Otitis media

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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 lifelong 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.

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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 a 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.
Epidemiology

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 against 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 mucociliary-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 characterized by persistent inflammation of the middle ear, as observed in CSOM. The predominant bacterial pathogens for CSOM — *P. aeruginosa* and *S. aureus* — 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. Evidence of the elevated inflammation includes high levels of IL-8 in the middle ear fluid and elevated mRNA and protein levels of TNFα, IL6, IL1β and INFγ in the middle ear mucosa compared with patients with chronic OM.

**[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%, with boys at slightly higher risk than girls. A range of genes regulating the innate immune response are associated with predisposition to OM. 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 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. 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]

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 immunization 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
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
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. 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. 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. 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.

[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%. 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. 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. The largest effects of these interventions were found in studies where the risk of children developing early postoperative ear discharge was high. 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. 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. 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, current guidance recommends ototopical antibiotic drops as first-line treatment in these children. There is some evidence that eardrops containing a combination of antibiotic(s) and a corticosteroid are superior over those containing antibiotic(s) alone.

[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). Current evidence assessing the effectiveness of quinolone versus non-quinolone containing eardrops is inconclusive, with quinolones having the advantage of being non-ototoxic. Limited evidence suggests that treating patients with CSOM with a combination of systemic and topical antibiotics is not more effective than topical antibiotics alone. 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.

[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
As in other fields of medicine, formal measurement of quality of life (QoL) in OM came late, dating mostly from the mid-1990s. 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.

**[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.
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. influenzae 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.

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.

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


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


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


*A comprehensive review of the innate and acquired immunology of the middle ear and Eustachian tube.*


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.


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*.


166. [http://www.isrctn.com/ISRCTN09599764](http://www.isrctn.com/ISRCTN09599764)


*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.*


189. [http://www.isrctn.com/ISRCTN49798431](http://www.isrctn.com/ISRCTN49798431)


**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.**


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


215. Streiner DL, Norman GR, Cairney J. *Health measurement scales: a practical guide to their development and use.* 2014; Oxford University Press, USA.


244. http://www.comet-initiative.org

245. http://www.ichom.org


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Competing interests
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 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 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

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Definition</th>
<th>Comment</th>
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<tr>
<td>Otitis media (OM) [1]</td>
<td>Inflammation of the middle ear without reference to aetiology or pathogenesis</td>
<td>Non-specific umbrella term for any condition associated with middle ear inflammation</td>
</tr>
<tr>
<td>Acute otitis media (AOM) [5]</td>
<td>Rapid onset of signs and symptoms of inflammation in the middle ear</td>
<td>Diagnosed when there is moderate to severe bulging of the tympanic membrane; mild bulging of the tympanic membrane and recent (&lt; 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) *</td>
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<td>Recurrent AOM [5]</td>
<td>≥3 well-documented and separate AOM episodes in the preceding 6 months or ≥4 episodes in the preceding 12 months with &gt; 1 episode in the past 6 months</td>
<td>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</td>
</tr>
<tr>
<td>Otitis media with effusion (OME) [8]</td>
<td>Fluid in the middle ear without signs or symptoms of acute ear infection</td>
<td>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</td>
</tr>
<tr>
<td>Chronic OME [181]</td>
<td>OME persisting for ≥3 months from date of onset (if known) or from date of diagnosis (if onset is unknown)</td>
<td>Chronic OME has much lower rates of spontaneous resolution compared to OME of new onset or following an episode of AOM</td>
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<tr>
<td>Chronic supplicative otitis media (CSOM) [13]</td>
<td>Chronic inflammation of the middle ear and mastoid mucosa with a non-intact tympanic membrane (perforation or ventilation tube) and persistent ear discharge</td>
<td>No consensus on duration of ear discharge needed for diagnosis, with recommendations ranging from 2 weeks to at least 3 months</td>
</tr>
<tr>
<td>Middle ear effusion (MEE) [181]</td>
<td>Fluid in the middle ear from any cause</td>
<td>MEE is present with both OME and AOM and might persist for weeks or months after the signs and symptoms of AOM resolve</td>
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Table 2. Diagnostic modalities for otitis media

<table>
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<tr>
<th>Modality</th>
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<tr>
<td>Signs and symptoms (obtained by history)</td>
<td>Includes ear-specific symptoms (ear pain, hearing loss), non-specific symptoms (nausea, irritability, sleep disturbance, anorexia), and signs (fever, vomiting)</td>
<td>Ear pain is most useful for diagnosing AOM and hearing loss for OME, but signs and symptoms alone have poor diagnostic accuracy</td>
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<tr>
<td>Symptom severity scales</td>
<td>Parent-reported measures of AOM severity using categorical responses or a faces scale</td>
<td>Not useful for AOM diagnosis, but can be used to rate severity, follow the course of disease, and to assess outcomes</td>
</tr>
<tr>
<td>Otoscopy</td>
<td>Visual examination of the ear canal and tympanic membrane with an otoscope</td>
<td>Bulging tympanic membrane is most useful for diagnosing AOM; opaque or cloudy tympanic membrane is most useful for diagnosing OME</td>
</tr>
<tr>
<td>Pneumatic otoscopy</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Otomicroscopy</td>
<td>Examination of the ear canal and tympanic membrane using the binocular, otologic microscope to obtain a magnified view with good depth perception</td>
<td>Primary use is to assess tympanic membrane abnormalities (atrophy, sclerosis, retraction pockets) and to help distinguish surface findings from middle ear pathology</td>
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<tr>
<td>Tympanometry</td>
<td>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</td>
<td>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).</td>
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<tr>
<td>Acoustic reflectometry</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>An imaging procedure, using ionizing radiation, to create a detailed scan of the temporal bone</td>
<td>Useful in surgical planning for CSOM but not useful for primary diagnosis of AOM, OME or CSOM</td>
</tr>
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</table>

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