Otitis media (OM) continues to be one of the most common childhood infections and is a major cause of morbidity in children. The pathogenesis of OM is multifactorial, involving the adaptive and native immune system, Eustachian-tube dysfunction, viral and bacterial load, and genetic and environmental factors. Initial observation seems to be suitable for many children with OM, but only if appropriate follow-up can be assured. In children younger than 2 years with a certain diagnosis of acute OM, antibiotics are advised. Surgical candidacy depends on associated symptoms, the child's developmental risk, and the anticipated chance of timely spontaneous resolution of the effusion. The recommended approach for surgery is to start with tympanostomy tube placement, eventually followed by adenoidectomy. The ideal intervention for OM, however, does not yet exist, and an urgent need remains to explore new and creative options based on modern insights into the pathophysiology of OM.

Otitis media (OM) is one of the most common childhood infections, the leading cause of doctors' visits by children,' and the most frequent reason children consume antibiotics or undergo surgery in developed countries. Annual costs in the USA are about US$3–5 billion, but the true impact is probably underestimated because indirect costs might be substantially higher.4

Acute OM (AOM) and otitis media with effusion (OME) are different stages of the OM continuum. AOM is defined as the presence of middle-ear effusion (MEE) in conjunction with the rapid onset of one or more signs or symptoms of inflammation in the middle ear, such as otalgia, otorrhoea, fever, or irritability.5 OME is defined as MEE without signs or symptoms of an acute infection.6 Although both disorders require MEE for diagnosis, the main clinical difference is the absence of acute signs and symptoms with OME. OME may occur de novo or as a sequel to AOM.7

The high incidence and high rate of spontaneous recovery from OM suggest that it is a natural phenomenon, inevitable like a common cold, and part of the gradual maturation of the child's immune system. Conversely, untreated AOM can lead to supplicative complications, such as acute mastoiditis. Hearing loss caused by OM might lead to behavioural changes and delays in communicative development.8,9 Antibiotics and surgery have only moderate efficacy for OM,9,10 and the former have potentially serious side-effects such as an increased antibiotic resistance.11 Management of OM, therefore, remains challenging and controversial.

Otitis media (OM) continues to be one of the most common childhood infections and is a major cause of morbidity in children. The pathogenesis of OM is multifactorial, involving the adaptive and native immune system, Eustachian-tube dysfunction, viral and bacterial load, and genetic and environmental factors. Initial observation seems to be suitable for many children with OM, but only if appropriate follow-up can be assured. In children younger than 2 years with a certain diagnosis of acute OM, antibiotics are advised. Surgical candidacy depends on associated symptoms, the child's developmental risk, and the anticipated chance of timely spontaneous resolution of the effusion. The recommended approach for surgery is to start with tympanostomy tube placement, eventually followed by adenoidectomy. The ideal intervention for OM, however, does not yet exist, and an urgent need remains to explore new and creative options based on modern insights into the pathophysiology of OM.

The rise in the number of publications listed on PubMed about OM from 250 in 1967 to 720 in 2000 reflects advances in all areas. Here we summarise the current state of knowledge, including advances in epidemiology, pathogenesis, diagnosis, clinical management, and prevention. To keep bias to a minimum we have used, whenever possible, systematic reviews and meta-analyses published by professional organisations12,13,19–23 and independent researchers.18–20 These integrative reports facilitate clinical decisions and serve as the policy foundation for evidence-based practice guidelines, economic assessments, and future research agendas.24

Advances in epidemiology

Most children have at least one episode of AOM, with a peak incidence between ages 6 and 11 months; by age 3 years, 50–85% of children have had acute OM.15,16 Recurrent AOM (≥3 episodes) is common, affecting 10–20% of children by age 1 year. Nearly 40% of older children eventually have six or more total episodes.26

The lack of acute symptoms with OM makes prevalence difficult to estimate, but the point prevalence of MEE on screening tests is about 20%.36 Peak incidence is at roughly age 1 year.25,26 In children with OME, the recurrence rate within 24 months is 50%.37 By age 3 years,
nearly all children have experienced at least one episode of MEE (includes AOM and OME). AOM and OME have high rates of spontaneous resolution.

