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 (CSOM). 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, CSOM is a leading cause of hearing loss. OM can be of bacterial or viral origin; during 'colds', viruses can ascend 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 (eardrum) for AOM and hearing loss for OME; diagnostic modalities include (pneumatic) otoscopy, tympanometry and audiometry. Symptomatic management of ear pain and fever is the mainstay of AOM treatment, reserving antibiotics for children with severe, persistent or recurrent infections. Management of OME largely consists of watchful waiting, with ventilation (tympanostomy) tubes primarily for children with chronic effusions and hearing loss, developmental delays or learning difficulties. The role of hearing aids to alleviate symptoms of hearing loss in the management of OME needs further study. Insertion of ventilation tubes and adenoidectomy are common operations for recurrent AOM to prevent recurrences, but their effectiveness is still debated. Despite reports of a decline in the incidence of OM over the past decade, attributed to the implementation of clinical guidelines that promote accurate diagnosis and judicious use of antibiotics and to pneumococcal conjugate vaccination, OM continues to be a leading cause for medical consultation, antibiotic prescription and surgery in high-income countries.

Otitis media (OM) or inflammation of the middle ear (comprising the middle ear cavity and ossicles; FIG. 1) is an umbrella term that encapsulates acute OM (AOM), OM with effusion (OME; 'glue ear') and chronic suppurative OM (CSOM)[1] (TABLE 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, 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 a subset of children have recurrent episodes of AOM[5] (TABLE 1). Recurrent episodes of AOM 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 AOM 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) per 10,000 individuals[2]. Perforation of the tympanic membrane (eardrum) can occur as a local sequela of AOM or as a complication associated with treatment with ventilation (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 a negative impact on language, behaviour and progress at school[9]. OME is very common, with 80% of children having had one or more episode of OME by 10 years of age. OME may occur as new-onset OME after a viral infection[10] or after AOM, when the inflammatory process subsides and MEE persists. In fact, after an AOM episode, all children

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have OME for some time[11,12]. OME in itself is a risk factor for AOM, demonstrating 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 due to damage to the inner ear) and intracranial complications[13]. The prevalence of this condition varies widely between countries, but it is most common in low-income and middle-income countries[2].

Since the publication of a landmark review on OM more than a decade ago[14], important developments worldwide have been made, in particular, regarding the prevention of OM through pneumococcal conjugate vaccination and treatment of OM following new guidelines that focus on accurate diagnosis and the 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 preventive and treatment options. We also discuss promising future directions of OM research that might guide clinicians and carers to optimize the health and well-being 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 (FIG. 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 1–4 years of age (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].

As OME is asymptomatic and may go undetected, its incidence and prevalence have 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[15–19], showing a point prevalence of OME on screening tests of up to 20%[20]. The peak incidence of OME is around 1 year of age; by 3 years of age, almost all children have experienced at least one episode of OME[18,21].

For CSOM, the average global incidence rate is estimated at 4.8 new episodes per 1,000 people (all ages) per year[2] (FIG. 2b). The total annual number of new CSOM episodes is 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[22,23], the United States[24–26], the Netherlands[27] and the UK[28] suggest a decline in OM incidence since the mid-1990s. This decline is attributed to the introduction of clinical guidelines that recommend stricter diagnostic criteria and the 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[2,29–31].

Social and environmental risk factors

The risk of OM is significantly influenced by numerous host and environmental factors (FIG. 3). Host factors that increase the risk of OM include: young age[32], male sex[33], race and ethnicity[33], genetic factors and a family history of OM[34], craniofacial anomaly such as cleft palate[35], atopy[34], immunodeficiency[36], upper respiratory tract infections (URTIs) and adenoid hypertrophy[34,37], and laryngopharyngeal reflux[38]. Environmental factors that increase the risk of OM include: low socioeconomic status, exposure to tobacco smoke[34], having older siblings[39], day-care attendance[32,39,40] and the use of a pacifier[41,42]. Having been breastfed protects against OM[43]. In developing countries, malnutrition, contaminated water, poor hygiene, overcrowding, human immunodeficiency virus infection, tuberculosis, malaria and poor access to health care increase the risk for chronicity and complications of OM[2,44,45].

Mechanisms/pathophysiology

Despite the high disease burden, OM in developed countries is usually uncomplicated and self-limiting, and rarely result in ongoing hearing problems or developmental delay[6]. However, in high-risk populations in both developing and developed countries, considerable hearing loss with life-long sequelae does occur more frequently. 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

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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 (FIG. 3).

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[46]. Indeed, the anatomy of the immature Eustachian tube in infants has a central role in the susceptibility to infections of the middle ear (FIG. 1). The Eustachian tube epithelium is the frontline defence 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.

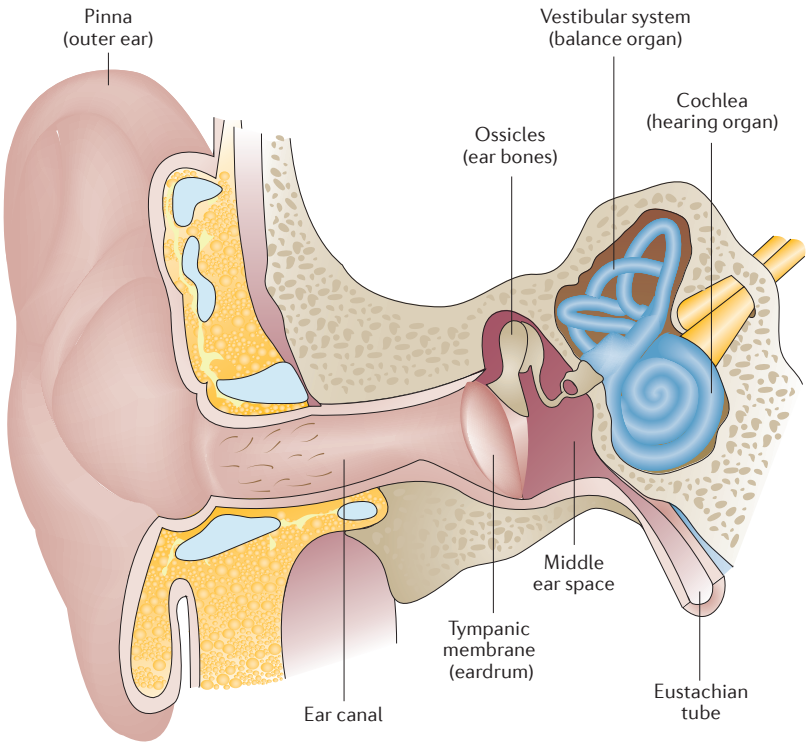

Figure 1 | **Anatomy of the human ear.** The ear can be divided into three parts: the outer, middle and inner ear. The outer ear comprises the auricle (or pinna) and the ear canal. The tympanic membrane (eardrum), a thin cone-shaped membrane, separates the outer ear from the middle ear. The middle ear comprises the middle ear cavity and the ossicles (the malleus, incus and 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.

