging even for physicians (Cavanaugh 1989, Abbott et al. 2014). Moreover, this study found similar concerns as others: the shape and size of the smartphone is challenging (Richards et al. 2015). In our study, the difficulties to synchronously retract the earlobe and stabilization of the examiners hands might explain why parental videos lack sufficient focus and anatomical view of the tympanic membrane.

The technical quality of the videos during the first week of intervention was significantly better in the immediate teaching group. However, after the teaching intervention the video qualities of the delayed teaching group attained that of the immediate teaching group. This data clearly shows that teaching and cerumen removal are necessary for families and primary care to benefit from the possibilities provided by parental smartphone otoscopy.

Parents succeeded technically excellently in performing smartphone otoscopy. This illustrates how the home environment and parental acquisition of the videos obviously created a secure atmosphere for the young child. Notably, visualization of the tympanic membrane by pneumatic otoscopy may be difficult even for experienced physicians in symptomatic young children who are at the highest risk for AOM and in the least cooperating age (Shaikh et al. 2010).

Currently, parents take their symptomatic child for a physician's appointment or to a busy emergency unit if AOM is suspected. Ear pain tends to be worst during the hours of the day when offices are closed. Interestingly, the Telehealth 2015 consumer survey reported that 30% of parents would select a video consultation for middle-of-the-night care (Modahl and Meinke 2015). The rapidly growing field of telemedicine may provide novel tools, care and educational methods to patients and health care professionals, and enhance appropriate use of health care resources (Utidjian and Abramson 2016). More studies are still required to examine the ultimate clinical usefulness of parent-performed smartphone otoscopy.

Implementation of parental smartphone otoscopy to the diagnostic chain of AOM could, at best, provide high quality tympanic membrane images or videos to be shared with the physician. The physician, in turn, could be able to detect or exclude

AOM and order appropriate therapy in a timely manner from a distance. Parental smartphone otoscopy could also reduce the number of unnecessary physician visits, function as an efficient educational tool for parents and students and work as a consultation tool between professionals. These possibilities merit further use and studies.

6.4 Strengths and limitations of Studies I-IV

The major strength of Studies I-IV is that the study populations included outpatients of an otitis-prone age. It is evident that families participating in these studies were motivated and cooperating, and thus the selection may have contributed to the conduction and success rates of parental home examinations. However, the parents who performed the home examinations with tympanometry, SG-AR or smartphone otoscope represented a vast range of educational and professional backgrounds. Although these results may not be applicable to older children, they are applicable to the most substantial group of young children, who require much primary care resources.

Since pneumatic otoscopy is considered to be the only diagnostic method for OM-related conditions in primary care, not using tympanocentesis as a diagnostic standard should not be considered as a limitation in Studies I-III. Moreover, three out of the five study physicians made over 90% of all otoscopic diagnoses and there was an excellent interobserver agreement with kappa values ranging from 0.80 to 0.92. The diagnostic criteria used to diagnose AOM, OME or healthy ears were stringent and specified on beforehand.

In Study I, parental tympanometry was performed at home either on the study visit day, or one day before the study visit day. It is thus possible that the middle ear findings changed during the time interval between the home examination and the study physician's reference standard examination at the study clinic. This may have led to differences between parental and physician tympanograms and to a potentially false reduction in the reliability of parental tympanometry.

In Study II, the study physicians performed pneumatic otoscopy on the same day as the parents performed the SG-AR examinations at home and it is unlikely that the middle ear findings changed substantially between these two examinations. This increases the reliability of the results. Study II demonstrates that parents can use the SG-AR technically reliably with a high success rate. Thus, parental use of the SG-AR should not be considered as a limiting factor when assessing the reliability of SG-AR level changes as indicators of the middle ear diagnoses (Study III).