Findings in population-based studies from Finland and the USA suggest increases in OM incidence of 68% and 39%, respectively, over the past 10–20 years. These trends should, however, be interpreted cautiously because changes in health-care systems, access to and use of care, and awareness of OM might have increased.

**Advances in pathogenesis**

OM is mainly an infectious disease, resulting from interplay between microbial load (viral and bacterial) and immune response. All factors known to cause OM relate to these two core elements (figure 1): host factors, such as age, genetic predisposition, and atopy relate to the impaired immune system, whereas environmental factors such as siblings (generally older), group day care, and season of year relate to microbial load. The Eustachian tube is the port of entry for middle-ear pathogens from the nasopharynx and Eustachian tube. This congestion causes congestion of the upper-respiratory mucosa, including the nasal mucosa, the nasopharynx, and Eustachian tube. The congestion causes tubal dysfunction with impaired clearance and pressure regulation of the middle ear. If sustained, the dysfunction might be followed by aspiration of potential pathogens (viruses and bacteria) from the nasopharynx to the middle ear. Bacteria or by-products stimulate local resident cells, attracting immune-effector cells and provoking the inflammatory response largely responsible for clinical manifestations.

The onset of OME, although it has fewer symptoms than AOM, probably involves a similar sequence of events. Excessive mucin production overwhelms normal mucociliary clearance mechanisms, resulting in a fluid-filled middle-ear cavity. The inciting factor is frequently residual inflammation after bacterial killing in AOM. In this context, OME might be viewed as a hangover or natural sequelae of AOM, which can take weeks or months to completely resolve. Conversely, the inciting factor might be de-novo MEE from inflammation of the middle-ear mucosa or inadequate pressure regulation caused by tubal dysfunction.

We describe factors involved in OM pathogenesis in greater detail, although none is pathognomonic. Several mechanisms might be involved in succession, but they probably act simultaneously.

**Eustachian-tube dysfunction**

For many years, physical obstruction of the Eustachian tube was thought to produce MEE because of negative middle-ear pressure and fluid transudation (ex vacuo theory). Presently, more complex theories describe the crucial role of the Eustachian tube in maintaining a healthy middle ear by: equilibration of pressure between the middle ear and ambient air (ventilatory function); protection against nasopharyngeal pressure variations and ascending secretions or pathogens (protective function); and clearance of secretions and debris towards the nasopharynx (clearance function).

Infants and young children are prone to OM because their Eustachian tubes are short, floppy, horizontal, and function poorly. Maturation of the tube is a gradual process, which explains the infrequency of OM after age 6–7 years. Eustachian-tube function can also be disturbed by endogenous or exogenous disorders, including viral infection of the nasopharynx and distal tube. Gastric acid may reflux into the middle ear, causing Eustachian-tube dysfunction and subsequent bacterial infection.

**Microbiology**

Streptococcus pneumoniae, Moraxella catarrhalis, and non-typeable Haemophilus influenzae are the predominant bacterial pathogens that cause OM. Penicillin resistance for pneumococci varies worldwide, ranging from less than 1% in the Netherlands, to 10–40% in the USA, and more than 80% in Korea and the Far East. β-lactamase is produced by about 20–50% of H influenzae and nearly all M catarrhalis. The impact of resistance on clinical outcomes, however, has been less striking because of the high rate of spontaneous OM resolution.

Viruses are an increasing cause of OM, alone or with bacterial co-pathogens. All respiratory viruses contribute, but viral OM is most frequently caused by respiratory syncytial virus or rhinovirus. Viral infection can substantially worsen clinical and bacteriological outcomes of OM. Exactly how viruses increase or extend middle-ear inflammation is unclear, but bacterial OM with viral co-infection has higher concentrations of some inflammatory mediators than bacterial OM alone.

**Immunology**

Waldeyer’s ring belongs to the mucosa-associated lymphoid tissue, which forms the primary defence against pathogens at the port of entry of the upper-respiratory tract—ie, the nasopharynx. The lymphoid cells of the adenoid can recognise and destroy nasopharyngeal pathogens. In addition, effector and memory lymphocytes are produced that migrate to neighbouring mucosal sites to reinforce the local immune capacity.

