Otitis media

Anne G. M. Schilder[1,7], Tasnee Chonmaitree[2], Allan W. Cripps[3], Richard M. Rosenfeld[4], Margaretha L. Casselbrant[5], Mark P. Haggard[6] and Roderick P. Venekamp[7]

ABSTRACT

Otitis media (OM) or middle ear inflammation is a spectrum of diseases including acute otitis media (AOM), otitis media with effusion (OME, 'glue ear') and chronic suppurative otitis media. OM is among the most common diseases in young children worldwide. Although OM may resolve spontaneously without complications, it can be associated with hearing loss and life-long sequelae. In developing countries, chronic suppurative OM is a leading cause of hearing loss. OM can be of viral or bacterial origin; during 'colds', viruses can ascent through the Eustachian tube to the middle ear and pave the way for bacterial otopathogens that reside in the nasopharynx. Diagnosis depends on typical signs and symptoms such as acute ear pain and bulging of the tympanic membrane (ear drum) for AOM and hearing loss for OME; diagnostic modalities include (pneumatic) otoscopy, tympanometry and audiometry. The use of antibiotics for AOM should be carefully considered given the self-limiting nature of the disease and the risk for adverse effects and antimicrobial resistance. Insertion of ventilation (tympanostomy) tubes and adenoidectomy are common operations for OM aimed at preventing AOM recurrences and restoring hearing; however, their effectiveness is still debated. The role of hearing aids to alleviate symptoms of hearing loss in the management of OME needs further study. Despite reports of a decline in OM incidence over the past decade, attributed to implementation of clinical guidelines promoting accurate diagnosis and judicious use of antibiotics and to pneumococcal conjugate vaccination, OM continues to be a leading cause for medical consultation and antibiotic prescription and surgery in high-income countries.

[1] EvidENT, Ear Institute, University College London, Royal National Throat Nose and Ear Hospital, London, UK.
[2] Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas, USA.
[3] School of Medicine and Menzies Health Institute Queensland, Griffith University, Queensland, Australia.
[4] Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York, USA.

[5] University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
[6] Department of Psychology, University of Cambridge, Cambridge, UK.
[7] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence to:
A.G.M.S.
a.schilder@ucl.ac.uk

[H1] INTRODUCTION

Otitis media (OM) or inflammation of the middle ear (consisting of the middle ear cavity and ossicles, Figure 1) is an umbrella term that encapsulates acute OM (AOM), OM with effusion (OME, 'glue ear') and chronic suppurative OM (CSOM) (Table 1).[1] These conditions are closely related and can overlap. OM is one of the most common diseases in young children. In high-income countries, it is also a leading cause for medical consultation and antibiotic prescription and surgery.[2-4]

AOM is characterized by the presence of fluid in the middle ear (that is, middle ear effusion (MEE)) together with signs and symptoms of an acute infection.[5] Many children occasionally have AOM, but an important group of children have recurrent episodes of AOM (Table 1).[5] Recurrent AOM episodes cause frequent episodes of acute ear pain, fever and general illness and considerable distress to children and their parents. Suppurative (pus-forming) complications of AOM, including acute mastoiditis, meningitis and brain abscesses, are rare given the high incidence of OM but potentially serious. These complications pose a threat in low-income countries in particular[6,7]; an estimated 21,000 people die from complications of OM every year[2]. The global prevalence of hearing loss associated with OM is estimated at 30 (range 0.7-95.0) per 10,000 individuals.[2] Perforation of the tympanic membrane (ear drum) can occur as a local sequela of AOM or as a complication associated with treatment with ventilation tubes (tympanostomy tubes).

OME is characterized by the presence of MEE behind an intact tympanic membrane, but in contrast to AOM, OME is not associated with signs and symptoms of an acute infection.[8] The main symptom of OME is a conductive hearing loss caused by impaired transduction of sound waves in the middle ear due to the presence of MEE. When this hearing loss persists or recurs frequently, it may have negative impact on language, behaviour and progress at school.[9]. OME is very common with 80% of children having had ≥1 episode of OME by the age of 10 years. OME may occur as a new onset OME after a viral infection[10] or may occur after AOM, when the inflammatory process subsides and MEE persists. In fact, after an AOM episode, all children have OME for some time.[11,12] OME in itself is a risk factor for AOM, illustrating the interrelatedness of these conditions.

CSOM is defined as chronic inflammation of the middle ear and mastoid cavity; persistent or recurrent ear discharge through an tympanic membrane perforation or a ventilation tube is the most prominent symptom.[13] CSOM causes a conductive hearing loss and might damage the middle ear ossicles. It also increases the risk for permanent sensorineural hearing loss (hearing loss owing to damage to the inner ear) and intracranial complications.[13] The of this condition varies widely between countries, but it is most common in low- and middle-income countries.[2]

Since publication of a landmark review on OM more than a decade ago[14], important developments worldwide have been made, in particular regarding prevention of OM through pneumococcal conjugate vaccination and treatment of OM following new guidelines focusing on accurate diagnosis and judicious use of antibiotics. These events have modified the epidemiology and clinical picture of OM worldwide. In this Primer, we provide a state-of-the art review of OM epidemiology, its underlying pathophysiology, diagnosis, impact on children and their families and preventative and treatment options. We also discuss promising future directions of OM research that might guide clinicians and carers to optimize the health and wellbeing of young children with OM.

[H1] Epidemiology

[H2] Incidence and prevalence

A recent systematic review on the global burden of OM estimated the average AOM incidence rate at 10.8 new episodes per 100 people per year.[2] This rate ranges from an average of 3.6 for central Europe to an average of 43.4 for Sub-Saharan West Africa and central Africa, reflecting that the burden of AOM varies with economic status (Figure 2A). The total annual number of new AOM episodes is estimated at 709 million, with 51% occurring in children <5 years of age. Global AOM incidence rates are highest in children aged 1-4 years (61 new episodes per 100 children per year) with a peak incidence in the first year of life (45.3 new episodes per 100 children per year).[2]

Since OME is asymptomatic and may go undetected, its incidence and prevalence has been difficult to establish accurately. The most reliable data on the epidemiology of OME come from large cohort studies of children from developing countries, mostly performed in the 1980s and 1990s [15-18] showing a point prevalence of OME on screening tests of up to 20%.[19] The peak incidence of OME is around 1 year of age; by 3 years, almost all children have experienced at least one episode of OME.[18,20]

For CSOM the average global incidence rate is estimated at 4.8 new episodes per 1,000 people (all ages) per year (Figure 2B).[2] The total annual number of new CSOM episodes was estimated at 31 million, with 22% occurring in children <5 years of age. Global CSOM incidence rates are highest in the first year of life (15.4 new cases per 1,000 children per year).[2]

Recent studies from Canada[21,22], the United States[23,24,25], Netherlands[26] and UK[27] suggest a decline in OM incidence since the mid 1990s. This decline is attributed to the introduction of clinical guidelines recommending stricter diagnostic criteria and judicious use of antibiotics in OM as well as the introduction of pneumococcal conjugate vaccination. By

contrast, studies from developing countries and indigenous populations continue to demonstrate a heavy burden of OM, particularly CSOM and its complications.[2,28-30]

[H2] Social and environmental risk factors

The risk of OM is significantly influenced by a number of host and environmental factors (Figure 3). Host factors increasing the risk of OM include: young age[31], male sex[32], race and ethnicity[32], genetic factors and a family history of OM[33], craniofacial anomaly such as cleft palate[34], atopy [33], immunodeficiency[35], upper respiratory tract infections (URTI) and adenoid hypertrophy [33,36], and laryngopharyngeal reflux[37]. Environmental factors increasing the risk of OM include: low socio-economic status, exposure to tobacco smoke[33], having older siblings[38], day care attendance[31,38,39], and use of a pacifier[40,41]. Having been breast-fed protects against OM.[42] In developing countries, malnutrition, contaminated water, poor hygiene, overcrowding, HIV, tuberculosis, malaria and poor access to health care increase the risk for chronicity and complications of OM.[2,43,44]

[H1] Mechanisms/pathophysiology

Despite the high disease burden, OM in developed countries is usually uncomplicated and self-limiting and does not result in ongoing hearing problems or developmental delay.[6] However, in high-risk populations in both developing and developed countries considerable hearing loss does occur with life-long sequelae. In these populations, the progression of disease is a complex aggregate continuum of exposures to numerous social, environmental and genetic risk factors. OM pathogenesis starts with early and dense bacterial colonization of the nasopharynx, early onset AOM, the establishment of an acute inflammatory cycle in the middle ear as a result of continuing exposure to infective agents, including bacterial persistence in the middle ear through biofilm formation, viral infections and finally severe chronic ear disease (Figure 4).

[H2] Eustachian tube anatomy

An anatomical and functioning Eustachian tube not only contributes to the protection of the middle ear against the influx of bacterial otopathogens and respiratory viruses, but is also essential for the drainage of secretions from the middle ear space and for pressure equalization.[1] Indeed, the anatomy of the immature Eustachian tube in infants has a central role in the susceptibility to infections of the middle ear (Figure 1). The Eustachian tube epithelium is the frontline defense against the passage and colonization of otopathogens from the nasopharynx. The Eustachian tube epithelium predominantly consists of ciliated respiratory epithelial cells, which produce antimicrobial proteins (such as lysozyme), interspersed with goblet cells, which produce both mucoid and serous mucus. The direction of mucociliary flow from the middle ear through the Eustachian tube to the nasopharynx in combination with epithelial secretion of antimicrobial proteins protects again bacterial colonization of the middle ear.

Anatomically, the Eustachian tube is shorter, wider and more horizontal in infants and young children (<1 year) than in adults, which facilitates otopathogen transmission through to the middle ear and increases the risk of OM.[48] Frequent placement of infants in the supine position can also exacerbate infection risk. As children grow, the skull base extends downward, increasing the angle of the Eustachian tube gradually from approximately 10° at birth to 45° in adults; concurrently, Eustachian tube length increases from 13mm to 35mm.[49] These anatomical changes as well as functional maturation of the immune system might contribute to a reduced risk of OM as children age, even in children at high-risk of OM.

[H2] Bacterial colonization and biofilms

Early colonization of the nasopharynx with bacterial otopathogens considerably increase the risk of subsequent episodes of OM[50,51] *Streptococcus pneumoniae* (or pneumococcus), nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* are the three dominant bacterial otopathogens reported globally, but the individual species and strain dominance are influenced by geographical location and pneumococcal conjugate vaccine use.[52,53] For example, Indigenous Australian children aged 1-3 months are more likely to have ≥2

otopathogens isolated from their nasopharynx than non-indigenous Australian children. In Indigenous Australian children, early carriage of nontypeable *H. influenzae* increases the risk of OM whereas in non-Indigenous Australian children early carriage of *M. catarrhalis* was associated with increased risk of OM. This difference between Indigenous and non-Indigenous Australian children is most likely the result of different environmental risk factors. [54] Only a few studies have examined the correlation of bacterial density or load in the nasopharynx with OM and those have been focused on children who are at specific risk for developing OM.[57,58] Nevertheless, these studies show that bacterial density in the nasopharynx is associated with increased risk of OM.

Bacterial biofilms (colonization of bacteria embedded in extracellular matrix and adherent to a surface), which are known to protect bacteria against antibiotic treatment[59,60] and the host's immune responses, have been demonstrated in middle ears of patients with CSOM[61,62], persistent OME[61,63] and those with OM who have failed antibiotic treatment.[63] Biofilms have been reported to occur in MEE[63], attached to the middle ear mucosa.[64] In animals, immunization against nontypeable *H. influenzae* resulted in more rapid resolution of an established biofilm infection, [65] suggesting that vaccination can induce immune responses that are effective against pathogens residing in biofilms in the middle ear.

[H2] Viral infection

AOM is always preceded by viral infection of nasopharyngeal and Eustachian tube epithelium — the so-called 'common cold' or viral URTI (Figure 5).[66] Bacterial otopathogens that are colonized in the nasopharynx do not cause any harm until virus initiates the inflammatory process in the nasopharynx. A wide variety of viruses that cause URTI symptoms can induce AOM development. These include the following viruses in the order of importance: respiratory syncytial virus (RSV), rhinovirus, adenovirus, coronavirus, bocavirus, influenza virus, parainfluenza virus, enterovirus and human metapneumovirus.[10,66] Viral infection creates changes in the nasopharyngeal mucosa by modifying host immune function[67], inducing cytokine activity and inflammatory mediators[68] and increasing bacterial colonization and

adherence through up-regulation of host cell-surface antigens that serve as bacterial receptor sites[69,70]. Viral infection also alters mucus properties and diminishes the normal mucociliary clearance by mucosal cells of the Eustachian tube and nasopharynx. This causes tubal dysfunction [69,71] leading to negative middle ear pressure, which occurs more severely in children < 24 months, compared with children 25-47 months.[72,73] Negative middle ear pressure facilitates influx of bacteria and/or viruses into the middle ear.[72] The risk for AOM development after URTI depends on the colonized bacterial otopathogens; the risk is lowest with no colonized bacteria and highest with colonization by all three pathogenic bacteria.[74]

The presence of live viruses in the middle ear, in addition to bacteria, is associated with increased inflammatory mediators and cytokines such as histamine, leukotriene B4 and IL-8, which can in turn interfere with antibiotic penetration into the middle ear.[75-78] Virus alone can cause AOM, both in experimental animals and in children[66]. Approximately 5% of the MEE isolated from children with AOM contain only viruses.[79] AOM following viral URTI often only occurs when the infection is severe enough to cause URTI symptoms and associated Eustachian tube dysfunction. Asymptomatic viral infection does not lead to AOM.[80] Viral infection not only leads to AOM, but also new onset OME. In children at the peak age incidence of OM (6-47 months), the rate of AOM and OME following URTI was 37% and 24%, respectively.[10]

[H3] The innate immunity.