Anatomically, the Eustachian tube is shorter, wider and more horizontal in infants and young children (<1 year of age) than in adults, which facilitates otopathogen transmission through to the middle ear and increases the risk of OM[47]. 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, the length of the Eustachian tube increases from 13 mm to 35 mm[48]. 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 who are at high risk of OM.

Bacterial colonization and biofilms

Early colonization of the nasopharynx with bacterial otopathogens considerably increases the risk of subsequent episodes of OM[49,50]. *Streptococcus pneumoniae* (or pneumococcus), non-typeable *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 (PCV) use[51,52]. For example, Indigenous Australian children 1–3 months of age are more likely to have two or more otopathogens isolated from their nasopharynx than non-Indigenous Australian children. In Indigenous Australian children, early carriage of non-typeable *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[53]. 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[54,55]. Nevertheless, these studies show that bacterial density in the nasopharynx is associated with increased risk of OM.

Bacterial biofilms (that is, colonization of bacteria embedded in the extracellular matrix and adherent to a surface), which are known to protect bacteria against antibiotic treatment[56,57] and the host's immune response, have been demonstrated in the middle ears of patients with CSOM[58,59], persistent OME[58,60] and those with OM who have failed antibiotic treatment[60]. Biofilms have been reported to occur in MEE[60], attached to the middle ear mucosa[61]. In animals, immunization against non-typeable *H. influenzae* resulted in more-rapid resolution of an established biofilm infection[62], suggesting that vaccination can induce immune responses that are effective against pathogens residing in biofilms in the middle ear.

Viral infection

AOM is always preceded by viral infection of the nasopharyngeal and Eustachian tube epithelium: the 'common cold' or viral URTI[63] (FIG. 4). Bacterial

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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	Nonspecific umbrella term for any condition associated with inflammation of the middle ear
Acute OM (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 (<48 hours) 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]	Three or more well-documented and separate AOM episodes in the preceding 6 months or four or more episodes in the preceding 12 months with more than one 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
OM 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[178]	OME persisting for ≥3 months from the date of onset (if known) or from the date of diagnosis (if onset is unknown)	Chronic OME has much lower rates of spontaneous resolution than new-onset OME or following an episode of AOM
Chronic suppurative OM (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 the duration of ear discharge needed for diagnosis, with recommendations ranging from 2 weeks to at least 3 months
Middle ear effusion (MEE)[178]	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 a temperature of ≥39°C[5]. Severe AOM is more common with bilateral disease[245,246], but the relationship is not consistent[247].

otopathogens that are colonized in the nasopharynx do not cause any harm until the 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[10,63]. Viral infection creates changes in the nasopharyngeal mucosa by modifying host immune function[64], inducing cytokine activity and inflammatory mediators[65] and increasing bacterial colonization and adherence through the upregulation of host cell surface antigens that serve as bacterial receptor sites[66,67]. Viral infection also alters the properties of mucus and diminishes the normal mucociliary clearance by mucosal cells of the Eustachian tube and the nasopharynx. This causes tubal dysfunction[66,68] leading to negative middle ear pressure, which occurs more severely in children <24 months of age than with children 25–47 months of age[69,70]. Negative middle ear pressure facilitates an influx of bacteria and/or viruses into the middle ear[69]. 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[71].

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 B_4 and IL-8, which can in turn interfere with antibiotic penetration into the middle ear[72–75]. Virus alone can cause AOM, both in experimental animals and in children[63]. Approximately 5% of the MEE isolated from children with AOM contain only viruses[76]. 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[77]. Viral infection not only leads to AOM but also to new-onset OME. In children at the peak age of incidence of OM (6–47 months), the rate of AOM and OME following URTI was 37% and 24%, respectively[10].

Innate immunity. Both bacteria and viruses induce middle ear inflammation and MEE[63]. The innate immune system includes physical barriers, such mucociliary generated flows of mucus, and innate defence molecules, such as lysozyme, defensins, complement factors, cytokines and chemokines[47,78]. These systems are responsible for initiating front-line responses to pathogens in the nasopharynx, Eustachian tube and middle ear. Activation of pattern recognition receptors, particularly Toll-like receptors (TLRs), by invading

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otopathogens, triggers the release of several of the antimicrobial proteins and pro-inflammatory cytokines[79,80]. Upregulation of these innate mechanisms is crucial for the rapid resolution of OM[81]. However, these cytokines and antimicrobial proteins can also have a pathophysiological role[80,82] that is characterized by persistent inflammation of the middle ear, as observed in CSOM[83]. The predominant bacterial pathogens for CSOM — *Pseudomonas aeruginosa* and *Staphylococcus aureus*[83,84] — form biofilms with other otopathogens and elicit an increased innate inflammatory responses, which might contribute to the chronicity of OM and progression to CSOM despite appropriate intervention[84]. Evidence of the increased inflammation includes high levels of IL-8 in the middle ear fluid[85] and increased mRNA and protein levels of tumour necrosis factor (TNF), IL-1β, IL-6 and interferon-γ (IFNγ) in the middle ear mucosa compared with patients with chronic OME[86].