Local production of secretory antibodies is another immunological defence mechanism of the upper-respiratory tract. Secretory IgA in nasopharyngeal secretions inhibits pathogen adherence (viral and...
bacterial) and reduces nasopharyngeal bacterial colonisation, which are both important protective factors against OM. Children with recurrent OM might lack secretory IgA. IgG also contributes to the immunological defence against OM. Children who have recurrent OM have low specific IgG2 antibodies to the polysaccharide capsule, which could be caused by immaturity of the immune response. Passively infused IgG antibodies against pneumococci protect against OM in experimental models.

Inflammation by bacterial or viral pathogens leads to complex regulation of cytokine production, each with its own potential role in OM pathogenesis. Tumour necrosis factor and interleukin 1 are prominent initial mediators, and interleukin 8 might be related to chronic inflammation. Cytokines also induce up-regulation of mucin genes resulting in secretion of mucin-rich fluid in the middle ear. Altered viscosity of MEE subsequently impairs mucociliary clearance. Other contributing factors of the adaptive and native immune system are currently being studied.

**Genetics**

In twin studies, monozygotic twins have a higher concordance rate in OM histories than dizygotic twins, which suggests a strong genetic component. The genetics of OM are, however, complex with many genes probably contributing. Recurrent OM is associated with genetically determined immunoglobulin markers, including allotype G2m(23). HLA-A2 antigen is associated with recurrent AOM, but not with OME. No clear association between the polymorphism of cytokine genes and recurrent AOM has been shown so far. Only in a subgroup of patients without allergic disorders was the interleukin 1-α gene polymorphism associated with recurrent OM.

OM might be initiated by up-regulation, activation, or both, of mucin genes, of which 12 have been identified in human beings. MUC1, MUC3, and MUC4 are membrane associated and might have a role in the adhesion of micro-organisms. MUC5AC and MUC5B might have a role in the accumulation of mucus and fluid in the middle-ear cavity.

**Environment**

Data from observational studies have been pooled in two meta-analyses to identify risk factors for AOM. AOM has a negative association with breastfeeding for 3 months or longer (relative risk 0.87) and positive associations with pacifier use (1.24), parental smoking (1.66), positive family history (2.63), and day care outside the home (2.45). Attendance of day care is the most consistent environmental risk factor for OM, with relative risk being proportionate to the number of children in a setting.

Having siblings (generally older) is also a risk factor, which, similar to day care, increases the incidence of upper-respiratory-tract infections. Conversely, findings have been less consistent for the decreased risk of OM related to breastfeeding (immunological properties of breastmilk) and increased risk with environmental tobacco smoke (reduced ciliary-beat frequency). Similarly, the association of OM with low socioeconomic status varies among studies.

**Advances in diagnosis**

MEE is a prerequisite for AOM and OME. Compared with myringotomy, which is the gold standard, pneumatic otoscopy offers the optimum balance of sensitivity (94%) and specificity (80%) in diagnosing MEE. Pneumatic otoscopy requires clinical skills because it combines visual assessment of tympanic-membrane mobility and appearance. Tympanometry is a simple and objective quantitative method of assessing tympanic-membrane mobility and middle-ear function, with similar sensitivity but lower specificity. Tympanometry results can be classified with quantitative measures (gradient or static admittance) or by pattern curves (A, C1, C2, or B).

Tympanometry with use of a type B (no impedance peak) or C2 curve (peak pressure <–200 mm water) as abnormal has 94% sensitivity for MEE but only 62% specificity. Acoustic reflectometry can also diagnose MEE, but studies are heterogeneous and performance is poorer than pneumatic otoscopy or tympanometry.

MEE associated with AOM may be documented by use of myringotomy, otorrhea through a tympanic-membrane perforation, or by limited or absent tympanic-membrane mobility on pneumatic otoscopy or tympanometry. The tympanic membrane might be full, bulging, opacified, or erythematous. Over 48 h, one or more signs or symptoms of middle-ear inflammation develop rapidly, including otalgia or pulling of the ear in infants, otorrhea, irritability in infants or toddlers, or fever. No one specific sign or symptom can reliably predict AOM, the importance of a red tympanic membrane is controversial.