Both bacteria and viruses induce middle ear inflammation and MEE.[66] Innate immune systems include physical barriers such mucocillary-generated flows of mucus and innate defense molecules such as lysozyme, defensins, complement factors, cytokines and chemokines[48,81]. These systems are responsible for initiating front-line responses to pathogens within the nasopharynx, Eustachian tube and middle ear. Activation of pattern recognition receptors, particularly Toll-like receptors by invading otopathogens, triggers the release of several of the antimicrobial proteins and pro-inflammatory cytokines.[82,83] Up-regulation of these innate mechanisms is critical for the rapid resolution of OM[84]. However,

these cytokines and antimicrobial proteins can also have a pathophysiological role[83,85] characterized by persistent inflammation of the middle ear, as observed in CSOM.[86] The predominant bacterial pathogens for CSOM — *P. aeruginosa* and *S. aureus*[86,87] — form biofilms with other otopatogens and elicit an elevated innate inflammatory responses, which might contribute to the chronicity of OM and progression to CSOM despite appropriate intervention.[87] Evidence of the elevated inflammation includes high levels of IL-8 in the middle ear fluid[88] and elevated mRNA and protein levels of TNFα, IL6, IL1β and INFγ in the middle ear mucosa compared with patients with chronic OME.[89]

[H3] The role of adaptive immunity.

The middle ear is an effective immunocompetent site that maintains essentially a 'sterile' environment within the middle ear. Adaptive immune responses reflect aspects of both mucosal and systemic immunity. Indeed, antigen-specific secretory IgA and IgG antibodies have been detected in the middle ear fluid and IgA-producing cells have been detected in the middle ear mucosa in response to infection. Research is only just commencing on the middle ear cell-mediated responses to infection, but early data suggest that Treg cells may play a pivotal part in controlling inflammation. The literature is unclear as to whether or not deficiencies in humoral immunity contribute to susceptibility to OM. More research is required to explore for aberrations in adaptive immune responses as potential risk factors for susceptibility to OM. [48]

[H2] Genetic factors

Estimates of heritability of AOM and OME range from 40% to 70%[90], with boys at slightly higher risk than girls [32]. A range of genes regulating the innate immune response are associated with predisposition to OM.[91] Some of the heritable risk for OM might result from cytokine polymorphisms, that can be otopathogen specific. For example, polymorphisms in *IL10*, *IL6* and *TNFA* genes are predictive of OM coincident with RSV and rhinovirus infection[92] whereas polymorphisms in a number of signal transduction pathways, such as TLR signalling, have been associated with both risk and disease severity of OM in human studies and mouse models.[48,83] Most polymorphisms described to date disrupt establishment of an effective

innate immune response, but TGFβ signalling pathway polymorphisms can be pathophysiological through interference with moderation of pro-inflammatory responses.[83,90] Although data with respect to deficiencies in specific antibody responses in OM-prone children to otopathogens are conflicting, the role of possible cell-mediated dysfunction is becoming clearer. The genetic contribution to these observations is unknown and it is possible that pathogen-host-environment interactions might have a role. Further research is needed to fully understand the role of these genetic factors in the pathogenesis of OM.

[H1] Diagnosis, screening and prevention

[H2] Signs and symptoms

Signs and symptoms obtained from the history-taking (including ear-specific and non-specific symptoms; Table 2) can raise suspicion for OM but are insufficient for accurate diagnosis. For example, typical signs and symptoms of AOM might be absent or subtle.[5] OME, by definition, does not have signs or symptoms of acute ear infection; children can be asymptomatic and have less obvious signs, such as hearing problems, or subtle findings, such as ear rubbing, clumsiness, disturbed sleep, language delay or poor school performance.[8]

Ear pain is the most consistent symptom of AOM, but only 50-60% of children with AOM complain of ear pain.[93,94] In young preverbal children, ear pain may manifest with ear manipulation (for example, tugging, rubbing or holding), excessive crying or with changes in the child's sleep and behaviour patterns.[5] These latter symptoms, however, are nonspecific and, like fever and vomiting, do not differentiate children with AOM from those with URTI.[95]

MEE is required for diagnosing both AOM and OME and its absence precludes a diagnosis of AOM or OME [5]. However, the difficulty of confirming MEE in primary care settings helps explain why AOM is widely over-diagnosed.[96-98] By contrast, OME might be underdiagnosed by paediatricians compared with otolaryngologists.[98] Ear discharge, or visible discharge in the external ear canal, can be present in AOM (with acute tympanic membrane perforation or

draining ventilation tube), CSOM (with chronic tympanic membrane perforation and persistent drainage), or acute otitis externa (inflammation of the external ear canal). Tympanic membrane bulging visualized by otoscopy is a key diagnostic feature for AOM.[5]

[H2] Diagnostic modalities

AOM is diagnosed by otoscopy and can be further assessed using a symptom severity scale. Pneumatic otoscopy is the primary diagnostic modality for OME, with tympanometry and otomicroscopy as adjunct measures. Acoustic reflectometry can be used by parents to assess MEE. Tympanic membrane perforation associated with CSOM may be diagnosed with otoscopy or otomicroscopy, but may require removal of ear discharge by suctioning for adequate visualization.

[H3] Symptom severity scales for AOM.

Several validated, parent-reported symptom scales have been developed to assess AOM severity. The AOM Severity of Symptoms Scale (AOMSOS) is a 7-item scale with response options of ‘no’, ‘a little’, or ‘a lot’ for the prevalence over the past 12 hours of ear pain, ear tugging, irritability, difficulty sleeping, eating less, less playful, and fever.[99] The overall AOMSOS score discriminates among children with and those without AOM, but all signs and symptoms can be present to varying degrees in children with normal ears.[93] Another severity measure, the AOM Faces Scale (AOM-FS), uses a scale with 7 choices ranging from 1 (not present, not a problem) to 7 (extreme problem).[100]

[H3] Otoscopy.

Otoscopy is the mainstay of AOM diagnosis (Table 2; Figure 6). Obstructing cerumen (ear wax) that prevents adequate visualization of the tympanic membrane must be removed to facilitate accurate diagnosis.[101] When performing otoscopy, the clinician assesses and records ear drum colour, opacity, position and integrity. A bulging ear drum, which is associated with a high level of bacterial pathogens in the MEE[102] is the most consistent sign of AOM[94,103] (Figure 5), and is the most useful features for differentiating AOM from OME.[104] As the bulging

subsides, the tympanic membrane may have a cobblestoned appearance (shagrination).[105,106] An opaque or cloudy tympanic membrane is highly predictive of MEE, regardless of cause.[103] Several image-based scales exist to standardize recording and interpretation of otoscopic findings.[106,107]

[H3] Pneumatic otoscopy.

Pneumatic otoscopy has been recommended as the primary diagnostic method for OME (Table 2) [8] because of its excellent diagnostic accuracy.[103,108] Otoscopy alone, without a pneumatic bulb, might overlook OME because the tympanic membrane might appear normal and ear-related symptoms can be minimal or absent. Conversely, pneumatic otoscopy can avoid false-positive diagnoses of OME caused by surface abnormalities in the tympanic membrane without MEE.[8] Distinctly impaired mobility of the tympanic membrane on pneumatic otoscopy is highly predictive of OME[94,103] and improves diagnostic accuracy over otoscopy alone.[109,110] However, the use of pneumatic otoscopy in clinical practice is variable across the world; in the United States alone prevalence ranges from 7% to 33%.[111,112] Training medical residents in pneumatic otoscopy is challenging[5], but can be enhanced with a structured, computerized curriculum with static and dynamic images of the tympanic membrane.[97]

[H3] Otomicroscopy.

Otomicroscopy might help more than simple otoscopy in diagnosing OME (Table 2) [113], but evidence is sparse and the need for special equipment and training often limits the examination to secondary care. Otomicroscopy is most useful for assessing tympanic membrane abnormalities (such as perforation, atrophy, tympanosclerosis, atelectasis and retraction pockets) that may be associated with COME.[114]

[H3] Tympanometry.

Tympanometry objectively measures tympanic membrane mobility and middle ear function (Table 2, Figure 6).[115] Compared with pneumatic otoscopy, tympanometry has comparable

sensitivity (range, 90-94%) but lower specificity (50-75% vs. 80% for tympanometry and pneumatic otoscopy, respectively) for diagnosing OME[116] Barriers to tympanometry in primary care settings include equipment cost and limited training, but tympanometry is easier to perform and more useful in managing children with OM than pneumatic otoscopy.[117] Tympanometry also estimates the equivalent ear canal volume, defined as the amount of air in front of the probe, normally 0.3-0.9 ml in children.[118] A low equivalent volume (<0.3 ml) could indicate an inaccurate reading because the ear canal is obstructed by cerumen or when the probe is pressed against the canal wall; a high equivalent volume (1.0-5.5 ml) occurs when the tympanic membrane is not intact because of a perforation or ventilation tube, and should prompt further examination if neither was initially suspected. Tympanometry is generally performed using a 226 Hz tone, but for children <6 months in age a 1,000 Hz probe tone is best as the 226 Hz tone is insensitive to MEE.[119]

[H3] Acoustic reflectometry.

Acoustic reflectometry measures how much sound is reflected off the tympanic membrane, with higher reflectivity indicating a greater probability of MEE (Table 2).[120] Advantages over tympanometry include ease of use, no requirement for a hermetic seal, and availability of an inexpensive consumer version, which can be used reliably by parents to monitor their child's middle ear status.[121] Reflectometry in some studies is less sensitive[122] and specific[123] than tympanometry in detecting MEE, but its high specificity and negative predictive values make reflectometry useful for ruling out MEE in children with upper respiratory tract infections[124].

[H2] Screening

AOM is symptomatic and does not require screening. However, even screening of OME, which is asymptomatic, has not been found useful because of the high incidence and recurrence in young healthy children[8], the self-limited nature of most episodes[6], and the lack of significant differences in developmental outcomes (language, behavioural problems, or intelligence scores) between children not screened for OME and children with OME identified

by screening who have received expeditious ventilation tube insertion.[125] Current guidelines, therefore, recommend against routine screening of otherwise healthy, asymptomatic children for OME.[8]

Conversely, screening for OME is recommended at age 12-18 months for children with sensory, physical, cognitive, or behavioural factors placing them at increased risk for developmental comorbidities (Box 1). [8] OME accounts for about two-thirds of newborn hearing screen failures.[126,127] Clinicians who manage these failures should know that only around 10% of children with OME identified by hearing screening may also have the targeted concurrent sensorineural hearing loss. This may interfere with detecting an underlying sensorineural hearing loss because it may take several months after resolution of MEE for the extra impact of an OME history on hearing ability to completely resolve.[128]

[H2] Prevention

Because OM is a multifactorial disease, a variety of strategies can be used for prevention. The strategies mainly focus on reducing modifiable risk factors such as bacterial and viral infections and environmental risks. Chemoprophylaxis using antibiotics and surgical interventions to reduce the burden of OM to children are discussed in the Management section.

[H3] Vaccines directed against bacterial otopathogens.

The goal of the vaccines is to reduce or eliminate nasopharyngeal colonization of *S. pneumoniae*, nontypeable *H. influenzae* and *M. catarrhalis*. The 7-valent pneumococcal conjugate vaccine (PCV7), directed against 7 serotypes of the *S. pneumonia,* became available in the United States and many European countries in 2000. The vaccine was added to the primary series of universal vaccination at 2, 4 and 6 months, with a booster dose at 12-15 months. PCV7 was associated with 29% reduction in AOM caused by pneumococcal serotypes contained in the vaccine, 6-7% reduction in overall AOM and 20% reduction in the use of ventilation tube for chronic recurrent OM.[129-131] PCV13, available a decade later, has been associated with further reduction of AOM, mastoiditis and ventilation tube insertions.[24]

The use of PCVs has led to replacement of serotypes of *S. pneumoniae* in the nasopharynx by the serotypes that are not covered by the vaccine and nontypeable *H. influenzae* in vaccinated children.[132,133] Nevertheless, the pneumococcal-associated AOM may continue to decrease with PCV vaccination as the serotypes with greater capacity to cause AOM are replaced by less otopathogenic serotypes.[134] There is now also growing evidence to support the hypothesis, at least in developed countries, that the prevention of OM associated with the pneumococcal serotypes present in the vaccine in young children results in a reduction of subsequent and more-complex disease caused by non-vaccine serotypes and nontypeable *H. influenzae*. Vaccination might, therefore, disrupt the continuum of evolution from pneumococcal-associated OM towards chronic OM.[135,136] However, in communities in which there is early and dense bacterial acquisition in the nasopharynx, and in some geographical regions such as Oceania, nontypeable *H. influenzae* may be a primary otopathogen [53].

Importantly, PCVs do not prevent OM episodes if vaccination occurs after the first episode.[137] The 10-valent pneumococcal vaccine with nontypeable *H. influenzae* protein D as carrier protein (PD-PCV10) was designed to protect against both *S. pneumoniae* and nontypeable *H. influenzae* and is available in Europe. Although effective for pneumococcal-associated OM, PD-PCV10 may be less protective for nontypeable *H. influenzae* than originally reported in a prototype vaccine study.[28,138-140] No other licensed vaccine against nontypeable *H. influenzae* or *M. catarrhalis* exists, but numerous vaccines are in various stages of development.