Adaptive immunity. The middle ear is an effective immunocompetent site that maintains essentially a 'sterile' environment. 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

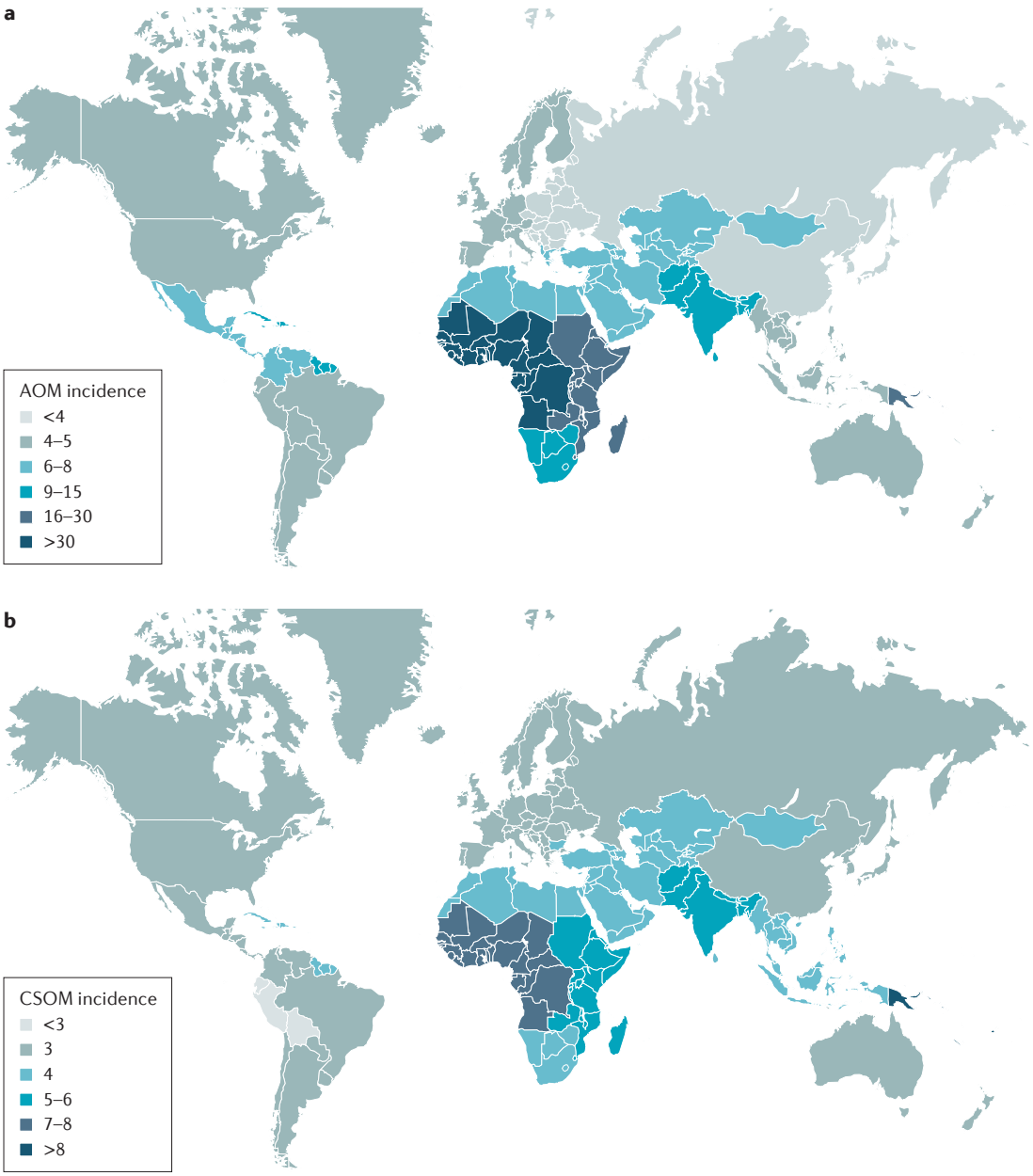

Figure 2 | **Global acute otitis media and chronic suppurative otitis media incidence. a** | Acute otitis media (AOM) incidence. Incidence rate estimates (per 100 people) in 2005 based on data from 39 papers conducted in six WHO regions. **b** | Chronic suppurative otitis media (CSOM) incidence. Incidence rate estimates (per 1,000 people) in 2005 based on data from 65 papers worldwide. Reproduced from REF. 2.

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response to infection. Research is only just commencing on the middle ear cell-mediated responses to infection, but early data indicate that regulatory T cells may play a pivotal part in controlling inflammation. The literature is unclear as to whether 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[47].

Genetic factors

Estimates of heritability of AOM and OME range from 40% to 70%[87], with boys at slightly higher risk than girls[33]. A range of genes that regulate the innate immune response are associated with a predisposition to OM[88]. Some of the heritable risk for OM might result from cytokine polymorphisms that can be specific to the otopathogen. For example, polymorphisms in *IL6*, *IL10* and *TNF* are predictive of OM coincident with RSV and rhinovirus infection[89], whereas polymorphisms in several signal transduction pathways, such as TLR signalling, have been associated with both risk and disease severity of OM in human studies and mouse models[47,80]. Most polymorphisms described to date disrupt the establishment of an effective innate immune response, but polymorphisms in the transforming growth factor-β (TGFβ) signalling pathway can be pathophysiological through interference with moderation of pro-inflammatory responses[80,87]. Although data with respect to deficiencies in specific antibody responses to otopathogens in children prone to OM 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.