The major strengths of Study IV were that the three evaluators analyzed all videos independently in a random order, fully blinded to the child's characteristics and that the use of smartphone otoscopy was studied in home conditions. The most important limitation of Study IV was that it did not include a diagnostic reference standard, such as a pneumatic otoscopy by the study physician, which the parental smartphone otoscopy examinations could have been compared to. One might also argue that the intervention was compound because it included teaching and cerumen removal. However, the main aim was to investigate the diagnostic quality of parentally obtained tympanic membrane videos in a real-life study-setting. Acquisition of reference diagnoses would have required more visits at the study clinic and this would have changed the whole study setting and prevented the investigation of home-use of the smartphone otoscope.

6.5 Practical implications

Currently, parents take their symptomatic child to a physician when they suspect AOM. Studies I-IV show that parents can perform home examinations with a tympanometer, SG-AR device or smartphone otoscope.

The implementation of parental examinations into practice is associated with several challenges. First of all, the implementation of parental home examinations would require a cultural change within health care providers and families. Teaching parents to use any of these devices requires time for the parents and the health care unit. Some parents would not necessarily be willing or motivated to pursue home examinations. Other parents, despite a home examination excluding AOM, would still want to see a physician if the child had comorbid symptoms (Cullen and Darke 2003). Importantly, if the child is acutely sick, AOM is not the only possible cause. Therefore, if parents would be concerned of the child's overall condition after performing exclusive home examinations of AOM, the child should be examined by a physician.

Who would provide for these devices? A very large proportion of young children have personal supplemental and voluntary health insurances in some areas of Finland (*e.g.,* Turku), which relieves parents from the financial burden related to the child's health and physicians may be more liberal when considering the required number of visits. Both of these considerations are very important from the primary care point of view and affect patients who do not have supplemental health insurances.

The three examined devices differ from each other. From a family point of view, the tympanometer is very expensive (approximately 2,000−3,000 €) and home-use

is unlikely. The SG-AR device, however, could be affordable for families (approximately 40 US$, available at www.amazon.com, addressed 26.8.2017). Furthermore, the professional SG-AR model was not diagnostically superior to the consumer model – a noteworthy observation when considering acquisition of an SG-AR device (Barnett et al. 1998). The consumer-marketed smartphone-enabled otoscope, in turn, is more expensive than the SG-AR device, but probably not too expensive for families (300 US$ April 19, 2017). The smartphone otoscope in this study was designed for iPhone models only and this might be considered as a limitation for wider use. Certainly, the compatibility of otoscopes with any smartphone model should be of top priority for the device manufacturers. Regardless of these aspects, a smartphone otoscope may be the home device worthwhile of purchasing.

In practice, the SG-AR examination is easier for parents than tympanometry, because it does not require an airtight seal between the ear canal and the ear speculum. As a result, the SG-AR examination is usually successful even with a crying or resisting child. Neither of these examination methods is unpleasant for the child. The smartphone otoscopy examination itself requires rather advanced parental examination skills compared to tympanometry or SG-AR, and teaching parents how to use the smartphone otoscope is necessary if high quality videos are to be obtained.

Importantly, the results of SG-AR and tympanometry are relatively easy to interpret even for parents, but this is not the case for smartphone otoscopy videos. Notably, cerumen is often present in a child's narrow ear canal and makes any otoscopy sometimes difficult and a health care professional is needed for cerumen removal. However, cerumen does not inhibit the use of SG-AR unless it occupies >50% of the ear canal (Block et al. 1998). Cerumen should not influence the diagnostic accuracy of tympanometry unless it obstructs more than half of the ear canal diameter (Block et al. 1999).

To date, the SG-AR has not gained a position as a widely used, recognized and reliable diagnostic tool, and implementation of the SG-AR for consumer use seems unlikely, unless there is considerable technical improvement. The diagnostic value of tympanometry has been widely recognized (Blomgren and Pitkäranta 2003), but still remains underused even among physicians (Jensen and Lous 1999, Abbott et al. 2014). The unquestionable advantage of the smartphone otoscope is that it enables a view of the tympanic membrane and its movement. For the first time, parents could actually have a tool which allows remote communication with their child's physician.

