# Acute otitis media in children-current treatment and prevention.

Gisselsson-Solén, Marie

*Published in:*
Current Infectious Disease Reports

*DOI:*
10.1007/s11908-015-0476-7

2015

# Acute Otitis Media in Children – Current Treatment and Prevention

Marie Gisselsson-Solen, MD, PhD, MSc
Dpt of Otorhinolaryngology, Head and Neck Surgery
Lund University Hospital
22185 Lund
Sweden

Tel +46 46 172815
Fax +46 46 171758

marie.gisselsson-solen@med.lu.se

**Key words**

Acute otitis media; treatment; prevention; antibiotics, watchful waiting, guidelines, vaccination, grommets, adenoidectomy

**Abstract**

Acute otitis media (AOM) is the most common bacterial infection in children, and has a very varied clinical spectrum, ranging from spontaneous resolutions to serious complications. The effect of antibiotics in AOM depends on the chosen outcome, but has been shown to reduce pain somewhat, and have a greater beneficial effect in severe cases of AOM. Today, not all episodes of AOM are treated with antibiotics, but most countries have issued guidelines that include an option of watchful waiting in many cases. Prevention of AOM reaches from modification of environmental risk factors to vaccinations and surgery. Conjugate pneumococcal vaccines and influenza vaccines have been shown to somewhat reduce the number of AOM episodes in different groups of children. Grommets, with or without adenoidectomy, are effective at least during the first 6 months after surgery.

# Acute Otitis Media in Children – Current Treatment and Prevention

## 1. Introduction

Acute otitis media (AOM) is the most common bacterial infection in children, and consequently the most common reason for antibiotic prescriptions in this age group. It is estimated that 50-80% of children experience at least one episode of AOM before their third birthday. The peak incidence is between 6 and 15 months[1]. Many episodes are self-healing, but some result in serious complications, of which the most important are mastoiditis, meningitis, facial paralysis, labyrintitis and sigmoid sinus thrombosis. In the pre-antibiotic era, complications to AOM were an important cause of child mortality. The most common bacteria are *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes*, the two streptococcal species being the most frequent in cases with complications. Bacteria residing in the nasopharynx enter the middle ear via the Eustachean tube, more frequently so during colds and other viral infections. 10-15% of all children have recurrent infections, defined as ≥3 episodes in 6 months or ≥4 in 12 months[2, 3].

## 2. Treatment

### *2.1 Antibiotics or watchful waiting?*

AOM is a disease with an extremely varying clinical picture, ranging from spontaneous recovery to life-threatening complications. This variability depends largely on the pathogen, with the two streptococcus-species often resulting in severe disease and sometimes in complications[4, 5], whereas the gram-negative pathogens result in milder infections and rarely cause complications. The main reason for treating AOM with antibiotics is to prevent complications. In developed countries, antibiotic treatment for AOM was almost universal from the 1950:s until the late 1990:s, when, starting in the Netherlands[6], the necessity of this strategy was questioned. As high antibiotic use has been associated with a high prevalence of resistant nasopharyngeal pathogens and vice versa[7-9], it seemed reasonable to limit the use of antibiotics in a disease with a high rate of spontaneous recovery. In 1990, the prevalence of antibiotic treatment for acute otitis media varied from 31 per cent in the Netherlands to more than 90 per cent in the USA, Australia, New Zealand, England and Wales[10]. In the last 25 years, most countries have followed suit and issued guidelines that advocate “watchful waiting” in many cases of AOM (Table 1).

The essence of the watchful waiting strategy is to primarily withhold antibiotics but to give the patient a possibility for a second examination and reconsideration of whether antibiotics are needed if the symptoms worsen or do not improve within 2-3 days. An alternative to this is to provide the patient with a “reserve prescription” that can be used in the above situation. Studies have shown that approximately one third of reserve prescriptions are filled[11, 12].

An important and unanimously agreed upon aspect in all cases of AOM, regardless of whether the patient is subject to watchful waiting or is given antibiotics, is to prescribe adequate analgesia.