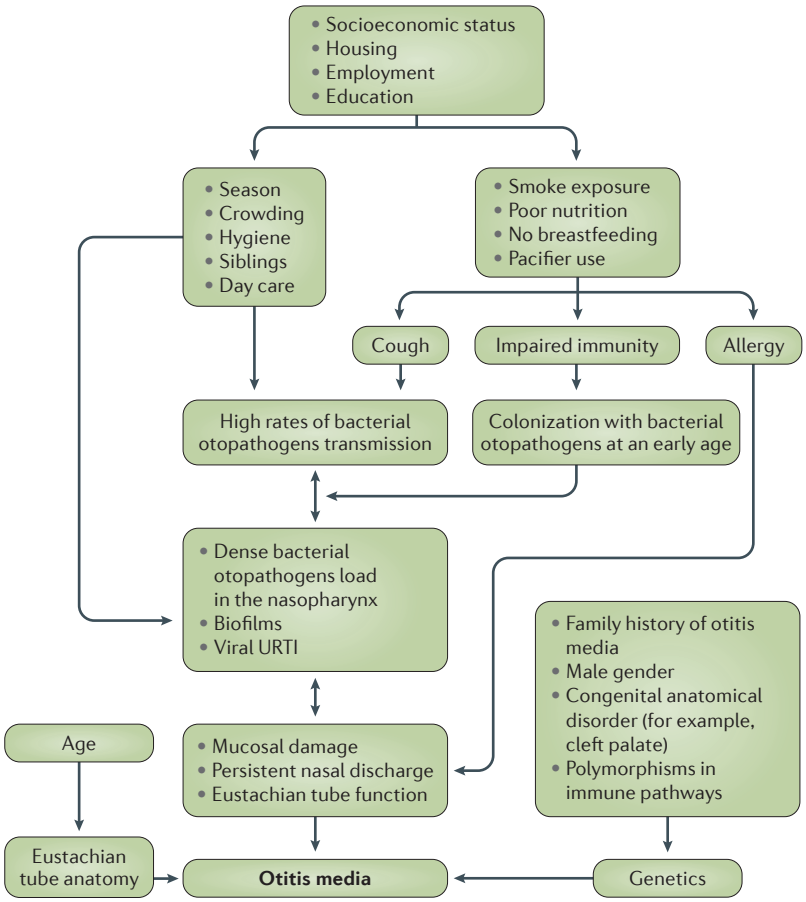

Figure 3 | **Causal pathways for otitis media.** Otitis media is a multifactorial disease. Specific host and environmental factors put children at risk for otitis media through various mechanisms, as illustrated in this diagram. Reducing the burden of otitis media will therefore require attention to more than a single risk factor. Given the complex causal pathways for otitis media, public health interventions may need to be prioritized differently for various at-risk populations and geographical regions. URTI, upper respiratory tract infection. Data from REFS 241–243.

Diagnosis, screening and prevention

Signs and symptoms

Signs and symptoms obtained from patient history (including ear-specific and nonspecific 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[90,91]. In young preverbal children, ear pain may manifest with ear manipulation (for example, tugging, rubbing or holding), excessive crying or with changes in sleep and behaviour patterns of the child[5]. However, these symptoms are nonspecific and, like fever and vomiting, do not differentiate children with AOM from those with URTI[92].

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 to explain why AOM is widely overdiagnosed[93–95]. By contrast, OME might be underdiagnosed by paediatricians compared with otolaryngologists[95]. 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). Bulging of the tympanic membrane, visualized by otoscopy, is a key diagnostic feature of AOM[5].

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 otomicroscopy and tympanometry 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.

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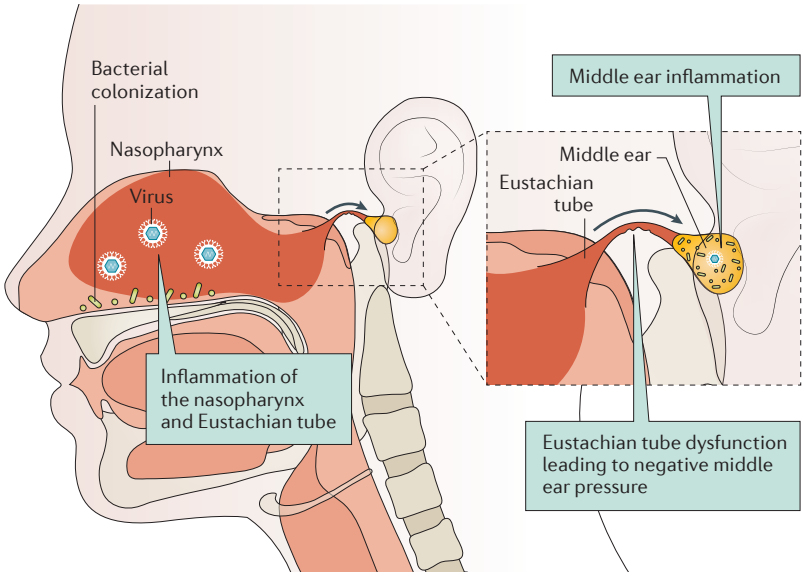

Figure 4 | **Steps in the pathogenesis of virus-induced acute otitis media.** The child might have a pre-existing nasopharyngeal bacterial colonization, which does not cause symptoms. When the child contracts a common cold, the viral infection initiates inflammation of the nasopharynx and the Eustachian 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 viruses in the nasopharynx to move into the middle ear causing infection and/or inflammation.

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[96]. The overall AOMSOS score discriminates among children with AOM and those without AOM, but all signs and symptoms can be present to varying degrees in children with normal ears[90]. Another severity measure, the AOM Faces Scale (AOM-FS), uses a scale with seven choices ranging from 1 (not present, not a problem) to 7 (extreme problem)[97].

Otoscopy. Otoscopy is the mainstay of AOM diagnosis (FIG. 5; TABLE 2). Obstructing cerumen (earwax) that prevents adequate visualization of the tympanic membrane must be removed to facilitate accurate diagnosis[98]. When performing otoscopy, the clinician assesses and records tympanic membrane colour, opacity, position and integrity. A bulging tympanic membrane, which is associated with a high level of bacterial pathogens in the MEE[99], is the most consistent sign of AOM[91,100] (FIG. 5) and is the most useful feature for differentiating AOM from OME[101]. As the bulging subsides, the tympanic membrane may have a cobblestoned appearance (shagrination)[102,103]. An opaque or cloudy tympanic membrane is highly predictive of MEE, regardless of cause[100]. Several image-based scales exist to standardize recording and interpretation of otoscopic findings[103,104].

Pneumatic otoscopy. Pneumatic otoscopy has been recommended as the primary diagnostic method for OME[8] (TABLE 2) because of its excellent diagnostic accuracy[100,105]. 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[91,100] and improves diagnostic accuracy over otoscopy alone[106,107]. However, the use of pneumatic otoscopy in clinical practice is variable worldwide; in the United States alone, prevalence ranges from 7% to 33%[108,109]. 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[94].

Otomicroscopy. Otomicroscopy might help more than simple otoscopy to diagnose OME[110] (TABLE 2), but evidence is sparse and the need for special equipment and training often limits 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 chronic OME[111].

Tympanometry. Tympanometry objectively measures tympanic membrane mobility and middle ear function[112] (FIG. 6; TABLE 2). Compared with pneumatic otoscopy, tympanometry has comparable sensitivity (range: 90–94%) but lower specificity (50–75% versus 80% for tympanometry and pneumatic otoscopy, respectively) for diagnosing OME[113]. 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[114]. 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[115]. A low equivalent volume (<0.3 ml) could indicate an inaccurate reading because the ear canal is obstructed by cerumen or that the probe is pressed against the canal wall; a high equivalent volume (1–5.5 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 of age, a 1,000 Hz probe tone is best as the 226 Hz tone is insensitive to MEE[116].