[H3] Vaccines directed against respiratory viruses.

As AOM is generally preceded by symptomatic viral URTI[10], prevention of viral URTI may make an impact on AOM incidence. To date, the only available vaccines against viral respiratory infection are for influenza virus. Trivalent flu vaccines (protecting against three influenza virus strains), both inactivated influenza vaccines and live-attenuated influenza vaccines, have been shown to reduce AOM during influenza seasons.[141-145] The vaccines work through

preventing influenza and influenza-associated AOM, which occurs in up to two-thirds of young children with influenza.[141] The effectiveness in AOM prevention varies from year to year depending on the level of influenza activity in the community and how well-matched the vaccines are for the circulating strains. Recommendations for influenza vaccination in children vary worldwide: influenza vaccines are recommended for children ≥6 months of age in the United States[146], whereas the recommendation is restricted to children from the age of 2 years in the UK[147] and is restricted to children with significant medical comorbidities including respiratory, cardiovascular, metabolic and renal disease in the Netherlands.[148]

[H3] Non-vaccine approaches to prevent viral URTI and AOM.

AOM occurs mostly on days 2-5 after URTI onset[10,149]; thus, early administration of antivirals during uncomplicated URTI may prevent AOM. Studies have shown reduction in AOM development by 43-85% in young children treated with oseltamivir within 12-48 hours of influenza symptom onset.[150,151] However, a recent meta-analysis of both children and adult data concluded that neither oseltamivir nor zanamivir significantly reduced OM risk.[152]

Echinacea, an immune-modulator and mild antiviral often used as a home remedy, has been reported to reduce risks of recurrent respiratory infections, including virologically confirmed cases, and OM.[153] Xylitol, a 5-carbon naturally occurring sugar alcohol with antibacterial properties, has been shown to prevent recurrent AOM with some success.[154-156] However, the successful dose regimens (that is, chewing gum or syrup given 5 times per day continuously for 2-3 months) are not practical. Probiotics, mostly *Lactobacillus* and *Bifidobacterium*, have been used to reduce risks of respiratory symptoms and OM and results have been encouraging but warrant further investigation.[157-160]

[H3] Environmental risk factors.

Avoidance of well-known environmental risks such as daycare attendance, exposure to tobacco smoke and use of pacifiers, especially during the OM peak age incidence (6-24 months), has been associated with reduction of OM.[39,161-163] On the other hand, the benefit of

breastfeeding in preventing OM has long been known. Breastfeeding protects against OM for the first 2 years and protection is greater for those who were exclusively breastfed and those who were breastfed for a long duration (≥6 months).[25,42,161,162] Current guidance recommends avoidance of tobacco smoke exposure, recommends exclusive breastfeeding for ≥6 months and discusses other lifestyles changes such as avoidance of supine bottle feeding, reducing use of pacifier and consideration of alternative child care arrangements (for example, with smaller groups or using a child minder).[5]

[H1] Management

[H2] AOM

Symptomatic management of ear pain and fever with analgesics at the appropriate age-adjusted dose is the mainstay of AOM management.[5] Both oral paracetamol and ibuprofen are effective in relieving ear pain.[164] Topical analgesics might provide additional brief benefit, but current evidence on their effectiveness in relieving ear pain is limited.[165] An ongoing UK trial is assessing the clinical and cost effectiveness of ear drops containing a combination of benzocaine and phenazone as compared to placebo drops and no drops in children aged 6 to 10 years presenting in primary care with AOM.[166]

Oral antibiotics reduce the duration of AOM symptoms and consecutive MEE, but lead to adverse effects like gastrointestinal symptoms and skin rash.[167] Their routine use in a condition as common as AOM also enhances the risk of antimicrobial resistance, both on a community as well as an individual level.[168] Because AOM runs a favourable natural course in most otherwise healthy children, with symptoms settling within a few days and complications being rare, the benefits and costs of antibiotic treatment need to be carefully weighed.[167] The benefits are most prominent in children <2 years in age with bilateral AOM and in those of any age presenting with acute ear discharge due to AOM.[169] Current guidance, therefore, recommends considering immediate antibiotics in these children.[170] Immediate antibiotics treatments is recommended in those with AOM who are <6 months in age, immunocompromised or have craniofacial malformations, as well as those with severe illness

due to AOM.[5,170] In children with uncomplicated, non-severe AOM who are not at increased risk of complications, watchful waiting or delayed antibiotic prescription (only filed when symptoms of AOM persist for 48-72 hours) is recommended. Watchful waiting involves careful monitoring of the disease course by the caregivers with specific instructions to return in case of persistent symptoms or worsening of the child's condition.[5,170] Limited evidence suggests that amoxicillin (with or without clavulanic acid) is more effective than macrolides and cephalosporin[171] and, therefore, first-line treatment with cefdinir, cefuroxime or clarithromycin have been recommended as alternatives in patients with penicillin allergy.[5,170] In choosing the appropriate antibiotic regimen, it is important that local antimicrobial resistance patterns are taken into account.

Topical and oral decongestants, antihistamines and corticosteroids have either not been proven effective or have shown conflicting results in resolving symptoms of AOM are, therefore, not recommended.[172,173] Tympanocentesis or myringotomy, a small incision of the tympanic membrane allowing the fluid to drain from the middle ear, may have a role in determining the pathogens causing AOM, but is ineffective as a treatment modality for AOM.[174-176]

[H2] Recurrent AOM

Management of children with recurrent AOM focuses on the prevention of further AOM episodes. Although immuniziation with pneumococcal conjugate vaccines in early infancy has proved effective in reducing children's risk of developing recurrent AOM, these vaccines are no longer effective for children with established rAOM.[137] Antibiotic prophylaxis in children with rAOM reduces the number of AOM recurrences by 1.5 per year (from 3 recurrences to 1.5).[177] However, their use is not recommended given the adverse effects associated with prolonged antibiotic treatment and emerging antibiotic resistance.

The role of ventilation tubes in the management of children with rAOM has not been fully established (Figure 7). Evidence on the benefits of ventilation tubes is mainly available for the first 6 months after insertion: with approximately one AOM episode being prevented the

magnitude of its effect is modest.[178-180] Although not definitive, current evidence regarding natural history and treatment benefits suggests that ventilation tubes are not helpful for rAOM without persistent MEE but are an appropriate option for managing rAOM with persistent MEE in one or both ears at the time of assessment for tube candidacy.[181]

The adenoids serve as a nasopharyngeal reservoir of respiratory pathogens and when enlarged may cause obstruction of the nasal airway and impair Eustachian tube function. Surgical removal of the adenoid, adenoidectomy, is practiced in children with rAOM to improve middle ear function and thereby prevent further AOM episodes. A recent meta-analysis combining the individual patient data of ten trials has shown that for recurrent AOM, adenoidectomy as a stand-alone operation or as an adjunct to ventilation tube insertion is most beneficial in children <2 years of age. The magnitude of the effect of this surgical intervention is, however, modest so these benefits should be carefully balanced against any harms associated with this surgical procedure.[182]

[H2] OME

The main sign or symptom of OME is hearing loss; management of OME is, therefore, primarily aimed at alleviating or restoring hearing. OME settles spontaneously in many children within several months[6] and medical treatments such as decongestants, antihistamines and (intranasal) corticosteroids are either ineffective or may cause adverse effects[184-186]. Consequently, current guidelines recommend a 3-month period of watchful waiting in children with OME who are not at particular risk for speech, language or learning problems.[181,183] Ventilation tubes are an option in those still with documented hearing difficulties after 3 months.[181,183,187] Adenoidectomy as a standalone operation or as an adjunct to tube insertion is most beneficial in children with OME aged ≥4 years.[182] In this subgroup of children, adjuvant adenoidectomy has been shown to reduce the need for ventilation tube re-insertions by around 10% as compared with tubes alone.[182] The role of hearing aids to alleviate hearing loss in children with OME is unresolved[181] Hearing aids are currently recommended for children with persistent bilateral OME in whom surgery is contraindicated or

not acceptable.[183] Recently, nasal balloon auto-inflation has been shown effective in clearing MEE and improving ear symptoms at 3 months in school-aged children with recent onset of OME presenting in primary care.[188] However, the effects observed were modest with a number needed to treat to benefit of 9 patients, at a cost of GBP£132 per case resolved.[188] Whether this approach reduces the need for ventilation tubes is yet to be answered. The same applies to an ongoing UK trial assessing the clinical and cost effectiveness of a 7-day course of oral corticosteroids in children aged 2-8 years with persistent bilateral OME and hearing loss.[189] Balloon dilatation of the Eustachian tube has been proposed as a novel treatment for children with persistent OME. There is however no evidence yet to support this management option.[190]

[H2] Ventilation tube-associated ear discharge

Many children with ventilation tubes develop episodes of acute ear discharge; reported incidence rates range from 26% to 75%.[191-193] These episodes may be accompanied by foul odour, pain, and fever and can reduce the child's quality of life. They are thought to be the result of AOM, whereby middle-ear fluid drains through the tube. Risk factors include young age, rAOM as the indication for tubes, recent history of recurrent URTIs and the presence of older siblings.[192] Bacterial biofilm formation on the ventilation tube may also play a role, in particular when ear discharge recurs or becomes chronic.

Episodes of ear discharge can occur in the immediate postoperative period or at a later stage. Management, therefore, focuses either on prevention at that early stage or treatment of episodes occurring later. Many perioperative interventions have been tested and shown to be of some benefit in preventing early postoperative ear discharge: saline washout of the middle ear or application of antibiotic with or without corticosteroid ear drops during tube surgery and the use of topical or systemic antibiotics during the early post-operative period.[194] The largest effects of these interventions were found in studies where the risk of children developing early postoperative ear discharge was high.[194] The bacterial otopathogens most commonly found in acute ear discharge in children with ventilation tubes are *H. influenzae*, *S.*

aureus and *P. aeruginosa* and most infections are polymicrobial.[195] Most ototopical antibiotic formulations cover these pathogens. Concerns, however, about their potential ototoxic side effects when used in patients with a non-intact tympanic membrane, have prompted many physicians to treat these children with systemic antibiotics. Quinolone (antibiotic) eardrops have so far not shown ototoxicity and are recommended in the US over systemic treatment.[181] Based upon a recent landmark trial showing that antibiotic and corticosteroid ear drops are the most clinically and cost-effective management strategy in children developing uncomplicated, acute ear discharge outside the immediate postoperative period[196,197], current guidance recommends ototopical antibiotic drops as first-line treatment in these children.[181] There is some evidence that eardrops containing a combination of antibiotic(s) and a corticosteroid are superior over those containing antibiotic(s) alone.[198,199]

[H2] CSOM

Topical quinolone has been shown to be more effective than no drug treatment, topical antiseptics and systemic antibiotics in clearing CSOM-related aural discharge in the short-term (less than 4 weeks).[200,201] Current evidence assessing the effectiveness of quinolone versus non-quinolone containing eardrops is inconclusive [201], with quinolones having the advantage of being non-ototoxic.[202] Limited evidence suggests that treating patients with CSOM with a combination of systemic and topical antibiotics is not more effective than topical antibiotics alone.[200] Two recent reviews comparing two different autologous graft materials to repair the tympanic membrane perforation (that is temporalis muscle fascia tympanoplasty with cartilage tympanoplasty), found fewer post-operative tympanic membrane perforations with a cartilage graft but no differences in terms of hearing.[203,204]

[H1] Quality of life

[H2] Measurement challenges

Traditionally, articles citing policy relevance of the impact of OM have focused on the economic burden of the relevant healthcare, which is for example USD$5 billion annually in the United

States [205] As in other fields of medicine, formal measurement of quality of life (QoL) in OM came late, dating mostly from the mid-1990s.[206] Most clinicians and researchers focus on capturing the impact of OM and OM management with disease-specific symptoms, not impact on QoL. Consequently, many instruments labelled 'QoL' are in fact OM symptom scores, and mapping such scores to generic QoL changes the scale but not the level of generality of the measure or its pattern of associations. Particular challenges of measuring generic QoL in OM, are expected small effect sizes (OM being a common but often 'mild' disease), inaccuracies owing to inevitable delay in documenting the essential parameter of persistence in an episodic condition such as OM, and the need for proxy (parent or other carer) response [207].

[H2] Instruments

For OM, various validated QoL instruments are now available. There are short questionnaires suitable for routine or audit use in a clinical setting and longer, more in-depth instruments for more intensive QoL research. The OM-6 [208] has an efficient 'any of the following' item format, which maximizes generality and ecological validity per item; it has a low burden for the responder, but consequently leaves ambiguity about details of the presentation profile. More-traditional instruments such as OM8-30 [206], its short form the OMQ-14 [209] and COMQ-12 for CSOM in adults [210], support from three to five scores. Brevity (few items) limits precision and reliability, hence study power. Given the use of large sample sizes, brevity will still permit 'positive findings', that is, they will avoid false-negative error but may leave true scope and effect sizes uncertain. Nevertheless, brevity encourages widespread routine adoption and the advent of large-scale data registries creates an opportunity not to be missed. Routine use of these questionnaires in the clinical setting can provide a useful link between research and practice in general.