The parental success rates in performing examinations at home with any of these devices can be considered excellent considering the young age of the children.

Apparently, children allow their mother and father to examine them without resistance at home, because children naturally trust their parents who make them feel safe. It even seemed, especially with the smartphone otoscope, that the children who first opposed the examination, learned to calm down and even enjoy the examinations. This only shows the importance of parental purposefulness and a high motivation to conduct home examinations.

In conclusion, the use of parental home examinations is not a barrier to the introduction of new approaches to the diagnostic procedures of AOM at primary care.

6.6 Future visions

AOM will most certainly burden families and health care in the years to come. The incidence figures of AOM in the Turku area between the years 2014 and 2016 show that approximately every fourth sick visit by young children (6–35 months) was related either to AOM or RTI, and that the diagnosis at every tenth sick visit was AOM. Future studies to alleviate this burden are needed. Measures to prevent AOM should continue to be needed.

Children deserve accurate AOM diagnostics. A child does not have AOM without MEE, acute onset of symptoms and inflammatory signs including bulging of the tympanic membrane (Lieberthal et al. 2013). Physicians should adhere to treatment guidelines. They should also request for and perform middle ear examinations with appropriate diagnostic tools. Inaccurate diagnostics of AOM lead to unnecessary antibiotic prescriptions, increased antibiotic resistance and unnecessary surgical treatments, all of which burden the child, families and health care systems worldwide (Pichichero and Poole 2001, Rosenfeld et al. 2013, Casey and Pichichero 2014).

For improved diagnostics, diagnostic tools need further development. Considering all that modern technology has provided, the invention of a totally new otoscope, even for home use, should be possible. The otoscope should be hand-held and be equipped with a high-quality video screen and illumination for optimal middle ear examination. The ear speculum should be designed to allow visualization of the whole tympanic membrane from a single angle of view. Air tightness between the ear speculum and the ear canal should not be necessary. This future otoscope should emit an automatic pressure wave resembling that of the tympanometer to provide objective signs of MEE and to facilitate the evaluation of the movement of the tympanic membrane. Or then, three-dimensional imagining properties should provide objective information about the middle ear cavity and the presence

of MEE. At best, this otoscope should simultaneously provide audiological information. All of this data should then be wirelessly transmitted to a database containing automated image processing tools to provide objective middle ear diagnoses. The process would be over in a few seconds. Naturally, the problematic nature of cerumen and its removal must be solved. Certainly, the envisioned high-technology otoscope would be cordially welcomed by the children, families, physicians and health care systems who all carry the burden of 709 million new episodes of AOM annually (Monasta et al. 2012).

Acceptance of telemedicine by health care professionals, parents and the community takes understandably place only gradually. However, cultural and technological development has changed the role of patients who are participating more actively in their own care. Various health applications are readily available. The continuous progress of smartphones with sophisticated camera qualities has allowed new research methods, and the use of mHealth will probably shift health care towards more patient-intrinsic designs (Bhavnani et al. 2016, Topol 2010). Industry estimations tell that in 2015 there were 500 million smartphone users who used a health-care application, and in 2018 more than 50% of the 3.4 billion smartphone and tablet users have downloaded health care applications (Research2guidance). Parents of the modern society and especially of the future societies are well acquainted with the new technology. Parents have access to and use various technological tools, such as social networks, messaging, imaging and video calls and manage daily affairs by mobile phones, tablets or computers.