Acoustic reflectometry. Acoustic reflectometry measures how much sound is reflected off the tympanic membrane, with higher reflectivity indicating a greater probability of MEE[117] (TABLE 2). Advantages over tympanometry include ease of use, no requirement for a hermetic seal and the availability of an inexpensive consumer version, which can be used reliably by

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parents to monitor the middle ear status of their child[118]. Reflectometry in some studies is less sensitive[119] and specific[120] than tympanometry in detecting MEE, but its high specificity and negative predictive values make reflectometry useful for ruling out MEE in children with URTIs[121].

Screening

AOM is symptomatic and does not require screening. However, even screening for OME, which is asymptomatic, has not been found to be 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 marked differences in developmental outcomes (language, behavioural problems or intelligence scores) between children who are not screened for OME and children with OME identified by screening who have received expeditious ventilation tube insertion[122]. Thus, current guidelines recommend against routine screening for OME of otherwise healthy, asymptomatic children[8].

Conversely, screening for OME is recommended at 12–18 months of age for children with sensory, physical, cognitive or behavioural factors that place them at increased risk for developmental comorbidities[8] (BOX 1). OME accounts for about two-thirds of newborn hearing screen failures[123,124]. Clinicians who manage these failures should know that only around 10% of children with OME who are identified by hearing screening may also have the targeted concurrent sensorineural hearing loss. This may interfere with the detection of an underlying sensorineural hearing loss because it may take several months after resolution of MEE for the extra effect of an OME history on hearing ability to completely resolve[125].

Prevention

Because OM is a multifactorial disease, various 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 in children are discussed in the Management section.

Vaccines directed against bacterial otopathogens. The goal of the vaccines is to reduce or eliminate nasopharyngeal colonization of *S. pneumoniae*, non-typeable *H. influenzae* and *M. catarrhalis*. The seven-valent PCV (PCV7), directed against seven serotypes of *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 a 29% reduction in AOM caused by pneumococcal serotypes contained in the vaccine, a 6–7% reduction in overall AOM and a 20% reduction in the use of ventilation tubes for chronic recurrent OM[126–128]. PCV13, available a decade later, has been associated with further reduction of AOM, mastoiditis and ventilation tube insertions[25].

Table 2 | **Diagnostic modalities for otitis media**

Modality	Description	Comment
Signs and symptoms (obtained by history)	Includes ear-specific symptoms (such as ear pain and hearing loss), nonspecific symptoms (such as nausea, irritability, sleep disturbance and anorexia) and signs (such as fever and 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	A bulging tympanic membrane is most useful for diagnosing AOM; an 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 the tympanic membrane is not intact
Otomicroscopy	Examination of the ear canal and tympanic membrane using the binocular otological microscope to obtain a magnified view with a good depth perception	Primary use is to assess tympanic membrane abnormalities (such as atrophy, sclerosis and 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
CT	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.

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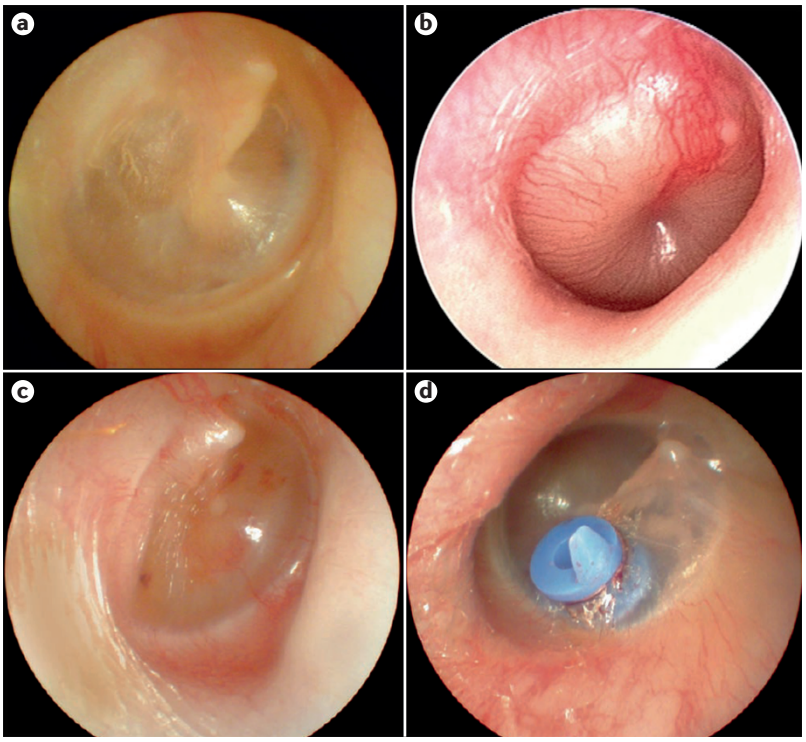

Figure 5 | **Otoscopical images. a** | Normal tympanic membrane. **b** | Red and bulging tympanic membrane indicative of acute otitis media. **c** | Otitis media with effusion. **d** | Presence of a ventilation tube in the tympanic membrane. Parts **a**, **c** and **d** reproduced with permission from REF. 244, Springer. Part **b** courtesy of D. McCormick, University of Texas Medical Branch, Galveston, Texas, USA.

The use of PCVs has led to the replacement of serotypes of *S. pneumoniae* in the nasopharynx by the serotypes that are not covered by the vaccine and non-typeable *H. influenzae* in vaccinated children[129,130]. Nevertheless, pneumococcal-associated AOM may continue to decrease with pneumococcal conjugate vaccination as the serotypes with greater capacity to cause AOM are replaced by less-otopathogenic serotypes[131]. 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 non-typeable *H. influenzae*. Vaccination might, therefore, disrupt the continuum of evolution from pneumococcal-associated OM towards chronic OM[132,133]. However, in communities in which there is early and dense bacterial acquisition in the nasopharynx, and in some geographical regions such as Oceania, non-typeable *H. influenzae* may be a primary otopathogen[52].