[H2] OME

The traditional picture of OME is semi-symptomatic and the major concern is with hearing loss and consequent problems with speech, language, communication, social engagement,

schooling and behaviour, readily illustrated in descriptive studies, rather than on health symptoms [211] These sequelae are largely generic, although not totally comprehensive for generic QoL. The literature on QoL in OME has preferred these cognitive or academic performance measures. For example, a large longitudinal cohort study found that a conjunction (synergism) of OM history with poor socio-developmental environment gave the worst outcomes on IQ.[212] Because of the importance of schooling for QoL, some knock-on effects from academic problems to generic QoL would be expected, but no quantitative case-control study has yet been done to demonstrate that link directly. Among children over age 5 years, , a 28-item (therefore, highly reliable) generic health questionnaire [213] showed consistent deficits on most subscales of QoL, even in those without concurrently active OM. In a very small uncontrolled study on OME management, pervasive QoL improvements measured by OM-6 were claimed after ventilation tubes insertion, compared to before the surgery [214], but interpretation is unclear. This limited treatment literature suggests that effective interventions do not necessarily result in measurable magnitudes of QoL improvement.[215]

[H2] Recurrent AOM

A large study among children with chronic or recurrent OM showed that children with rAOM or a combination of rAOM and OME scored worse in 4 out of 6 domain items in the OM-6 (physical suffering, emotional distress, activity limitations and caregiver concerns) than children with OME alone [217] In children with OM history diagnosed in primary and secondary care, the number of AOM episodes was found to be a strong determinant of the child's QoL [218]. A primary care-based cohort study confirmed sleep disturbance as an important correlate of loss of QoL in parents with rAOM.[219] In a clinical population of children with rAOM, the impact on generic QoL equalled that of a comparison group of children with asthma [216], a useful anchor on magnitude of impact. Two studies have addressed the impact of the fact that QOL questionnaires are completed by of the proxy (caregiver), given that the QOL of the caregiver is also affected by OM episodes of the patients [218,219]. A distinct dose/response effect between the number of episodes and the reduction in QOL of the caregiver has been observed [216]. Insertion of ventilation tubes in children with rAOM or combined rAOM and OME group

resulted in an important improvement on the OM-6 scale .[217] A recent trial showed that a reduction of episodes by adenoidectomy did not lead to a measurable corresponding improvement in QoL in young children with rAOM.[220] Vaccination improved specific but not generic QOL outcomes.[221]

[H1] Outlook

A decline in OM incidence over the past decade has been reported, which might in part be attributed to pneumococcal conjugate vaccination, implementation of clinical guidelines emphasizing accurate diagnosis and more judicious use of antibiotics. Nevertheless, OM continues to be among the most common diseases of infants and children and a prime indication for antibiotic prescribing and surgery in children.[2-4] With growing concerns about emerging antimicrobial resistance, further research should be designed to achieve further reduction in antibiotic use in OM by improving its diagnosis and implementation of guidelines. A better understanding of OM pathophysiology is also necessary to develop novel preventative and therapeutic approaches.

[H2] Pathophysiology

Further studies are needed to examine the relationship between environmental risk factors, bacterial density in the nasopharynx, bacterial biofilm formation, genetics and OM particularly in respect to disease severity. Specific interactions between bacteria and viruses in the nasopharynx may enhance AOM risk in children.[25,222] Future research should focus on the interplay between viruses and bacteria. Better understanding of these complex mechanisms could lead to new bacterial and viral vaccines that would help to reduce the burden of AOM. Currently, research is ongoing focusing on the innate immune responses and interactions with otopathogens to better understand the balance between the processes of effective recovery from infection versus facilitation of chronic inflammation. Whereas a number of genetic polymorphisms have been described in genes encoding for proteins involved in innate immunity, their clinical relevance to risk and severity of disease is yet unknown in children.

Improved understanding of the interactions between host innate immune system and otopathogens may lead to a wider range of treatment options.[223]

[H2] Diagnosis

AOM tends to be over-diagnosed (and thus over-treated), especially in the primary care setting, owing to difficulties of confirming MEE.[96-98] Improving MEE diagnosis requires further work to determine the optimal methods for teaching (pneumatic) otoscopy to trainees and clinicians and to develop cost-effective methods to accurately detect MEE, such as handheld (ultrasonography or tympanometry) devices. Multifrequency tympanometry and wideband acoustic transfer functions are promising technologies for identifying middle ear disorders, but limited evidence restricts conclusions on their diagnostic accuracy.[224] Future research is needed to investigate whether these techniques provide any added value over current diagnostic tests.

[H2] Biomarkers

Thus far, investigators have studied biomarkers in the serum and nasopharyngeal secretions and correlated them with AOM diagnosis, types of bacteria or viruses, and outcome. High serum Intercellular Adhesion Molecule 1 (ICAM1) was found in children with AOM compared to healthy children.[225] At time of AOM onset, serum S100-A12 protein was elevated and this returned to normal during recovery.[226] In children with AOM, high serum granulocyte-colony stimulating factor (G-CSF) concentrations predicted RSV-induced AOM whereas high IL-13 concentrations predicted early clinical failure of antibiotic treatment.[227] Elevated serum IL-10 was associated with pneumococcal-induced AOM.[228] A serum biomarker risk score has been developed to predict the presence and recovery from AOM caused by nontypeable *H. influenzae*.[229] In nasopharyngeal secretions, IL-1B and lactate dehydrogenase concentrations were associated with the risk for AOM development after viral URTI.[230,231] These data together suggest that specific systemic and local biomarkers are helpful in predicting AOM development, microbiology and clinical outcome. Further studies are required to explore other biomarkers and to evaluate the usefulness of biomarker determination in clinical practice.

[H2] Prevention

Although vaccination against *S. pneumoniae* has been associated with a decline in OM incidence, widespread use of PCVs has been associated with shifts in pneumococcal serotypes and increased importance of nontypeable *H. influenzae* as a cause of AOM.[24,25,27,129-134] There is a need for effective pneumococcal vaccines that cover more serotypes and effective vaccines for *H. influenza*e and *M. catarrhalis.* In theory, protein-based vaccines would be simpler and less costly to produce than conjugate vaccines. There are several protein vaccine antigens of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* at various stages of development; licensing these vaccines will be an additional challenge.[232-37] So far, influenza virus vaccination is the only viral vaccine that has been shown of some efficacy in OM. Future goals to prevent OM by preventing viral URTI will need to include vaccines against other viruses. Considerable efforts have been made in RSV vaccine development; numerous RSV vaccines are in phases I and II clinical trials.[238] Further work is needed to establish whether other viral vaccines are able to prevent OM.[235] Probiotics have been used in preventing OM with some encouraging results [157-160], but further studies are required to identify the most promising probiotic strains and to elucidate the mechanisms by which probiotics prevent OM. A recent systematic review provided an overview of the global microbiology of AOM and OME between 1970 and 2014.[53] There are clear regional and temporal differences which have been influenced by the introduction of pneumococcal conjugate vaccines. Hence it is important that ongoing microbial surveillance be introduced to monitor shifts in causative otopathogens.

[H2] Treatment

Remarkably, most trials so far in OM have excluded the children that are most prone to the condition: those with Down syndrome and craniofacial malformations like cleft palate. High-quality studies evaluating the use of screening for OME and effectiveness of various management strategies in these in at-risk children are a priority. Current approaches that need further work include topical antibiotics for AOM with ear discharge due to a spontaneous tympanic membrane perforation. Topical antibiotics approach has proven very effective in

children with ventilation tubes[196], but it is uncertain if these results are also applicable to children without tubes.[239] In addition, ongoing research on transtympanic delivery of drugs (that is without a tympanic membrane perforation or tube) is very promising. In a chinchilla model, an application of an antibiotic-containing (ciprofloxacin) gel to the tympanic membrane achieved antibiotic concentrations in middle ear fluid adequate for AOM treatment.[240,241] Further work is needed to establish what methods of application are most practical and effective in humans. The role of hearing aids and other acoustic approaches such as sound field amplification in the management of children with OME is currently unresolved; there is an urgent need for high quality evidence, particularly in at-risk children.[181] In CSOM, various novel adjuvant treatments have been tested aimed at enhancing tympanic membrane perforation repair, including biomolecules to stimulate growth of the perforation edges and bioengineered scaffolds.[242,243] Further work is necessary to establish its role in clinical practice.

Across all areas of epidemiology, prevention and treatment of OM, it is important that clinicians and researchers agree on disease definitions, study methodologies and core outcome measures so that results can be pooled or contrasted across future studies.[244-247] Recently, a recommendation has been made for the outcomes that should be measured in studies of the management of OME in children with cleft palate.[248] We encourage the development of core outcome sets for all patient groups and all manifestations of OM including generic impact. We strongly recommend that parents and children be systematically consulted, at an appropriate level of detail, about the goals and that they are are involved in the planning process as well as in all other stages of research in OM. By adding relevance to the children with OM and theirs carers, high quality research with the statistical power and freedom from confounding can be given additional ability to change practice for the better.

References

1. Bluestone CD. Definition, terminology, and classification. In: Rosenfeld RM, Bluestone CD (eds). Evidence-based Otitis Media, 2nd ed. Hamilton: BC Decker Inc, 2003;121.
2. Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One* 2012;7:e36226.

Comprehensive review providing global estimates on the burden of disease caused by OM.

3. Gulliford M, Latinovic R, Charlton J, Little P, van Staa T, Ashworth M. Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. *J Public Health* 2009;31:512-20.
4. Cullen K, Hall M, Golosinskiy A. Ambulatory surgery in the United States, 2006. National health statistics reports, no. 11, revised. Hyattsville, MD: National Center for Health Statistics, 2009.
5. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. Clinical Practice Guideline The Diagnosis and Management of Acute Otitis Media. *Pediatrics* 2013;133(2):346.
6. Rosenfeld RM, Kay D. Natural history of untreated otitis media. *Laryngoscope* 2003;113:1645-57.
7. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United kingdom general practice research database. *Pediatrics* 2009;123:424-30.
8. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: otitis media with effusion (update). *Otolaryngol Head Neck Surg* 2016 (Suppl 1):S1-S41.
9. Bennett KE, Haggard MP, Silva PA, Stewart IA. Behaviour and development effects of otitis media with effusions into the teens. *Arch Dis Child* 2001;85:91–5.
10. Chonmaitree T, Revai K, Grady JJ, Clos A, Patel A, Nair S, et al. Viral upper respiratory tract infection and otitis media complication in young children. *Clin Infect Dis* 2008;46:815-23.

Large prospective study reports clear relationship between viral URTI and AOM and OME in children at the peak age incidence of otitis media.

11. Alho O, Oja H, Koivu M, Sorri M. Risk factors for chronic otitis media with effusion in infancy. Each otitis media episode induces a high but transient risk. *Arch Otolaryngol Head Neck Surg* 1995;121:839-43.
12. Claessen JQ, Appelman CL, Touw-Otten FW, Hordijk GJ, de Melker RA. Persistence of middle ear dysfunction after recurrent acute otitis media. *Clin Otolaryngol Allied Sci* 1994;19:35-40.
13. Verhoeff M, van der Veen EL, Rovers MM, Sanders EAM, Schilder AGM. Chronic suppurative otitis media: a review. *Int J Pediatr Otorhinolaryngol* 2006;70:1-12.
14. Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM. Otitis Media. *Lancet* 2004;363:465-73.

Landmark review on otitis media summarizing the state of knowledge, including advances in epidemiology, pathogenesis, diagnosis, clinical management, and prevention up to 2004.

15. Tos M. Epidemiology and natural history of secretory otitis. *Am J Otol.* 1984;5:459–62.
16. Zielhuis GA, Rach GH, Van den Broek P. The occurrence of otitis media with effusion in Dutch pre-school children. *Clin Otolaryngol Allied Sci*. 1990;15:147-53.
17. Williamson IG, Dunleavey J, Bain J, et al. The natural history of otitis media with effusion--a three-year study of the incidence and prevalence of abnormal tympanograms in four South West Hampshire infant and first schools. *J Laryngol Otol. 1994*;108:930–4.
18. Paradise JL, Rockette HE, Colborn K, Bernard BS, Smith CG, Kurs-Lasky M, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics* 1997;99:318–33.
19. Casselbrant ML, Mandel EM. Epidemiology. In: Rosenfeld RM, Bluestone CD, eds. Evidence-based otitis media. Hamilton, ON: BC Decker; 1999:117–36.
20. Marchant CD, Shurin PA, Turczyk VA, Wasikowski DE, Tutihasi MA, Kinney SE. Course and outcome of otitis media in early infancy: a prospective study. *J Pediatr* 1984;104:826–31.
21. Wals P, Carbon M, Sévin E, Deceuninck G, Ouakki M. Reduced physician claims for otitis media after implementation of pneumococcal conjugate vaccine program in the province of Quebec, Canada. *Pediatr Infect Dis J* 2009;28:e271-4.
22. Thomas EM. Recent trends in upper respiratory infections, ear infections and asthma among young Canadian children. *Health Reports* 2010:21:1-6.
23. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for 460 acute respiratory tract infections in US ambulatory settings. *JAMA* 2009;302:758–66.
24. Marom T, Tan A, Wilkinson GS, Pierson KS, Freeman JL, Chonmaitree T. Trends in Otits Media-related Health Care Utilization in the United States, 2001-2011. *JAMA Pediatr* 2014;168:68-75.
25. Chonmaitree T, Trujillo R, Jennings K, Alvarez-Fernandez P, Patel JA, Loeffelholz MJ, et al. Acute otitis media and other complications of viral respiratory infection. *Pediatrics* 2016;137(4). pii:e2015355.
26. Plasschaert AI, Rovers MM, Schilder AG, Verheij TJ, Hak E. Trends in doctor consultations, antibiotic perscription, and specialist referrals for otitis media in children: 1995-2003. *Pediatrics* 2006;117:1879-1986.
27. Lau WC, Murray M, El-Turki A, Saxena S, Ladhani S, Long P, Sharland M, Wong IC, Hsia Y. Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. *Vaccine* 2015;33:5072-9.
28. Leach, AJ, Wigger C, Andrews R, Chatfield M, Smith-Vaughn H, Morris PS. Otitis media in children vaccinated during consecutive 7-valent or 10-valent pneumococcal conjugate vaccination schedules. *BMC Pediatrics* 2014;14:200.
29. Dallaire F, Dewailly E, Vezina C, Bruneau S, Ayotte P. Portrait of outpatient visits and hospitalizations for acute infections in Nunavik preschool children. *Can J Public Health* 2006;97:362-368.
30. Morris PS, Leach AJ, Silberberg P, Mellon G, Wilson C, Hamilton E, et al. Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. *BMC Pediatr* 2005;5:27.
31. Todberg T, Koch A, Andersson M, Olsen S, Lous J, Homoe P. Incidence of Otitis Media in a Contemporary Danish National Birth Cohort. *PLoS One* 2014;9:e111732.