MEE associated with OME can be detected by screening or as an incidental finding because there are no acute infectious symptoms. Some children, however, manifest non-infectious discomfort, including hearing loss, irritability, clumsiness, or sleep disruption. Preschool and entrant screening programmes for OME are of uncertain efficacy, but aggressive screening to identify and treat asymptomatic infants with persistent OME does not improve developmental outcomes.

Most children with OME have mild hearing impairment, with mean three-frequency pure-tone average hearing levels of 25 dB. Overall, hearing levels range from 10 to 40 dB, based on the volume (not viscosity) of MEE. Parents' reports are unreliable for assessment of the presence or absence of OM-related hearing loss, and cannot substitute for formal audiological assessment of infants or children with persistent OME.

**Advances in clinical management**

**Watchful waiting vs initial antibiotics for AOM**

In three independent meta-analyses (table 1), with varying sample sizes and methods of data pooling, around 80% of children with AOM had spontaneous clinical relief within 2–14 days, with a 95% CI of about 70–90%. The rate for children younger than 2 years is less certain because not all source articles contained young children. Findings from studies restricted to this population suggest a lower spontaneous resolution of about 30% after a few days. All rates exclude MEE, which normally resolves within 3 months of an AOM episode.

High rates of spontaneous resolution plus only slight benefits from antimicrobials (table 2) suggest that some children with AOM are suitable for initial observation. Cates reduced median antibiotic prescriptions by 31%, compared with 12% in a control practice, when children with non-severe AOM were given a safety-net prescription, which parents redeemed only if children did not improve within 2 days. When Little and colleagues randomly assigned 315 children aged 6 months to 10 years with AOM to initial or deferred antibiotics, only 24% of the deferred group eventually filled the prescription. The New York State Department of Health

For personal use. Only reproduce with permission from The Lancet.
distributed guidelines for judicious observation of children with AOM (table 3).49-60 These guidelines were developed according to the principles of evidence-based medicine and discussed with participants from the Netherlands, UK, Agency for Healthcare Research and Quality, and the Center for Disease Control.

The withholding of initial antibiotics from mostly older children with AOM does not increase suppurative complications in randomised trials.2 Whether restrictive antibiotic use increases acute mastoiditis at the population level is also unresolved, but the potential increase is only two cases per 100,000 person-years and must be weighed against potential adverse effects.96 Risks of antibiotics include allergic reactions, gastric upset, accelerated bacterial resistance, and unfavourable changes in nasopharyngeal bacterial flora.97-100 Antibiotics can not only fail to eradicate the organisms, but can induce MEE without oral steroids have significant benefits, they are small in magnitude (15-20% absolute rate increase) and only transient (no difference after a few weeks).19,23,25-33 Medical interventions other than antibiotics and steroids have unproved efficacy for OME, including antihistamine-decongestant combinations,19-25 oral mucolytics,26 and Eustachian-tube autoinflation.11

Favourable rates of spontaneous resolution plus only slight and transient benefits of antibiotic treatment suggest that most otherwise healthy children with OME be observed for 3 months or longer before intervention is considered. Antibiotics, if used, should be given in one 10-day course; longer, repetitive, or prophylactic regimens are ineffective and inappropriate. Oral steroids have a very limited role in management because of only transient benefits and significant potential adverse reactions (behavioural changes, weight gain, idiosyncratic reactions). Antihistamines and decongestants are ineffective for OME.19

Table 1: Meta-analyses of otitis media natural history and spontaneous resolution