Importantly, PCVs do not prevent OM episodes if vaccination occurs after recurrent AOM has developed[134]. PCV10 with non-typeable *H. influenzae* protein D as carrier protein (PD-PCV10) was designed to protect against both *S. pneumoniae* and non-typeable *H. influenzae* and is available in Europe. Although effective for pneumococcal-associated OM, PD-PCV10 may be less protective for non-typeable *H. influenzae* than originally reported in a prototype vaccine study[29,135–137]. No other licensed vaccine against non-typeable *H. influenzae* or *M. catarrhalis* exists, but numerous vaccines are in various stages of development.

Vaccines directed against respiratory viruses. As AOM is generally preceded by symptomatic viral URTI[10], the 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 influenza vaccines (protecting against three influenza virus strains), both inactivated influenza vaccines and live attenuated influenza vaccines, have been shown to reduce AOM during 'flu' seasons[138–142]. The vaccines work by preventing influenza virus infection and influenza-associated AOM, which occurs in up to two-thirds of young children with influenza virus infection[138]. The effectiveness of 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[143], whereas the recommendation is restricted to children from 2 years of age in the United Kingdom[144] and is restricted to children with substantial medical comorbidities, including respiratory, cardiovascular, metabolic and renal disease in the Netherlands[145].

Non-vaccine approaches to prevent viral URTI and AOM. AOM occurs mostly on days 2–5 after URTI onset[10,146]; thus, early administration of antivirals during uncomplicated URTI may prevent AOM. Studies have shown a reduction in the development of AOM by 43–85% in young children treated with oseltamivir within 12–48 hours of influenza symptom onset[147,148]. However, a recent meta-analysis of both children and adult data concluded that neither oseltamivir nor zanamivir significantly reduced the risk of OM[149].

Echinacea, an immune modulator and mild antiviral that is often used as a home remedy, has been reported to reduce the risk of recurrent respiratory infections, including virologically confirmed cases, and OM[150]. Xylitol, a five-carbon naturally occurring sugar alcohol with antibacterial properties, has been shown to prevent recurrent AOM with some success[151–153]. However, the successful dose regimens (that is, chewing gum or syrup given five times per day continuously for 2–3 months) are not practical. Probiotics, mostly *Lactobacillus* and *Bifidobacterium*, have been used to reduce the risk of respiratory symptoms and OM; results have been encouraging but warrant further investigation[154–157].

Environmental risk factors. Avoidance of well-known environmental risks, such as day-care attendance, exposure to tobacco smoke and the use of pacifiers, especially during the OM peak age of incidence (6–24 months), has been associated with a reduction of OM[40,158–160]. Conversely, the benefit of breastfeeding in preventing OM has long been known. Breastfeeding protects

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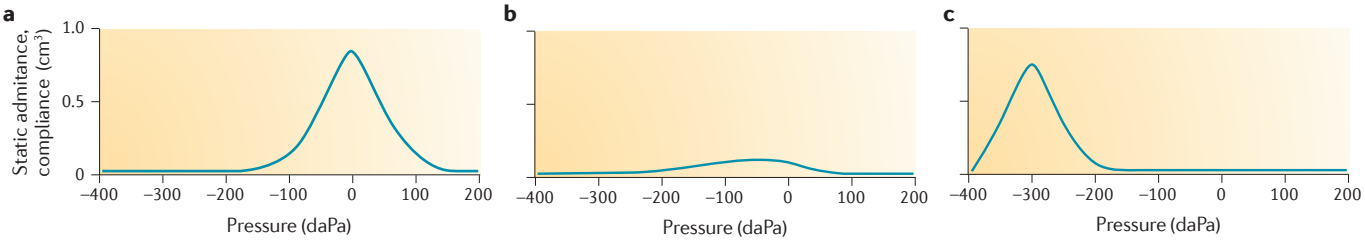

Figure 6 | **Tympanogram.** The tympanometric curve, or tracing, is categorized as type A, B or C based on middle ear pressure and the presence or absence of a discernable peak. **a** | The type A tympanogram curve has a sharp peak and normal middle ear pressure and therefore a low probability of middle ear effusion. **b** | 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 (earwax) 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 curve (intermediate probability of effusion) has negative middle ear pressure with a sharp (C1) or rounded (C2) peak.

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)[26,43,158,159]. Current guidance recommends avoidance of tobacco smoke exposure, recommends exclusive breastfeeding for ≥6 months and discusses other lifestyles changes, such as avoiding supine bottle feeding, reducing the use of a pacifier and considering alternative child care arrangements (for example, with smaller groups or using a child minder)[5].

Management

AOM

Symptomatic management of ear pain and fever with analgesics at the appropriate age-adjusted dose is the mainstay of AOM treatment[5]. Both oral paracetamol and ibuprofen are effective in relieving ear pain[161]. Topical analgesics might provide additional brief benefit, but current evidence on their effectiveness in relieving ear pain is limited[162]. An ongoing UK trial is assessing the clinical and cost-effectiveness of ear drops that contain a combination of benzocaine and phenazone compared with placebo drops and no drops in children 6–10 years of age presenting in primary care with AOM[163].

Oral antibiotics reduce the duration of AOM symptoms and consecutive MEE, but lead to adverse effects, such as gastrointestinal symptoms and skin rash[164]. 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[165]. Because AOM runs a favourable natural course in children who are otherwise healthy, with symptoms settling within a few days and complications being rare, the benefits and costs of antibiotic treatment need to be carefully weighed[164]. The benefits are most prominent in children <2 years of age with bilateral AOM and in those of any age presenting with acute ear discharge due to AOM[166]. Thus, current guidance recommends considering immediate antibiotics in these children[167]. Immediate antibiotic treatment is recommended in those with AOM who are <6 months of age, immunocompromised or have craniofacial malformations, as well as those with severe illness due to AOM[5,167]. 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[5,167]. Limited evidence suggests that amoxicillin (with or without clavulanic acid) is more effective than macrolides and cephalosporin[168], and, therefore, first-line treatment with cefdinir, cefuroxime or clarithromycin has been recommended as an alternative in patients with penicillin allergy[5,167]. When 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 to be effective or have shown conflicting results in resolving symptoms of AOM and are therefore not recommended[169,170]. Tympanocentesis or myringotomy, a small incision of the tympanic membrane that allows 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[171–173].