32. Macintyre EA, Karr CJ, Koehoorn M, Demers P, Tamburic L, Lencar C, et al. Otits media incidence and risk factors in a population-based birth cohort. *Paediatr Child Health* 2010;15:437-42.
33. Zhang Y, Xu M, Zhang J, Zeng L, Wang Y, Zheng QY. Risk factors for chronic and recurrent otitis media - a meta-analysis. *PLoS One* 2014;9:e86397.
34. Austeng ME, Akre H, Overland B, Abdelnoor M, Falkenberg ES, Kvaerner KJ. Otitis media with effusion in children with Down syndrome. *Int J Pediatr Otorhinolaryngol* 2013;77:1329-32.
35. Wilson NW, Hogan MB. Otitis media as a presenting complaint in childhood immunodeficiency diseases. *Curr Allergy Asthma Rep.* 2008, 6:519-24.
36. Aydemir G, Ozkurt FE. Otitis media with effusion in primary schools in Princes' Islands, Istanbul: prevalence and risk factors. *J Int Med Res*, 2011;39(3):866-72.
37. O'Reilly RC, Soundar S, Tonb D, Bolling L, Yoo E, Nadal T, et al. The role of gastric pepsin in the inflammatory cascade of pediatric otitis media. *JAMA Otolaryngol Head Neck Surg* 2015;141:350-7.
38. Brennan-Jones CG, Whitehouse AJO, Park J, Hegarty M, Jacques A, Eikelboom RH, et al. Prevalence and risk factors for parent-reported otitis media during early childhood in the Western Australian Pregnancy Cohort (Raine) Study. *Journal of Paediatrics and Child Health* 2015:51:403-9.
39. De Hoog MLA, Venekamp RP, van der Ent CK, Schilder A, Sanders EA, Damoiseaux RA, et al. Impact of early daycare on healthcare resource use related to upper respiratory tract infections during childhood: prospective WHISTLER cohort study. *BMC Med* 2014;12:107.
40. Salah M, Abdel-Aziz M, Al-Farok A, Jebrini A. Recurrent acute otitis media in infants: analysis of risk factors. *Int J Pediatr Otorhinolaryngol* 2013;77:1665-9.
41. Rovers MM, Numans ME, Langenbach E, Grobbee DE, Verheij TJ, Schilder AG. Is pacifier use a risk factor for acute otitis media? A dynamic cohort study. *Fam Pract* 2008;25:233-6.
42. Bowatte G, Tham R, Allen KJ, Tan DJ, Lau M, Dai X, et al. Breast feeding and childhood acute otitis media: a systematic review and meta-analysis. *Acta Paediatr Suppl* 2015;104:85-95.
43. Lasisi AO, Olaniyan FA, Muibi SA, Azeez IA, Abdulwasiu KG, Lasisi TJ, et al. Clinical and demographic risk factors associated with chronic suppurative otitis media. *Int J Pediatr Otorhinolaryngol* 2007;71:1549-54.
44. Taipale A, Pelkonen T, Paipale M, Bernardino L, Peltola H, Pitkäranta. Chronic suppurative otitis media in children of Luanda, Angola. *Acta Paediatr* 2011;100:e84-8.
45. Wiertsema SP, Leach AJ. Theories of otitis media pathogenesis, with a focus on Indigenous children. Med J Aust 2009;191:S50-4.
46. Vijayasekaran S, Coates H, Thornton RB, Wiertsema SP, Kirkham LA, Jamieson SE, et al. New findings in the pathogenesis of otitis media. *Laryngoscope* 2012;122:S61-2.
47. Lehmann D, Arumugaswamy A, Elsbury D, Finucane J, Stokes A, Monck R, et al. The Kalgoorlie Otitis Media Research Project: rationale, methods, population characteristics and ethical considerations. Paediatr Perinat Epidemiol 2008;22:60-71.
48. Massa HM, Lim DJ, Cripps AW. Middle ear and eustachian tube mucosal immunology. In: Russel MW, Lambrecht B (eds). *Mucosal Immunology*, 4th ed, 2015;1423-1942.
A comprehensive review of the innate and acquired immunology of the middle ear and Eustachian tube.

49. Bluestone CD, Klein JO. Otitis media and eustachian tube dysfunction. In: Bluestone CD, Stoole SE, Alper CM (eds). *Pediatric Otolaryngology*, 4th ed, 2003;497-535.
50. Faden H, Duffy L, Wasielewski R, Wolf J, Krystofik D, Tung Y. Relationship between nasopharyngeal colonization and the development of otitis media in children. *J Infect Dis* 1997;175:1440-5.
51. Leach AJ, Boswell JB, Asche V, Nienhuys TG, Mathews JD. Bacterial colonization of the nasopharynx predicts very early onset and persistence of otitis media in Australian aboriginal infants. *Pediatr Infect Dis J* 1994;13:983-9.
52. Coker TR, Chan LS, Newberry SJ, Limbos MA, Suttorp MJ, Shekelle PG. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. *JAMA* 2010;304:2161-9.
53. Ngo CC, Massa HM, Thornton RB, Cripps AW. Predominant bacteria isolated from the middle ear fluid of children experiencing otitis media: A systematic review. *PLoS One* 2016;11(3):e0150949.

Systematic review provides recent global estimates on the predominant bacterial pathogens involved in otitis media.

54. Sun W, Jacoby P, Riley TV, Bowman J, Leach AJ, Coates H, et al. Association between early bacterial carriage and otitis media in Aboriginal and non-Aboriginal children in a semi-arid area of Western Australia: a cohort study. *BMC Infect Dis* 2012;12:366.
55. Darboe MK, Fulford AJC, Secka O, Prentice AM. The dynamics of nasopharyngeal streptococcus pneumoniae carriage among rural Gambian mother-infant pairs. *BMC Infect Dis* 2010;10:195.
56. Gratten M, Gratten H, Poli A, Carrad E, Raymer M, Koki G. Colonisation of Haemophilus influenzae and Streptococcus pneumoniae in the upper respiratory tract of neonates in Papua New Guinea: primary acquisition, duration of carriage, and relationship to carriage in mothers. *Biol Neonate* 1986;50:114-20.
57. Watson K, Carville K, Bowman T, Jacoby P, Riley TV, Leach AJ, et al. Upper respiratory tract bacterial carriage in Aboriginal and non-Aboriginal children in a semi-arid area of Western Australia. *Pediatr Infect Dis J* 2006;25:782-90.
58. Smith-Vaughan H, Byun R, Nadkarni M, Jacques NA, Hunter N, Halpin S, et al. Measuring nasal bacterial load and its association with otitis media. *BMC Ear Nose Throat Disord* 2006;6:10.
59. Slinger R, Chan F, Ferris W, Yeung SW, St Denis M, Gaboury I, et al. Multiple combination antibiotic susceptibility testing of nontypeable Haemophilus influenzae biofilms. Diagn Microbiol Infect Dis 2006;56:247-53.
60. Garcia-Cobos S, Moscoso M, Pumarola F, Arroyo M, Lara N, Pérez-Vázquez M, et al. Frequent carriage of resistance mechanisms to β-lactams and biofilm formation in Haemophilus influenzae causing treatment failure and recurrent otitis media in young children. J Antimicrob Chemother 2014;69:2394-9.
61. Lampikoski H, Aarnisalo AA, Jero J, Kinnari, TJ. Mastoid biofilm in chronic otitis media. *Otol Neurotol* 2012;33:785-8.
62. Gu X, Keyoumu Y, Long L, Zhang H. Detection of bacterial biofilms in different types of chronic otitis media. *Eur Arch Otorhinolaryngol* 2014;271:2877-83.

63. Van Hoecke H, De Paepe AS, Lambert E, Van Belleghem JD, Cools P, Van Simaey L, et al. Haemophilus influenzae biofilm formation in chronic otitis media with effusion. Eur Arch Otorhinolaryngol. 2016 Mar 5. [Epub ahead of print]
64. Hall-Stoodley L, Hu FZ, Gieseke A, Nistico L, Nguyen D, Hayes J, et al. Direct detection of bacterial biofilms on the middle-ear mucosa of children with chronic otitis media. *JAMA* 2006;296:202-11.
65. Novotny LA, Jurcisek JA, Ward MO Jr, Jordan ZB, Goodman SD, Bakaletz LO. Antibodies against the majority subunit of Type IV pili disperse nontypeable Haemophilus influenzae biofilms in a LuxS-dependent manner and confer therapeutic resolution of experimental otitis media. Mol Microbiol 2015;96:276-92.
66. Nokso-Koivisto J, Marom T, Chonmaitree T. Importance of viruses in acute otitis media. *Curr Opin Pediatr* 2015;27:110-5.
67. Abramson JS, Hudnor HR. Role of the sialophorin (CD43) receptor in mediating influenza A virus-induced polymorphonuclear leukocyte dysfunction. *Blood* 1995;85:1615-9.
68. Patel JA, Nair S, Revai K, Grady J, Chonmaitree T. Nasopharyngeal acute phase cytokines in viral upper respiratory infection: impact on acute otitis media in children. *Pediatr Infect Dis J* 2009;28:1002-7.
69. Bakaletz LO. Immunopathogenesis of polymicrobial otitis media. *J Leukoc Biol.* 2010;87:213-22.

Comprehensive review covering the host innate and acquired immune response involved in the pathogenesis of AOM, including information on viral-induced pathological changes in the nasopharynx and middle ear in animal models.

70. Avadhanula V, Rodriguez CA, Devincenzo JP, Wang Y, Webby RJ, Ulett GC, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. *J Virol* 2006;80:1629-36.
71. Pittet LA, Hall-Stoodley L, Rutkowski MR, Harmsen AG. Influenza virus infection decreases tracheal mucociliary velocity and clearance of Streptococcus pneumoniae. *Am J Respir Cell Mol Biol* 2010;42:450-60.
72. Buchman CA, Brinson GM. Viral otitis media. *Curr Allergy Asthma Rep.* 2003;3:335-40.
73. Revai K, Patel JA, Grady JJ, Chonmatree T. Tympanometric findings in young children during upper respiratory tract infections with and without acute otitis media. *Pediatr Infect Dis J* 2008;27:292-5.
74. Revai K, Mamidi D, Chonmaitree T. Association of nasopharyngeal bacterial colonization during upper respiratory tract infection and the development of acute otitis media. *Clin Infect Dis.* 2008;46:e34-7.
75. Canafax DM, Yuan Z, Chonmaitree T, Deka K, Russlie HQ, Giebink GS. Amoxicillin middle ear fluid penetration and pharmacokinetics in children with acute otitis media. *Pediatr Infect Dis J* 1998;17:149-56.
76. Chonmaitree T, Patel JA, Lett-Brown MA, Uchida T, Garofalo R, Owen MJ. Virus and bacteria enhance histamine production in middle ear fluids of children with acute otitis media. *J Infect Dis* 1994;169:1265-70.