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Time</th>
<th>Result* (% [95% CI])</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasziou, 1994</td>
<td>Acute OM clinical cure</td>
<td>7-14 days</td>
<td>81 (69-94)</td>
<td>Weighted regression</td>
</tr>
<tr>
<td>Marcy, 2001</td>
<td>Acute OM clinical success†</td>
<td>1-7 days</td>
<td>81 (72-90)</td>
<td>Random effects</td>
</tr>
<tr>
<td>Marcy, 2001</td>
<td>Acute OM pain free</td>
<td>24 h</td>
<td>62 (56-67)</td>
<td>Binomial proportion</td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Acute OM pain free</td>
<td>2-7 days</td>
<td>79 (77-82)</td>
<td>Binomial proportion</td>
</tr>
<tr>
<td>Takata, 2002</td>
<td>OME tymp B→A</td>
<td>3 months</td>
<td>23 (6-39)</td>
<td>Random effects, age &gt;3 years</td>
</tr>
<tr>
<td>Takata, 2002</td>
<td>OME tymp B→C→A</td>
<td>3 months</td>
<td>43 (29-56)</td>
<td>Random effects, age &gt;3 years</td>
</tr>
<tr>
<td>Rosenfeld, 2003</td>
<td>OME tymp B→A</td>
<td>3 months</td>
<td>28 (14-41)</td>
<td>Random effects, age &gt;2 years</td>
</tr>
<tr>
<td>Rosenfeld, 2003</td>
<td>OME tymp B→A/C</td>
<td>3 months</td>
<td>51 (56-61)</td>
<td>Random effects, age &gt;2 years</td>
</tr>
</tbody>
</table>

Tymp A=tympanogram peak < -100 mm water. Tymp B=flat tympanogram with no peak. Tymp C=tympanogram peak > -199 mm water. *Rate of spontaneous resolution for placebo controls or untreated cohort. †Reported originally as clinical failure; transformed for consistency with other studies.

Table 2: Meta-analyses of antimicrobials for treating or preventing acute OM

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Time</th>
<th>Result* (% [95% CI])</th>
<th>Number needed to treat Tacoma, 2002</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams, 1993</td>
<td>Acute OM per child-month, sulfisoxazole prophylaxis</td>
<td>10 weeks to 2 years</td>
<td>Absolute rate difference 0-20 (0.07 to 0.32)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bonati, 1992</td>
<td>Any acute OM in trial, antibiotics prophylaxis</td>
<td>2-6 months</td>
<td>Absolute rate difference 0-11 (0.03 to 0.19)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Williams, 1993</td>
<td>Any acute OM in trial, antibiotics prophylaxis</td>
<td>10 weeks to 2 years</td>
<td>Absolute rate difference 0-0 (0.00 to 0.03)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Clinical cure, antibiotics vs no antibiotics‡</td>
<td>7-14 days</td>
<td>Absolute rate difference 0-14 (0-09 to 0-19)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Clinical improvement, antibiotics vs placebo</td>
<td>&lt;7 days</td>
<td>Odds ratio 1-31 (0-83 to 2-08)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Marcy, 2001</td>
<td>Clinical failure, amoxicillin vs no antibiotics‡</td>
<td>2-7 days</td>
<td>Absolute rate difference 0-12 (0-22 to 0-03)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Persistent pain, antibiotics vs placebo</td>
<td>24 h</td>
<td>Odds ratio 1-03 (0-76 to 1-39)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Persistent pain, antibiotics vs placebo</td>
<td>2-7 days</td>
<td>Odds ratio 0-61 (0-48 to 0-77)</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Abnormal tym, antibiotics vs placebo</td>
<td>1 month</td>
<td>Odds ratio 0-91 (0-62 to 1-32)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Recurrent acute OM, antibiotics vs placebo</td>
<td>2 months</td>
<td>Odds ratio 0-57 (0-36 to 0-91)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Bonati, 1992</td>
<td>Any acute OM in trial, antibiotics prophylaxis</td>
<td>2-6 months</td>
<td>Odds ratio 0-23 (0-16 to 0-34)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Clinical cure, antibiotics vs no antibiotics‡</td>
<td>2-7 days</td>
<td>Absolute rate difference 0-14 (0-09 to 0-19)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Glasziou, 2002</td>
<td>Clinical improvement, antibiotics vs placebo</td>
<td>&lt;7 days</td>
<td>Odds ratio 1-31 (0-83 to 2-08)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Marcy, 2001</td>
<td>Clinical failure, amoxicillin vs no antibiotics‡</td>
<td>2-7 days</td>
<td>Absolute rate difference 0-12 (0-22 to 0-03)</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