Recurrent AOM

Management of children with recurrent AOM focuses on the prevention of further AOM episodes. Although immunization with PCVs in early infancy has proven to be effective in reducing the risk of a child developing recurrent AOM[126], these vaccines are no longer effective for children with established recurrent AOM[134]. Antibiotic prophylaxis in children with recurrent AOM reduces the number of AOM recurrences by 1.5 per year (from 3 recurrences to 1.5)[174]. 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 recurrent AOM has not been fully established (FIG. 7). Evidence on the benefits of ventilation tubes is mainly available for the first 6 months after insertion: with approximately one AOM episode being

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prevented, the magnitude of its effect is modest[175–177]. Although not definitive, current evidence regarding natural history and treatment benefits suggests that ventilation tubes are not helpful for recurrent AOM without persistent MEE but are an appropriate option for managing recurrent AOM with persistent MEE in one or both ears at the time of assessment for tube candidacy[178].

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. Adenoidectomy — that is, surgical removal of the adenoid — is practiced in children with recurrent AOM 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 standalone operation or as an adjunct to ventilation tube insertion is most beneficial in children <2 years of age[179]. However, the magnitude of the effect of this surgical intervention is modest, so these benefits should be carefully balanced against any harms associated with this surgical procedure.

OME

The main sign or symptom of OME is hearing loss; thus, the management of OME is 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[180–182]. 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[178,183]. Ventilation tubes are an option in children with OME still with documented hearing difficulties after 3 months[178,183,184]. Adenoidectomy as a standalone operation or as an adjunct to tube insertion is most beneficial in children with OME ≥4 years of age[179]. In this subgroup of children, adjuvant adenoidectomy has been shown to reduce the need for ventilation tube re-insertions by around 10% compared with tubes alone[179]. The role of hearing aids to alleviate hearing loss in children with OME is unresolved[178]. 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 to be effective in clearing MEE and improving ear symptoms at 3 months in school-aged children presenting in primary care with a recent onset of OME[185]. However, the effects observed were modest with a number needed to treat to benefit of nine patients, at a cost of GBP£132 per case resolved[185]. 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 effectiveness and cost-effectiveness of a 7-day course of oral corticosteroids in children 2–8 years of age with persistent bilateral OME and hearing loss[186]. Balloon dilatation of the Eustachian tube has been proposed as a novel treatment for children with persistent OME. However, there is no evidence yet to support this management option[187].

Box 1 | **Risk factors for developmental difficulties in children with OME**

- Permanent hearing loss independent of otitis media with effusion (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

Ventilation tube-associated ear discharge

Many children with ventilation tubes develop episodes of acute ear discharge; reported incidence rates range from 26% to 75%[188–190]. These episodes may be accompanied by foul odour, pain and fever and can reduce the quality of life (QOL) of the child. They are thought to be the result of AOM, in which middle ear fluid drains through the tube. Risk factors include young age, recurrent AOM as the indication for tubes, recent history of recurrent URTIs and the presence of older siblings[189]. The formation of bacterial biofilms on the ventilation tube may also have a role, particularly 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 that occur at a later stage. Many perioperative interventions have been tested and have shown to be of some benefit in preventing early postoperative ear discharge: saline washout of the middle ear or application of antibiotics with or without corticosteroid ear drops during tube surgery and the use of topical or systemic antibiotics during the early postoperative period[191]. The largest effects of these interventions were found in studies in which the risk of children developing early postoperative ear discharge was high[191]. The bacterial otopathogens most commonly found in acute ear discharge occurring beyond the immediate postoperative period in children with ventilation tubes are *H. influenzae*, *S. aureus* and *P. aeruginosa*, and most infections are polymicrobial[192]. Most ototopical antibiotic formulations cover these pathogens. However, concerns about their potential ototoxic adverse effects when used in patients with a non-intact tympanic membrane have prompted many physicians to treat these children with systemic antibiotics. Quinolone (an antibiotic) ear drops have so far not shown ototoxicity and are recommended in the United States over systemic treatment[178]. Based on a recent landmark trial showing that ear drops containing a combination of antibiotics and a corticosteroid are the most clinically effective and cost-effective management strategy in children developing uncomplicated, acute ear discharge beyond the immediate postoperative period[193,194], current guidance recommends ototopical antibiotic drops as first-line treatment in these children[178]. There is some evidence that ear drops containing a combination of antibiotics and a corticosteroid are superior over those containing antibiotics alone[195,196].

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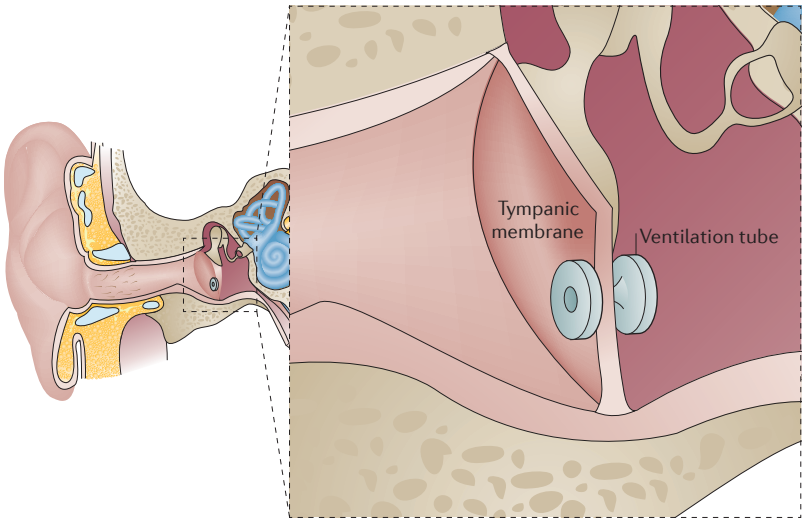

Figure 7 | **Ventilation tubes.** Ventilation (tympanostomy) tubes are tiny plastic tubes put into the tympanic membrane (eardrum) during a short operation under general anaesthesia. The tubes usually stay in place for 6–12 months and fall out themselves. The main indications for this surgical procedure are the restoration of hearing in children with chronic otitis media with effusion ('glue ear') and the prevention of recurrences in children who have recurrent acute otitis media (AOM) by draining the fluid from the ear and improving its ventilation. In addition, by providing access to the middle ear, ventilation tubes may allow for local antibiotic treatment of AOM rather than systemic treatment.