77. Chonmaitree T, Patel JA, Sim T, Garofalo R, Uchida T, Sim T, et al. Role of leukotriene B4 and interleukin-8 in acute bacterial and viral otitis media. *Ann Otol Rhinol Laryngol* 1996;105:968-74.
78. Jossart GH, Cranafax DM, Erdmann GR, Lovdahl MJ, Russlie HQ, Juhn SK, et al. Effect of Streptococcus pneumoniae and influenza A virus on middle ear antimicrobial pharmacokinetics in experimental otitis media. *Pharm Res* 1994;11:860-4.
79. Chonmaitree T, Ruohola A, Hendley JO. Presence of viral nucleic acids in the middle ear: Acute otitis media pathogen or bystander? *Pediatr Infect Dis* J 2012,31:325-330.
80. Chonmaitree T, Alvarez-Fernandez P, Jennings K, Trujillo R, Marom T, Loeffelholz MJ, et al. Symptomatic and asymptomatic respiratory viral infections in the first year of life: association with acute otitis media development. *Clin Infect Dis* 2015;60:1-9.
81. Murphy TF, Chonmaitree T, Barenkamp S, Kyd J, Nokso-Koivisto J, Patel JA, et al. Panel 5: Microbiology and immunology panel. Otolaryngol Head Neck Surg 2013;148:E64-89.
82. Trune DR, Kempton B, Hausman FA, Larrain BE, MacArthur CJ. Correlative mRNA and protein expression of middle and inner ear inflammatory cytokines during mouse acute otitis media. *Hear Res* 2015;326:49-58.
83. Leichtle A, Lai Y, Wollenberg B, Wasserman SI, Ryan AF. Innate signaling in otitis media: pathogenesis and recovery. *Curr Allergy Asthma Rep* 2011;11:78-84.
84. Kurabi A, Pak K, Ryan AF, Wasserman SI. Innate Immunity: Orchestrating Inflammation and Resolution of Otitis Media. *Curr Allergy Asthma Rep* 2016;16:6.
85. Mittal R, Kodiyan J, Gerring R, Mathee K, Li JD, Grati M, et al. Role of innate immunity in the pathogenesis of otitis media. *Int J Infect Dis* 2014;29:259-67.
86. Morris P. Chronic suppurative otitis media. *BMJ Clin Evid* 2012;pii:0507.
87. Mittal R, Lisi CV, Gerring R, Mittal J, Mathee K, Narasimhan G, et al. Current concepts in the pathogenesis and treatment of chronic suppurative otitis media. *J Med Microbiol* 2015;64:1103-16.
88. Elmorsy S, Shabana YK, Raouf AA, Nagger ME, Bedir T, Taher S, et al. The role of IL8 in different types of otitis media and bacterialogical correlation. *J Int Adv Otol* 2010;6:269-73.
89. Si Y, Zhang ZG, Chen SJ, Zheng YQ, Chen YB, Liu Y, et al. Attenuated TLRs in middle ear mucosa contributes to susceptibility of chronic suppurative otitis media. *Hum Immunol* 2014;75:771-6.
90. Rye MS, Bhutta MF, Cheeseman MT, Burgner D, Blackwell JM, Brown SD, et al. Unraveling the genetics of otitis media: from mouse to human and back again. *Mammalian Genome* 2011;22:66-82.
91. Mittal R, Robalino G, Gerring R, Chan B, Yan D, Grati M, et al. Immunity genes and susceptibility to otitis media: a comprehensive review. *J Genet Genomics* 2014;41:567-81.
92. Alper CM, Winther B, Hendley JO, Doyle WJ. Cytokine polymorphisms predict the frequency of otitis media as a complication of rhinovirus and RSV infections in children. *Eur Arch Otorhinolaryngol* 2009;266:199-205.
93. Shaikh N, Hoberman A, Paradise JL, Rockette HE, Kurs-Lasky M, Colborn DK, et al. Responsiveness and construct validity of a symptom scale for acute otitis media. *Pediatr Infect Dis J* 2009;28:9–12.
94. Rothman R, Owens T, Simel DL. Does this child have acute otitis media? *JAMA* 2003;289:1633-40.

95. Laine MK, Tähtinen PA, Ruuskanen O, Huovinen P, Ruohola A. Symptoms or symptom-based scores cannot predict acute otitis media at otitis-prone age. *Pediatrics* 2010;125:1154-61.
96. Rosenfeld RM. Diagnostic certainty for acute otitis media. *Int J Pediatr Otorhinolaryngol* 2002;64:89-95.
97. Kaleida PH, Ploof DL, Kurs-Lasky M, Shaikh N, Colborn DK, Haralam MA, et al. Mastering diagnostic skills: enhancing proficiency in otitis media, a model for diagnostic skills training. *Pediatrics* 2009;124:e714-20.
98. Pichichero ME, Poole MD. Assessing diagnostic accuracy and tympanocentesis skills in the management of otitis media. *Arch Pediatr Adolesc Med* 2001;155:1137-42.
99. Shaikh N, Hoberman A, Paradise JL, Wald ER, Switze GE, Kurs-Lasky, et al. Development and preliminary evaluation of a parent-reported outcome instrument for clinical trials in acute otitis media. Pediatr Infect Dis J 2009; 28:5-8.
100. Friedman NR, McCormick DP, Pittman C, Chonmaitree T, Teichgraeber DC, Uchida T, et al. Development of a practical tool for assessing the severity of acute otitis media. *Pediatr Infect Dis J* 2006;25:101-7.
101. Roland PS, Smith TL, Schwartz SR, Rosenfeld RM, Ballachanda B, Earll JM, et al. Clinical practice guideline: cerumen impaction. *Otolaryngol Head Neck Surg* 2008;139:S1-S21.
102. McCormick DP, Lim-Melia E, Saeed K, Baldwin CD, Chonmaitree T. Otitis media: can clinical findings predict bacterial or viral etiology? *Pediatr Infect Dis J* 2000;19:256–258.
103. Karma PH, Penttilä MA, Sipilä, Kataja MJ. Otoscopic diagnosis of middle ear effusion in acute and non-acute otitis media. I. The value of different otoscopic findings. *Int J Pediatr Otorhinolaryngol* 1989;17:37-49.
104. Shaikh N, Hoberman A, Kaleida PH, Rockette HE, Kurs-Lasky M, Hoover H, et al. Otoscopic signs of otitis media. *Pediatr Infect Dis J* 2011;30:822-6.
105. Armengol CE, Hendley JO. Shagrination during acute otitis media. *J Pediatr* 2014;164:870.
106. Lundberg T, Hellström S, Sandström H. Development and validation of a new grading scale for otitis media. *Pediatr Infect Dis J* 2013;32:341-5.
107. McCormick DP, Saeed KA, Pittman C, Baldwin CD, Friedman N, Teichgraeber DC, et al. Bullous myringitis: a case-control study. *Pediatrics* 2003;112:982-86.
108. P Shekelle, G Takata, LS Chan, R Mangione-Smith, PM Corley, T Morphew, and S Morton. Diagnosis, Natural History and Late Effects of Otitis Media with Effusion: Evidence Report/Technology Assessment No. 55. Rockville, MD: Agency for Healthcare Research and Quality; 2003. AHRQ publication 03-E023.
109. Jones WS, Kaleida PH. How helpful is pneumatic otoscopy in improving diagnostic accuracy? *Pediatrics* 2003112:510-513.
110. American Academy of Pediatrics. Section on Infectious Diseases. A view through the otoscope: distinguishing acute otitis media from otitis media with effusion [video]. Available at: http://www2.aap.org/sections/infectdis/video.cfm. Accessed January 5, 2016.
111. Forrest CB, Fiks AG, Bailey LC, Localio R, Grundmeier RW, Richards T, et al. Improving adherence to otitis media guidelines with clinical decision support and physician feedback. *Pediatrics* 2013;131:e1071-81.
112. Lannon C, Peterson LE, Goudie A. Quality measures for the care of children with otitis media with effusion. *Pediatrics* 2011;127:e1490-7.

113. Lee DH. How to improve the accuracy of diagnosing otitis media with effusion in a pediatric population. *Int J Pediatr Otorhinolaryngol* 2010;74:151-3.
114. Schilder AG, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-72.
115. Onusko E. Tympanometry. *Am Fam Physician* 2004;70:1713-1720.
116. Takata GS, Chan LS, Morphew T, Mangione-Smith R, Morton SC, Shekelle P. Evidence assessment of the accuracy of methods of diagnosing middle ear effusion in children with otitis media with effusion. *Pediatrics* 2003;112:1379-87.
117. Abbott P, Rosenkranz S, Hu W, Gunsekera H, Reath J. The effect and acceptability of tympanometry and pneumatic otoscopy in general practitioner diagnosis and management of childhood ear disease. *BMC Fam Pract* 2014;15:181-90
118. American Speech-Language-Hearing Association. Guideline for screening infants and children for outer and middle ear disorders, birth through 18 years. In: *Guidelines for Audiologic Screening*. Rockville, MD: American Speech-Language-Hearing Association; 1997:15-22.
119. Hunter LL, Preve BA, Kei J, Sanford CA. Pediatric application of wideband acoustic immittance measures. *Ear Hear* 2013; 34(Suppl 1):36S-42S.
120. Combs JT, Combs MK. Acoustic reflectometry: spectral analysis and the conductive hearing loss of otitis media. *Pediatr Infect Dis J* 1996; 15:683-6.
121. 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.
122. Chianese J, Hoberman Paradise JL, Colborn DK, Kearney D, Rockette HE, et al. Spectral gradient acoustic reflectometry compared with tympanometry in diagnosing middle ear effusion in children aged 6 to 24 months. *Arch Pediatr Adolesc Med* 2007; 161:884-8.
123. Muderris T, Yazici A, Bercin S, Yalciner G, Sevil E, Kiris M. Consumer acoustic reflectometry: accuracy in diagnosis of otitis media with effusion in children. *Int J Pediatr Otorhinolaryngol* 2013; 77:1771-4.
124. Puhakka T, Pulkkinen JU, Silvennoinen H, Heikkinen T. Comparison of spectral gradient acoustic reflectometry and tympanometry for detection of middle-ear effusion in children. *Pediatr Infect Dis J* 2014;33:e183-6.
125. Simpson SA, Thomas CL, van der Linden M, MacMillan H, van der Wouden JC, Butler CC. Identification of children in the first four years of life for early treatment for otitis media with effusion. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD004163. DOI: 10.1002/14651858.CD004163.pub2.
126. Boone RT, Bower CM, Martin PF. Failed newborn hearing screens as presentation for otitis media with effusion in the newborn population. *Int J Pediatr Otorhinolaryngol* 2005;69:393-397.
127. Holster IL, Hoeve LJ, Wieringa MH, Willis-Lorrier RMS, de Gier HHW. Evaluation of hearing loss after failed neonatal hearing screening. *J Pediatr* 2009;155:646-50.
128. Boudewyns A, Declau F, Van den Ende J, Van Kerschaver E, Dirckx S, Hofkens-Van den Brandt A, , et al. Otitis media with effusion: an underestimated cause of hearing loss in infants. *Otol Neurotol* 2011;32:799-804.

129. Fortanier AC, Venekamp RP, Boonacker CWB, Hak E, Schilder AGM, Sanders EAM, et al. Pneumococcal conjugate vaccines for preventing otitis media. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD001480. DOI: 10.1002/14651858.CD001480.pub4.
130. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;344:403-9.
131. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000;19:187-95.
132. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2010;29:304-9.
133. Casey JR, Kaur R, Friedel VC, Pichichero ME. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. *Pediatr Infect Dis* J 2013;32:805-9.
134. Shea KM, Weycker D, Stevenson AE, Strutton DR, Pelton SI. Modeling the decline in pneumococcal acute otitis media following the introduction of pneumococcal conjugate vaccines in the US. *Vaccine* 2011;29:8042-8.
135. Dagan R, Pelton S, Bakaletz L, Cohen R. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. *Lancet Infect Dis.* 2016;16:480-92.

Review providing evidence to support the hypothesis that prevention of vaccine-serotype pneumococcal otitis media in early life lead to a reduction of subsequent and more complex disease caused by non-vaccine serotypes and nontypeable *H. influenzae*.

136. Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near-elimination of otitis media caused by 13-valent pneumococcal conjugate vaccine (PCV) serotypes in southern Israel shortly after sequential introduction of 7-valent/13-valent PCV. *Clin Infect Dis.* 2014;59:1724-32.
137. Veenhoven R, Bogaert D, Uiterwaal C, Brouwer C, Kiezebrink H, Bruin J, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. *Lancet* 2003;361:2189-95.
138. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. *Lancet* 2006;367:740-8.
139. van den Bergh MR, Spijkerman J, Swinnen KM, François NA, Pascal TG, Borys D, et al. Effects of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D-conjugate vaccine on nasopharyngeal bacterial colonization in young children: a randomized controlled trial. *Clin Infect Dis* 2013;56:e30-9.
140. Tregnaghi MW, Sáez-Llorens X, López P, Abate H, Smith E, Pósleman A, et al. Efficacy of pneumococcal nontypable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in young Latin American children: A double-blind randomized controlled trial. *PLoS Med* 2014;11:e1001657.
141. Heikkinen T, Ruuskanen O, Waris M, Ziegler T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. *Am J Dis Child* 1991;145:445-8.

142. Clements DA, Langdon L, Bland C, Walter E. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month old children in day care. *Arch Pediatr Adolesc Med* 1995;149:113-7.
143. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med* 2007;356:685-96.
144. Block SL, Heikkinen T, Toback SL, Zheng W, Ambrose CS. The efficacy of live attenuated influenza vaccine against influenza associated acute otitis media in children. *Pediatr Infect Dis J* 2011;30:203-7.
145. Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD010089. DOI: 10.1002/14651858.CD010089.pub2.
146. Committee on Infectious Diseases, American Academy of Pediatrics. Recommendations for prevention and control of influenza in children, 2015–2016. *Pediatrics* 2015;136:792-808.
147. http://www.nhs.uk/conditions/vaccinations/pages/which-children-are-eligible-for-the-flu-vaccine.aspx
148. Rijksinstituut voor Volksegezondheid en Milieu/LCI. Richtlijn influenza (griep). 2003 p. 1–19.
149. Koivunen P, Kontiokari T, Neimelä M, Pokka T, Uhari M. Time to development of acute otitis media during an upper respiratory tract infection in children. *Pediatr Infect Dis J* 1999;18:303-5.
150. Winther B, Block SL, Reisinger K, Dutkowski R. Impact of oseltamivir treatment on the incidence and course of acute otitis media in children with influenza. *Int J Pediatr Otorhinolaryngol* 2010;74:684-8.
151. Heinonen S, Silvennoinen H, Lehtinen P, Vainionpää R, Vahlberg T, Ziegler T, et al. Early oseltamivir treatment of influenza in children 1-3 years of age: a randomized controlled trial. *Clin Infect Dis* 2010;51:887-94.
152. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub4.
153. Schapowal A, Klein P, Johnston SL. Echinacea reduces the risk of recurrent respiratory tract infections and complications: A meta-analysis of randomized controlled trials. *Adv Ther* 2015;32:187-200.
154. Uhari M, Kontiokari T, Koskela M, Niemelä M. Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ* 1996;9:1180-4.
155. Azarpazhooh A, Limeback H, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD007095. DOI: 10.1002/14651858.CD007095.pub2.
156. Vernacchio L, Corwin MJ, Vezina RM, Pelton SI, Feldman HA, Coyne-Beasley T, et al. Xylitol syrup for the prevention of acute otitis media. *Pediatrics* 2014;133:289-95.
157. Niittynen L, Pitkäranta A, Korpela R. Probiotics and otitis media in children. *Int J Pediatr Otorhinolaryngol* 2012;76:465-70.