NS=not significant, Tymp=B-tympanogram. *Outcome more common in antibiotic group when absolute rate difference >0 or odds ratio >1. †Number needed to treat to achieve one successful outcome; relevant only if p<0.05. ‡All studies, except one, placebo controlled. Number needed to treat calculated as reciprocal of random effects absolute rate difference with use of raw data provided by researchers.
in assessing surgical candidacy explain the impressive small-area variations in tube insertion rates, which are strongly influenced by opinions of the primary-care physicians.\textsuperscript{114} Asymptomatic children with a persistent OME identified by screening or intense surveillance generally derive minimal benefits from surgery.\textsuperscript{115,116} Conversely, symptomatic children with OME who present for assessment have larger changes in quality of life and development.\textsuperscript{117,118} The impact of surgery on high-risk children with OME has not been assessed in randomised controlled trials because of ethical and logistic concerns.

Surgical candidacy for otitis media depends largely on associated symptoms (eg, otalgia, hearing loss), the child's developmental risk (table 4), and the anticipated chance of timely spontaneous resolution of the effusion. For a particular child, surgery is appropriate if the objective benefits are deemed meaningful, particularly from the standpoint of language, learning, and overall development (table 4). Duration of OME should not be the sole operative criterion. A healthy child with chronic bilateral OME but normal development could be safely observed for months or even years until spontaneous resolution occurs, but a high-risk child could be a surgical candidate after weeks or months, dependent on individual circumstances. Extended observation (eg, more than 6–12 months) of any child with significant MEE-associated hearing loss is not recommended.

When a decision is made to proceed with surgery for otitis media, we recommend the following approach based on methodologically sound clinical trials. For initial surgery use myringotomy and tympanostomy tube placement and withhold adenoidectomy unless nasal obstruction is present. For repeat surgery, use myringotomy, with or without tube placement, and adenoidectomy, irrespective of adenoid size. Tonsillectomy should be withheld unless other indications for surgery exist, such as frequently recurrent tonsillitis or pharyngeal obstruction.

Tonsillectomy alone—ie, without adenoidectomy—is not recommended to treat OME. Although tonsillectomy is ineffective\textsuperscript{119} or of limited efficacy,\textsuperscript{15} the risks of haemorrhage (about 2%) and additional hospital admission outweigh any potential benefits unless a distinct indication for tonsillectomy exists. Myringotomy alone, without adenoidectomy or tube insertion, is ineffective for OME, because the incision closes within several days, which is insufficient for mucosal recovery.\textsuperscript{108,110} Laser-assisted myringotomy extends the ventilation up to 3 weeks,\textsuperscript{112} but efficacy has not been shown in randomised trials.

**Table 4: Factors affecting threshold for surgical intervention in children with OM**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Lowers surgical threshold</th>
<th>Raises surgical threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmentally at-risk child*</td>
<td>Yes (major factor)</td>
<td>No</td>
</tr>
<tr>
<td>Hearing and auditory function</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Language or academic achievement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal or delayed</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Tympanic membrane structure</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Unfavourable†</td>
<td>Favourable</td>
</tr>
<tr>
<td>Recurrent acute OM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imbalance, clumsiness, vertigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*§Cleft palate, Down’s syndrome, autism spectrum disorder or other pervasive developmental disorder, attention deficit or hyperactive disorder, speech or language delays, syndrome or cranial facial disorder, sensorineural hearing loss, psychomotor retardation or sensory defects, intellectual impairment, cognitive deficits, or problems at school. †Epistaxis, retraction pocket, or thickened and hypervascular tympanic membrane. ‡Environmental tobacco smoke; group day care (≥4–6 children); less responsive home or childcare environment. §Physical symptoms, sleep disturbance, emotional distress, activity limitations, etc.

**Figure 2: Four pictures of tympanic membrane**

Complications and sequelae
Complications during AOM episodes include perforation of the tympanic membrane, mastoiditis, facial paralysis, labyrinthitis, and external otitis. Disturbance in vestibular, balance, and gross motor function can also occur.

The MEE that accompanies AOM and OME may have developmental consequences, because of long-term or frequent episodes of hearing loss. Conclusive evidence is lacking, however, that temporary hearing loss affects language development, behaviour, or quality of life for most otherwise healthy children. Negative effects have been reported mainly in the first years of life, especially for language development, but results vary greatly among studies. Conflicting findings might be caused by shortcomings in methods, such as failure to confirm the duration and severity of the OM or the level of hearing impairment. In other studies, potential confounders that also contribute to a child's communicative skills, such as the intelligence quotient of the child or the educational level of the parent, have not been taken into account.