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 (<4 weeks)[197,198]. Current evidence assessing the effectiveness of quinolone-containing versus non-quinolone-containing eardrops is inconclusive[198], with quinolones having the advantage of being non-ototoxic[199]. Limited evidence suggests that treating patients with CSOM with a combination of systemic and topical antibiotics is not more effective than topical antibiotics alone[197]. Two reviews comparing two different autologous graft materials to repair tympanic membrane perforation (that is, temporalis muscle fascia tympanoplasty with cartilage tympanoplasty) found fewer postoperative tympanic membrane perforations with a cartilage graft but no differences in terms of hearing[200,201].

Quality of life

Measurement challenges

Traditionally, articles focusing on the impact of OM in terms of policy have focused on the economic burden of the relevant health care, which is, for example, US$5 billion annually in the United States[202]. As in other fields of medicine, formal measurement of QOL in patients with OM came late, dating mostly from the mid-1990s[203]. Most clinicians and researchers focus on capturing the effect of OM and OM management with disease-specific symptoms, not the effect 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[204].

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 questionnaire[205] 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 (REF. 203), its short form the OMQ-14 (REF. 206) and COMQ-12 for CSOM in adults[207], support from three to five scores. Brevity (few items) limits precision and reliability, and 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.

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, which are readily demonstrated in descriptive studies, rather than on health symptoms[208]. These sequelae are largely generic, although not totally comprehensive for generic QOL. The literature on QOL in patients with 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 a poor environment for social development gave the worst outcomes on IQ[209]. 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 >5 years of age, a 28-item (therefore, highly reliable) generic health questionnaire[210] showed consistent deficits on most subscales of QOL, even in those without concurrently active OM. In a very small uncontrolled study on the management of OME, pervasive QOL improvements measured by OM-6 were claimed after the insertion of ventilation tubes compared to before the surgery[211], but interpretation is unclear. This limited treatment literature suggests that effective interventions do not necessarily result in measurable magnitudes of QOL improvement[212].

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Recurrent AOM

A large study among children with chronic or recurrent OM showed that children with recurrent AOM or a combination of recurrent AOM and OME scored worse in four out of six domain items in the OM-6 scale (physical suffering, emotional distress, activity limitations and caregiver concerns) than children with OME alone[213]. In children with a history of OM diagnosed in primary and secondary care, the number of AOM episodes was found to be a strong determinant of QOL[214]. A primary care-based cohort study confirmed sleep disturbance as an important correlate of loss of QOL in parents of children with recurrent AOM[215]. In a clinical population of children with recurrent AOM, the effect on generic QOL equalled that of a comparison group of children with asthma[216], a useful measure on the magnitude of impact. Two studies have addressed the effect of the fact that QOL questionnaires are completed by the proxy (caregiver), given that the QOL of the caregiver is also affected by OM episodes of the child[214,215]. 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 recurrent AOM or those with combined recurrent AOM and OME resulted in an important improvement on the OM-6 scale[213]. 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 recurrent AOM[217]. Vaccination improved specific but not generic QOL outcomes[218].

Outlook

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

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 the risk of AOM in children[26,219]. 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 and focuses 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 numerous genetic polymorphisms have been described in genes encoding proteins involved in innate immunity, their clinical relevance to risk and severity of disease is still unknown in children. Improved understanding of the interactions between the host innate immune system and otopathogens may lead to a wider range of treatment options[220].

Diagnosis

AOM tends to be overdiagnosed (and thus overtreated), especially in the primary care setting, owing to difficulties of confirming MEE[93–95]. 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[221]. Future research is needed to investigate whether these techniques provide any added value over current diagnostic tests.

Biomarkers

Thus far, investigators have studied biomarkers in serum and nasopharyngeal secretions and have correlated them with AOM diagnosis, types of bacteria or viruses, and outcome. High serum levels of intercellular adhesion molecule 1 were found in children with AOM compared with healthy children[222]. At the time of AOM onset, the serum levels of S100-A12 were increased, which returned to normal during recovery[223]. In children with AOM, high serum concentrations of granulocyte colony-stimulating factor predicted RSV-induced AOM, whereas high concentrations of IL-13 predicted early clinical failure of antibiotic treatment[224]. Increased serum concentrations of IL-10 were associated with pneumococcal-induced AOM[225]. A serum biomarker risk score has been developed to predict the presence and recovery from AOM caused by non-typeable *H. influenzae*[226]. In nasopharyngeal secretions, IL-1B and lactate dehydrogenase concentrations were associated with the risk for AOM development after viral URTI[65,227]. Together, these data indicate 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 the incidence of OM, widespread use of PCVs has been associated with shifts in pneumococcal serotypes and the increased importance of non-typeable *H. influenzae* as a cause of AOM[25,26,28,126–131]. There is a need for effective pneumococcal vaccines

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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[228–233]. So far, influenza virus vaccination is the only viral vaccine that has shown 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 the development of RSV vaccines; numerous RSV vaccines are in phase I and phase II trials[234]. Further work is needed to establish whether other viral vaccines are able to prevent OM[231]. Probiotics have been used in the prevention of OM with some encouraging results[154–157], 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 (REF. 52). There are clear regional and temporal differences that have been influenced by the introduction of PCVs. Hence, it is important that ongoing microbial surveillance is introduced to monitor shifts in causative otopathogens.

Treatment

Remarkably, most trials so far of OM have excluded the children that are most prone to the condition: those with Down syndrome and craniofacial malformations, such as cleft palate. High-quality studies evaluating the use of screening for OME and the effectiveness of various management strategies in these 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. The topical antibiotic approach has proven very effective in children with ventilation tubes[193], but it is uncertain if these results are also applicable to children without tubes[235]. In addition, ongoing research on trans-tympanic delivery of drugs (that is, without a tympanic membrane perforation or tube) is very promising. In a chinchilla model, the application of an antibiotic-containing (ciprofloxacin) gel to the tympanic membrane achieved antibiotic concentrations in middle ear fluid that were adequate for AOM treatment[236,237]. 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[178]. In CSOM, various novel adjuvant treatments have been tested aimed at enhancing the repair of tympanic membrane perforation, including biomolecules to stimulate growth of the perforated edges and bioengineered scaffolds[238,239]. Further work is necessary to establish the role of these treatments 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 (for more information see http://www.comet-initiative.org; http://www.ichom.org; http://www.ideal-collaboration.net; and http://www.invo.org.uk). 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[240]. 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 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 capacity to change practice for the better.

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Competing interests
The authors declare no competing interests.

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