158. Kumpu M, Lehtoranta L, Rovainen M, Rönkkö E, Ziegler T, Söderlund-Venermo M, et al. The use of the probiotic Lactobacillus rhamnosus GG and viral findings in the nasopharynx of children attending day care. *J Med Virol* 2013;85:1632-8.
159. Luoto R, Ruuskanen O, Waris M, Kalliomäki M, Salminen S, Isolauri E, et al. Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants: a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2014;133:405-13.
160. Liu S, Hu P, Du X, Zhou T, Pei X. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. *Indian Pediatr* 2013;50:377-81.
161. Uhari M, Mäntysaari K, Niemelä M. A meta-analytic review of the risk factors for acute otitis media. *Clin Infect Dis* 1996;22:1079-83.
162. Daly KA, Giebink GS. Clinical epidemiology of otitis media. *Pediatr Infect Dis J* 2000;19(Suppl):S31-6.
163. Nelson AM. A comprehensive review of evidence and current recommendations related to pacifier usage. *J Pediatr Nurs* 2012;27:690-9.
164. Bertin L, Pons G, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G, et al. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fundam Clin Pharmacol* 1996;10(4):387-92.
165. Foxlee R, Johansson A, Wejfalk J, Dawkins J, Dooley L, Del Mar C. Topical analgesia for acute otitis media. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD005657. DOI: 10.1002/14651858.CD005657.pub2.
166. http://www.isrctn.com/ISRCTN09599764
167. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD000219. DOI: 10.1002/14651858.CD000219.pub4.
168. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay D. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;340:c2096.
169. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;368:1429-35.

Meta-analysis of individual patient data providing important information on subgroups of children with AOM (children <2 years in age with bilateral AOM and in those of any age presenting with acute ear discharge due to AOM) that do benefit most from oral antibiotics.

170. Centre for Clinical Practice at NICE (UK). Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care. London: National Institute for Health and Clinical Excellence (UK); 2008 Jul. (NICE Clinical Guidelines, No. 69.) Available from: http://www.ncbi.nlm.nih.gov/books/NBK53632/
171. Venekamp RP, Damoiseaux RA, Schilder AG. Acute otitis media in children. Clin Evid (Online) 2014; pii: 0301.

172. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD001727. DOI: 10.1002/14651858.CD001727.pub4.
173. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH Jr, et al. A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. *Journal of Pediatrics* 2003;143:377-85.
174. van Buchem FL, Dunk JH, van't Hof MA. Therapy of acute otitis media: myringotomy, antibiotics, or neither? A double blind study in children. *Lancet* 1981;318:883–887.

Landmark RCT providing evidence that tympanocentesis is not effective in children with AOM thereby changing first-line management recommendations of this condition across the world.

175. Engelhard D, Cohen D, Strauss N, et al. Randomised study of myringotomy, amoxicillin/clavulanate, or both for acute otitis media in infants. *Lancet* 1989;2:141–143.
176. Kaleida PH, Casselbrant ML, Rockette HE, et al. Amoxicillin or myringotomy or both for acute otitis media: results of a randomised clinical trial. *Pediatrics* 1991;87:466–474.
177. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD004401. DOI: 10.1002/14651858.CD004401.pub2.
178. McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD004741. DOI: 10.1002/14651858.CD004741.pub2.
179. Hellström S, Groth A, Jörgensen F, Pettersson A, Ryding M, Uhlén I, et al. Ventilation tube treatment: a systematic review of the literature. *Otolaryngol Head Neck Surg* 2011;145:383-95.
180. Lous J, Ryborg CT, Thomsen JL. A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *Int J Pediatr Otorhinolaryngol* 2011;75:1058-61.
181. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, et al. Clinical practice guideline: Tympanostomy tubes in children. *Otolaryngol Head Neck Surg* 2013;149(1 Suppl):S1-35.
182. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton MJ. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technol Assess* 2014;18(5):1-118.
183. National Institute for Health and Clinical Excellence. Surgical Management of Otitis Media with Effusion in Children. NICE Clinical Guideline 60. Developed by the National Collaborating Centre for Women's and Children's Health 2008. http://www.nice.org.uk/nicemedia/pdf/CG60NICEguideline.pdf.
184. Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD003423. DOI: 10.1002/14651858.CD003423.pub3.
185. Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No.: CD001935. DOI: 10.1002/14651858.CD001935.pub3.

186. Venekamp RP, Burton MJ, van Dongen TMA, van der Heijden GJ, van Zon A, Schilder AGM. Antibiotics for otitis media with effusion in children. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No.: CD009163. DOI: 10.1002/14651858.CD009163.pub4.
187. Rovers MM, Black N, Browning GG, Maw R, Zielhuis GA, Haggard MP. Grommets in otitis media with effusion: an individual patient data meta-analysis. *Arch Dis Child* 2005;90(5):480-5.
188. Williamson I, Vennik J, Harnden A, et al. An open randomised study of autoinflation in 4- to 11-year-old school children with otitis media with effusion in primary care. *Health Technol Assess* 2015;19(72).
189. http://www.isrctn.com/ISRCTN49798431
190. Miller BJ, Elhassan HA. Balloon dilatation of the Eustachian tube: an evidence-based review of case series for those considering its use. *Clin Otolaryngol* 2013;38(6):525-532.
191. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg* 2001;124:374-80.
192. van Dongen TM, van der Heijden GJ, Freling HG, Venekamp RP, Schilder AG. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. *PLoS One* 2013;8(7):e69062.
193. Ah-Tye C, Paradise JL, Colborn DK. Otorrhea in young children after tympanostomy-tube placement for persistent middle-ear effusion: prevalence, incidence, and duration. *Pediatrics* 2001;107:1251-8.
194. Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.: CD008512. DOI: 10.1002/14651858.CD008512.pub2.
195. Van Dongen TM, Venekamp RP, Wensing AM, Bogaert D, Sanders EA, Schilder AG. Acute otorrhea in children with tympanostomy tubes: prevalence of bacteria and viruses in the post-pneumococcal conjugate vaccine era. *Pediatric Infect Dis J* 2015;34:355-60.
196. van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med* 2014;370(8):723-33.

Landmark RCT providing evidence that topical antibiotics are more effective than oral antibiotics and initial observation in children with ventilation tubes who develop acute ear discharge beyond the immediate postoperative period.

197. van Dongen TM, Schilder AG, Venekamp RP, de Wit GA, van der Heijden GJ. Cost-effectiveness of treatment of acute otorrhea in children with tympanostomy tubes. *Pediatrics* 2015;135(5):e1182-9.
198. Roland PS, Kreisler LS, Reese B, Anon JB, Lanier B, Conroy PJ, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tubes. *Pediatrics* 2004;113(1 Pt 1):e40-6.
199. Roland PS, Anon JB, Moe RD, Conroy PJ, Wall GM, Dupre SJ. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with

acute otitis media and otorrhea through tympanostomy tubes. *Laryngoscope* 2003;113(12):2116-22.

200. Macfadyen CA, Acuin JM, Gamble CL. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD005608. DOI: 10.1002/14651858.CD005608.
201. Macfadyen CA, Acuin JM, Gamble CL. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD004618. DOI: 10.1002/14651858.CD004618.pub2.
202. Pappas S, Nikolopoulos TP, Korres S, Papacharalampous G, Tzangalurakis A, Ferekidis E. Topical antibiotic ear drops: are they safe? *Int J Clin Pract* 2006;60(9):115-9.
203. Iacovou E, Vlastarakos PV, Papacharalampous G, Kyrodimos E, Nikolopoulos TP. Is cartilage better than temporalis muscle fascia in type I tympanoplasty? Implications for current surgical practice. *Eur Arch Otorhinolaryngol.* 2013;270(11):2803-2813.
204. Mohamad SH, Khan I, Hussain SS. Is cartilage tympanoplasty more effective than fascia tympanoplasty? A systematic review. *Otol Neurotol.* 2012;33(5):699-705.
205. Klein JO. The burden of otitis media. *Vaccine* 2001;19 Suppl 1:S2-8.
206. *Dakin H, Petrou S, Haggard* M, Benge S, Williamson I. Mapping analyses to estimate health utilities based on responses to the OM8-30 otitis media questionnaire. *Quality of Life Research* 2010;19:65-80.
207. Sneeuw KC, Sprangers MA, Aaronson NK, The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. *J Clin Epidemiol* 2002;55:1130-43.
208. Rosenfeld RM, Goldsmith AJ, Tetlus L, Balzano A. Quality of life for children with otitis media. *Arch Otolaryngol Head Neck Surg* 1997;123:1049-54.
209. Milovanovic, J., Filipovic, S. A., Marchisio, P., et al. Precision-scored parental report questions and HL-scaled tympanometry as informative measures of hearing in otitis media 1: Large-sample evidence on determinants and complementarity to pure-tone audiometry. *International journal of pediatric otorhinolaryngology*,2016; *83*, 113-131.
210. Phillips, J. S., Haggard, M., & Yung, M. (2014). A new health-related quality of life measure for active chronic otitis media (COMQ-12): development and initial validation. Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 35(3), 454–8
211. Bellussi L, Mandala M, Passali FM, Passali GC, Lauriello M, Passali D. Quality of life and psycho-social development in children with otitis media with effusion. *Acta Otorhinolaryngol Ital* 2005;25:359.
212. Hall AJ, Maw R, Midgley E, Golding J, Steer C. Glue ear, hearing loss and IQ: An association moderated by the child's home environment. *PLoS ONE* 2014;9:e87021.
213. Goldberg, D. P., & Hillier, V. F. (1979). A scaled version of the General Health Questionnaire. Psychological Medicine 1979;, 9, 139–145.http://doi.org/10.1017/S0033291700021644
214. Chow Y, Wabnitz DA, Ling J. Quality of life outcomes after ventilating tube insertion for otitis media in an Australian population. *Int J Pediatr Otorhinolaryngol* 2007;71:543-7.
215. Streiner DL, Norman GR, Cairney J. *Health measurement scales: a practical guide to their development and use.* 2014; Oxford University Press, USA.

216. Heidemann, CH, Godballe C, Kjeldsen AD, Johansen ECJ, Faber CE, Lauridsen HH. The Otitis Media-6 questionnaire: psychometric properties with emphasis on factor structure and interpretability. *Health Qual Life Outcomes* 2013;11:201.
217. Boruk M, Lee P, Faynzilbert Y, Rosenfeld R. Caregiver well-being and child quality of life. *Otolaryngol Head Neck Surg* 2007;136:159-68.
218. Ryborg CT, Søndergaard J, Lous J, Munck A, Larsen PV, Thomsen JL. Quality of life in children with otitis media--a cohort study. *Fam Pract* 2014;31:30-7.
219. Brouwer CNM, Rovers MM, Maille AR, Veenhoven RH, Grobbee DE, Sanders, EAM, et al. The impact of recurrent acute otitis media on the quality of life of children and their caregivers. *Clin Otolaryngol* 2005;30:258-265.
220. Kujala T, Alho OP, Kristo A, Uhari M, Renko M, Pokka T, et al. Quality of life after surgery for recurrent otitis media in a randomized controlled trial. *Pediatr Infect Dis J* 2014;33:715-9.
221. Brouwer CN, Maillé AR, Rovers MM, Veenhoven RH, Grobbee, DE, Sanders EA, et al. Effect of pneumococcal vaccination on quality of life in children with recurrent acute otitis media: a randomized, controlled trial. *Pediatrics* 2005;115:273-9.
222. Pettigrew MM, Gent JF, Pyles RB, Miller AL, Nokso-Koivisto J, Chonmaitree T. Viral-bacterial interactions and risk of acute otitis media complicating upper respiratory tract infection. J Clin Microbiol, 2011, 49: 3750-5.
223. Marom T, Marchisio P, Tamir SO, Torretta S, Gavriel H, Esposito S. Complementary and alternative medicine treatment options for otitis media: a systematic review. *Medicine (Baltimore)*. 2016;95:e2695.
224. Sanford CA, Schooling T, Frymark T. Determining the presence of absence of middle ear disorders: an evidence-based systematic review on the diagnostic accuracy of selected assessment instruments. *Am J Audiol* 2012; 21:251-68.
225. Liu K, Casey J, Pichichero M. Serum intercellular adhesion molecule 1 Variations in young children with acute otitis media. *Clin Vaccine Immunol.* 2010;17:1909-16.
226. Liu K, Pichichero ME. Clinical significance of serum S100A12 in acute otitis media in young children. *Pediatr Infect Dis J* 2012;31:e56-8.
227. Patel JA, Nair S, Grady JJ, Revai R, Victor S, Brasier AR, et al. Systemic cytokine response profiles associated with respiratory virus-induced acute otitis media. *Pediatr Infect Dis J* 2009,28:407-411.
228. Liu K, Kaur R, Almudevar A, Pichichero ME. Higher serum levels of interleukin 10 occur at onset of acute otitis media caused by Streptococcus pneumoniae compared to Haemophilus influenzae and Moraxella catarrhalis. *Laryngoscope* 2013;123:1500-5.
229. Pichichero ME, Almudevar A. Serum cytokine biomarkers accurately predict presence of acute otitis media infection and recovery caused by Haemophilus influenzae. *Int J Pediatr Otorhinolaryngol* 2016;83:200-4.
230. Patel JA, Nair S, Revai K, Grady JJ, Chonmaitree T. Nasopharyngeal acute phase cytokines in viral upper respiratory infection: impact on acute otitis media in children. *Pediatr Infect Dis J* 2009,28:1002-7.
231. Ede LC, O'Brien J, Chonmaitree T, Han Y, Patel JA. Lactate dehydrogenase as a marker of nasopharyngeal inflammatory injury during viral upper respiratory infection: implications for acute otitis media. *Pediatr Res.* 2013;73:349-54.