Advances in prevention
Research in the past decade has focused on pneumococcal vaccines for preventing OM, because *S pneumoniae* is the most common bacterial pathogen. The 23-valent polysaccharide vaccine covers 90% of all known pneumococcal infections in developed countries, but has no efficacy for preventing OM in children younger than 2 years. The vaccine has marginal benefit for older children, favouring those with previous AOM episodes.

The conjugate vaccines, in which the pneumococcal capsular saccharides are covalently coupled to a carrier protein, are immunogenic in children as young as 2 months. Three immunisations in healthy infants at the age of 2, 4, and 6 months are highly effective against invasive pneumococcal infections. For mucosal infections such as AOM, however, efficacy is only marginal with 6–7% fewer episodes. In children followed up to age 3–5 years, vaccination reduced OM visits by 8%, antibiotic prescriptions by 6%, recurrent AOM by 10–26%, and tube insertions by 24%. Reduced efficacy for OM compared with invasive disease may be caused by any of the other pathogens causing AOM, or non-vaccine serotypes that replace vaccine-type pneumococci in the nasopharynx

Viral vaccines can also prevent AOM. In four randomised trials of influenza virus vaccine, prevention of antecedent viral infection prevented AOM. Fewer episodes of AOM were reported in vaccinated children than in unvaccinated children during the influenza season (30–36% relative reduction), but only small differences were seen over a follow-up period of 1 year. Respiratory syncytial virus is recovered from the middle ear more than other viruses, and is especially capable of causing middle-ear inflammation. An effective vaccine against respiratory syncytial virus might substantially reduce AOM incidence, but the multifactorial pathogenesis of OM suggests that a combined viral-bacterial vaccine is required.

Xylitol is a polyol sugar-alcohol that inhibits the growth of *S pneumoniae*, which could potentially reduce pneumococcal carriage and subsequent AOM. In two randomised trials, xylitol chewing gum reduced AOM incidence by 46%, but the dosing schedule (five times daily) is unacceptable to most families. Conversely, xylitol consumed only during upper-respiratory-infection episodes was ineffective in preventing AOM.

Several approaches to preventing AOM have been unsuccessful. Although suppression of virus-induced host inflammatory response in the nasopharynx might prevent AOM, intranasal fluticasone propionate administered during viral upper-respiratory infections has no effect and might increase AOM incidence. Despite their ability to prevent bacterial adhesion to respiratory cells, oligosaccharides were ineffective in preventing AOM in a randomised trial in 507 children.

Other preventive approaches that have been studied and for which an effect has been seen include probiotics, *streptococci*, immunoglobulins, and antiviral treatment with a neuraminidase inhibitor (oseltamivir). Further clinical investigation is, however, warranted to confirm these findings.

Antimicrobial prophylaxis can successfully prevent AOM (table 2), but the impact is small—about 0·11 episodes per month of prophylaxis. Prevention of one episode of AOM would, therefore, entail 9 months of prophylaxis for one child. This small benefit must be balanced against drug-induced side-effects and bacterial resistance, suggesting that prophylaxis should be used infrequently and for short duration, such as until the end of the viral upper-respiratory-infection season.

Future direction
The ideal intervention, preventive or curative, for OM would be non-toxic and have sustained efficacy for at least several months. Such an intervention does not yet exist, and, therefore, an urgent need remains to explore new and creative treatments based on modern insights into the pathophysiology of OM.

Conflict of interest statement
None declared.

Acknowledgments
We thank Lieke Sanders, Department of Pediatric Immunology, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, for commenting on an earlier draft.

References


19 Zegers BJM. Immunoglobulin isotype-specific antibody responses to respiratory viruses in the middle ear during acute otitis media. Vaccine 1999; 17: 2064–70.


28 Zegers BJM. Immunoglobulin isotype-specific antibody responses to respiratory viruses in the middle ear during acute otitis media. Vaccine 1999; 17: 2064–70.