To benefit from the possibilities of telemedicine in pediatric otorhinolaryngology, high quality images or videos are essential. Especially in young struggling children with narrow ear canals this might be challenging. Removal of cerumen is one of most important ways to increase the image quality and thus the accuracy of middle ear diagnostics (Eikelboom et al. 2005, Lundberg et al. 2008). Tympanometry and pre-defined image or video analysis methods combined with patient history could improve accurate remote diagnosis and the quality of management advice (Eikelboom et al. 2005, Lundberg et al. 2013). In addition to the middle ear examination itself, the quality of the device (field size, illumination, color accuracy and usability) is important for image/video quality (Mbao et al. 2003). The educational value of these new examination tools for families, professionals and students is most likely high. Larger studies considering the diagnostic accuracy, consumer use and cost-effectiveness in the pediatric population are warranted.

Pediatric telemedicine is an attractive platform for health care services. Importantly, families and patients have been satisfied and open-minded for the remote possibilities pediatric telemedicine could provide. Healthcare systems should endorse existing telemedicine projects and implement new services which

meet the needs and expectations of professionals and patients. More studies are required to evaluate the diagnostic value and usefulness of the smartphone otoscope in primary care. Studies are also needed to investigate the clinical usefulness, primary care and family resource saving effects of parent-performed examinations to identify children who need and who do not need a physician visit because of suspected AOM.

Finally, high quality research, technical development and implementation of new diagnostic methods and innovations into the clinical practice of OM are needed. This requires funding, open-minded cooperation between health care units and specialists in different organizations, and not least, participating families.

7 SUMMARY AND CONCLUSIONS

These studies show that parents of a wide range of educational and professional backgrounds can perform tympanometry, SG-AR or smartphone otoscopy at home after instructions on the use of these devices. In all these studies, parents achieved a high success rate in performing home examinations on their young child.

Study I demonstrate that parental tympanometric examinations are as reliable as those performed by physicians. Parental tympanometric examinations could be used for the detection of MEE in a symptomatic child. A flat tympanogram would necessitate further middle ear examinations and thus a physician visit. Conversely, a peaked tympanogram obtained after an episode of AOM excludes MEE and could eliminate the need for a follow-up appointment.

Studies II and III show that, in symptomatic children, SG-AR levels 4–5 are mainly related to the presence of MEE. This finding necessitates a physician visit for an accurate diagnosis of the condition of the middle ear. Unfortunately, SG-AR level 1 is an insufficient screening tool to reliably exclude MEE in symptomatic children. In asymptomatic children, however, SG-AR level 1 excludes MEE reliably. Furthermore, in a middle ear that is initially healthy, unchanging SG-AR levels between two separate measurements effectively excludes a diagnosis of emergent acute otitis media. However, maybe time and technology has passed the SG-AR, since it has not obtained the position of a generally used, adjunctive tool.

Study IV indicates that the ability of physicians to detect or exclude AOM from parent-performed smartphone otoscopy videos is good regardless of the technical quality of the videos. The ability of physicians to detect or exclude AOM is excellent from videos with sufficient technical quality. Implementation of parental smartphone otoscopy to clinical practice requires physician/primary care resources. Physicians are needed to remove cerumen and to teach parents how to perform high quality smartphone otoscopy. Nevertheless, the ability to detect or exclude AOM is a most significant finding and could well eliminate some unnecessary primary care appointments. This could reduce overdiagnosis and expedite initiation of therapy.

To answer the aim of this thesis: Parents could indeed have a role in the diagnostic chain of AOM. The implementation of parental examinations into clinical use may also reduce the high burden AOM puts on families and primary care. Families in a whirlpool of OM could be particularly eager to pursue rapid home examinations, if this facilitates exclusion or detection of MEE. For this, tympanometry or SG-AR could be used, or videos of the tympanic membrane obtained by smartphone otoscopy could be relayed to their child's physician for remote diagnosis of AOM.

The reduction in physician visits could relieve the burden of stressed families and release physician resources for other duties.

Implementation of these results into primary care is a challenging task. It requires experimenting and further studies – this opportunity needs to be grasped. Technical progress of diagnostic tools is essential and continues to be of high priority and interest worldwide.

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