232. Pettigrew MM, et al. Panel 6: Vaccines. *Otolaryngol Head Neck Surg 2016;* Accepted for publication - In press.
233. Daniels CC, Rogers PD, Shelton CM. A Review of Pneumococcal Vaccines: Current Polysaccharide Vaccine Recommendations and Future Protein Antigens. *J Pediatr Pharmacol Ther.* 2016;21:27-35.
234. Murphy TF. Vaccines for nontypeable Haemophilus influenzae: the future Is now. *Clin Vaccine Immunol.* 2015;22:459-66.
235. Cripps AW, Otczyk DC. Prospects for a vaccine against otitis media. *Expert Rev Vaccines* 2006;5:517-34.
236. Murphy TF, Bakaletz LO, Kyd JM, Watson B, Klein DL. Vaccines for otitis media: proposals for overcoming obstacles to progress. Vaccine 2005;23:2696-702.
237. Murphy TF Vaccine development for non-typeable Haemophilus influenzae and Moraxella catarrhalis: progress and challenges. *Expert Rev Vaccines* 2005;4:843-53.
238. Mazur NI, Martinón-Torres F, Baraldi E, Fauroux B, Greenough A, Heikkinen T, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *Lancet Respir Med* 2015;11:888-900.
239. Venekamp RP, Prasad V, Hay AD. Are topical antibiotics an alternative to oral antibiotics for children with acute otitis media and ear discharge? *BMJ* 2016;352:i308.
240. Khoo X, Simons EJ, Chiang HH, Hickey JM, Sabharwal V, Pelton SI, et al. Formulations for trans-tympanic antibiotic delivery. *Biomaterials* 2013;34(4):1281-8.
241. Media ISfO. 18th International Symposium on Recent Advances in Otitis Media. In: Rosenfeld R, ed. 18th International Symposium on Recent Advances in Otitis Media. National Harbor, MD, USA, 2015:p390. http://www.otitismediasociety.org/2015-symposium.html
242. Hong P, Bance M, Gratzer PF. Repair of tympanic membrane perforation using novel adjuvant therapies: a contemporary review of experimental and tissue engineering studies. *Int J Pediatr Otorhinolaryngol.* 2013;77(1):3-12.
243. Kanemaru S, Umeda H, Kitani Y, Nakamura T, Hirano S, Ito J. Regenerative treatment for tympanic membrane perforation. *Otol Neurotol.* 2011;32(8):1218-23.
244. http://www.comet-initiative.org
245. http://www.ichom.org
246. http://www.ideal-collaboration.net
247. http://www.invo.org.uk
248. Harman NL, Bruce IA, Kirkham JJ, Tierney S, Callery P, O'Brien K, et al. The Importance of Integration of Stakeholder Views in Core Outcome Set Development: Otitis Media with Effusion in Children with Cleft Palate. *PLoS One* 2015;10(6):e0129514**.**
249. Leibovitz E, Asher E, Piglansky L, Givon-Lavi N, Satran R, Raiz S, et al. Is bilateral acute otitis media clinically different than unilateral acute otitis media? *Pediatr Infect Dis J* 2007;26:589-92.
250. McCormick DP, Chandler SM, Chonmaitree T. Laterality of acute otitis media: different clinical and microbiological characteristics. *Pediatr Infect Dis J* 2007;26:583-8.
251. Uitti JM, Laine MK, Tähtinen PA, Ruuskanen O, Ruohola A. Symptoms and otoscopic signs in bilateral and unilateral acute otitis media. *Pediatrics* 2013; 131:e398-405.

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All other authors declare no competing financial or non-financial interests.

Box 1. Risk factors for developmental difficulties in children with OME

- Permanent hearing loss independent of OME
- Suspected or confirmed speech and language delays
- Autism-spectrum disorder and other pervasive developmental disorders
- Syndromes (for example, Down syndrome) or craniofacial disorders that include cognitive, speech or language delays
- Blindness or uncorrectable visual impairment
- Cleft palate, with or without associated syndrome
- Developmental delay

Figure 1. Anatomy of the human ear The ear can be divided into three parts: the outer, middle and inner ear. The outer ear consists of the auricle (or pinna) and the ear canal. The tympanic membrane (ear drum), a thin cone-shaped membrane, separates the outer from the middle ear. The middle ear consists of the middle ear cavity and the ossicles (malleus, incus, stapes) which are attached to the tympanic membrane. The oval window connects the middle ear with the inner ear which includes the semicircular ducts and the cochlea. The middle ear cavity is connected to the nasopharynx by the Eustachian tube.

Figure 2. Global AOM and CSOM incidence. A | AOM incidence. Incidence rate estimates (per 100 people) in 2005 based on data from 39 papers conducted in six WHO regions. b | CSOM incidence. Incidence rate estimates (per 100 people) in 2005 based on data from 65 papers worldwide. (permission: Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. PLoS One 2012;7:e36226.) [2]

Figure 3. Causal pathways for otitis media. Otitis media is a multifactorial disease. Specific host and environmental factors put children at risk for otitis media through various mechanisms as illustrated in this diagram. Reducing the burden of OM will therefore require attention to more than a single risk factor. Given the complex causal pathways for OM, public health interventions may need to be prioritized differently for various at risk populations and geographical regions. Diagram based on data obtained from [47].

Figure 4. Steps in the pathogenesis of virus-induced acute otitis media. The child might have a pre-existing nasopharyngeal bacterial colonization, which does not cause symptoms. When the child contracts a common cold, the viral infection initiates inflammation of the nasopharynx and the Eustachian tube, leading to increased adherence and colonization of bacteria and other activating mechanisms. Eustachian tube dysfunction follows, leading to negative middle ear pressure, allowing bacteria and/or virus in the nasopharynx into the middle ear causing infection and/or inflammation.

Figure 5. Otoscopical images. A | normal tympanic membrane. B | Red and bulging tympanic membrane indicative for acute otitis media. C | Otitis media with effusion. D | Presence of a ventilation tube in the tympanic membrane.

Figure 6. Tympanogram. The tympanometric curve, or tracing, is categorized as type A, B, or C based on middle ear pressure and the presence or absence of a discernable peak. A | Type A tympanogram. The type A tympanogram curve has a sharp peak and normal middle ear pressure and therefore a low probability of middle ear effusion. b | Type B tympanograms. The type B tympanogram curve has a flattened shape with no discernible peak pressure and has a high probability of middle ear effusion. A flat tympanogram with a normal equivalent ear canal volume usually indicates middle ear effusion. A flat tympanogram associated with a low equivalent ear canal volume indicates probe obstruction by cerumen or contact with the ear canal. A flat tympanogram with a high volume indicates a patent ventilation tube or a tympanic membrane perforation. C |Type C tympanogram curves (intermediate probability of effusion) have negative middle ear pressure with a sharp (C1) or rounded (C2) peak.

Figure 7 | Ventilation tubes. Ventilation tubes (tympanostomy tubes) are tiny plastic tubes put into the eardrum (tympanic membrane) during a short operation under general anaesthesia. The tubes usually stay in place for 6-12 months and fall out themselves. Ventilation tubes can prevent further AOM episodes by draining the fluid from the ear and improving its ventilation. In addition, by providing access to the middle ear, they may allow for local antibiotic treatment of AOM rather than systemic.

Table 1. Otitis media definitions and terminology

Preferred term	Definition	Comment
Otitis media (OM) [1]	Inflammation of the middle ear without reference to aetiology or pathogenesis	Non-specific umbrella term for any condition associated with middle ear inflammation
Acute otitis media (AOM) [5]	Rapid onset of signs and symptoms of inflammation in the middle ear	Diagnosed when there is moderate to severe bulging of the tympanic membrane; mild bulging of the tympanic membrane and recent (< 48h) onset of ear pain or intense erythema of the tympanic membrane; or acute ear discharge not caused by otitis externa (inflammation of the external ear canal) *
Recurrent AOM [5]	≥3 well-documented and separate AOM episodes in the preceding 6 months or ≥4 episodes in the preceding 12 months with > 1 episode in the past 6 months	Children without persistent MEE tend to have a good prognosis and often improve spontaneously; children with persistent MEE have a poorer prognosis and might benefit from ventilation tubes
Otitis media with effusion (OME) [8]	Fluid in the middle ear without signs or symptoms of acute ear infection	Diagnosed by one or more of the following: reduced tympanic membrane mobility on pneumatic otoscopy, reduced tympanic membrane mobility on tympanometry, opaque tympanic membrane or a visible air-fluid interface behind the tympanic membrane on otoscopy
Chronic OME [181]	OME persisting for ≥3 months from date of onset (if known) or from date of diagnosis (if onset is unknown)	Chronic OME has much lower rates of spontaneous resolution compared to OME of new onset or following an episode of AOM
Chronic suppurative otitis media (CSOM) [13]	Chronic inflammation of the middle ear and mastoid mucosa with a non-intact tympanic membrane (perforation or ventilation tube) and persistent ear discharge	No consensus on duration of ear discharge needed for diagnosis, with recommendations ranging from 2 weeks to at least 3 months
Middle ear effusion (MEE) [181]	Fluid in the middle ear from any cause	MEE is present with both OME and AOM and might persist for weeks or months after the signs and symptoms of AOM resolve
* The degree of bulging does not reflect AOM severity. Severe AOM is defined as having moderate-to-severe ear pain, ear pain for at least 48 hours, or temperature 39C or higher.[5] Severe AOM is more common with bilateral disease[249,250], but the relationship is not consistent.[251]		

Table 2. Diagnostic modalities for otitis media

Modality	Description	Comment
Signs and symptoms (obtained by history)	Includes ear-specific symptoms (ear pain, hearing loss), non-specific symptoms (nausea, irritability, sleep disturbance, anorexia), and signs (fever, vomiting)	Ear pain is most useful for diagnosing AOM and hearing loss for OME, but signs and symptoms alone have poor diagnostic accuracy
Symptom severity scales	Parent-reported measures of AOM severity using categorical responses or a faces scale	Not useful for AOM diagnosis, but can be used to rate severity, follow the course of disease, and to assess outcomes
Otoscopy	Visual examination of the ear canal and tympanic membrane with an otoscope	Bulging tympanic membrane is most useful for diagnosing AOM; opaque or cloudy tympanic membrane is most useful for diagnosing OME
Pneumatic otoscopy	Examination of the middle ear using an otoscope to create an air-tight (hermetic) seal in the ear canal and then squeezing (or releasing) the attached rubber bulb to change the pressure in the ear canal and see how the tympanic membrane reacts	A normal tympanic membrane moves briskly with applied pressure, but the movement is minimal or sluggish when there is fluid in the middle ear; no motion is observed if tympanic membrane is not intact
Otomicroscopy	Examination of the ear canal and tympanic membrane using the binocular, otologic microscope to obtain a magnified view with good depth perception	Primary use is to assess tympanic membrane abnormalities (atrophy, sclerosis, retraction pockets) and to help distinguish surface findings from middle ear pathology
Tympanometry	An objective measure of middle ear function that requires an air-tight seal in the ear canal. Tympanometry provides a graph showing how energy admitted to the ear canal is reflected back to an internal microphone while the canal pressure is varied from negative to positive (pressure admittance function) and can be performed with a portable (handheld) unit or a desktop machine	If the middle ear is filled with fluid, tympanic membrane vibration is impaired and the result is a flat, or nearly flat, tracing. If the middle ear is filled with air but at a higher or lower pressure than the surrounding atmosphere, the peak on the graph will be shifted in position based on the pressure (to the left if negative, to the right if positive).
Acoustic reflectometry	Uses a transducer and microphone at the entrance of the ear canal, without an air-tight seal, to measure how much sound is reflected off the tympanic membrane.	Higher reflectivity levels indicate a greater probability of effusion, but unlike tympanometry it only assess the probability of effusion and cannot measure middle ear function
Computed tomography	An imaging procedure, using ionizing radiation, to create a detailed scan of the temporal bone	Useful in surgical planning for CSOM but not useful for primary diagnosis of AOM, OME or CSOM

AOM, acute otitis media; CSOM, chronic suppurative otitis media; OME, otitis media with effusion.