Some patients have been shown to benefit more from antibiotics than others, and are prescribed antibiotics at the first consultation. Different countries have in their guidelines made different decisions on whom to include in this latter group, but children under 6 or 12 months, patients with a spontaneously perforated tympanic membrane, children below 2 years of age with bilateral AOM and adult patients are frequently found in this group, whereas most guidelines recommend that routine antibiotic prescription should be avoided in mild to moderate cases and when there is diagnostic uncertainty.

The efficacy of antibiotics for AOM is something that has been debated extensively. To date, less than 20 RCT:s evaluating the effect of antibiotics compared to either placebo or watchful waiting have been published. These trials have reported very varying effects of antibiotics, but have also been very heterogeneous. They have used varying inclusion criteria, thus being more or less stringent in their diagnosis, meaning that some trials have allowed inclusion of children with otitis media with effusion, myringitis or even the common cold, thus making the results of these trials less applicable for children with a certain diagnosis of AOM. The exclusion criteria have also varied, for example, children with more severe AOM or children below the age of 1 have often been excluded, thus again reducing the applicability of the results for these groups. Various types of antibiotics have been used, and it is likely that the effect of an antibiotic with a certain antimicrobial profile and a certain degree of penetration into the middle ear differs from another antibiotic with other characteristics. Trials have also used different outcomes with varying specificity, something that can affect the effect size[13]. For example, if the outcome is pain relief, which is an outcome rather unspecific for AOM, the effect of antibiotics will be smaller than if the outcome is treatment failure or tympanic membrane perforation, both being more specific for AOM. A recent Cochrane review evaluating the effect of antibiotics in AOM found a risk ratio of 0.7 for pain relief at 2-3 days, but a risk ratio of 0.4 for development of a tympanic membrane perforation[14]. A meta-analysis with recalculated figures for treatment failure as the outcome has yielded an effect size very similar to that of tympanic membrane perforation; a risk ratio of 0.4[13]. Thus, it is important to acknowledge what one wants to achieve with antibiotic treatment. Another meta-analysis with individual patient data, evaluating the effect of antibiotics in AOM, showed that children with perforated AOM and children under 2 years with bilateral AOM were those who benefitted most from antibiotic treatment[15], something which is mirrored in many guidelines. For these groups, the number needed to treat was 3 and 4, respectively, compared to 20 for pain at 2-3 days.

If antibiotics are given mainly to reduce the risk of complication, what effect do they have on eg mastoiditis? Clearly, we cannot prevent all cases of mastoiditis by administering antibiotics, but at the population level, a retrospective cohort study from the UK showed that antibiotics halve the risk of mastoiditis after AOM, however, due to the low incidence of mastoiditis, 4800 patients need to be given antibiotics in order to prevent one case of mastoiditis[16].

Hospital data analysed in another UK study revealed almost a doubling in admissions for mastoiditis and of mastoidectomies in 0-4-year-olds between 1993 and 2002; a period during which the number of antibiotic prescriptions was halved[17]. Similarly, a comparative study using data from several countries, comparing the incidence of

acute mastoiditis with antibiotic prescription rates, showed that the mastoiditis incidence in the Netherlands (antibiotic prescription rate 31% was about twice that in the US (antibiotic prescription rate>90%). In Sweden, with a 37-52% reduction in antibiotic prescriptions in children of different ages between 1987 and 2004, no accompanying increase in mastoiditis incidence was seen[18].

The choice of antibiotic differs according to the current resistance patterns of the country in question. In a country like Sweden, with low incidence of antimicrobial resistance, it is still possible to recommend penicillin V as the first-hand choice [19], whereas in a country like Japan, where the common AOM pathogens are often highly resistant to antibiotics, significantly broader antibiotics, often in combination with myringotomy, have to be used[20]. Globally, the most common recommendation is probably a 5-10 day course of amoxicillin, and in patients with allergy to penicillin, a macrolide. How many times a day antibiotics should be administered is a trade-off between efficacy and compliance. For betalactams, the time for which drug levels exceed the minimum inhibitory concentration correlates best with bacterial eradication, and since the half-life of eg amoxicillin is only about 1 hour, it should ideally be administered several times a day. However, as compliance usually declines with an increasing number of administrations per day, a compromise of 3 times a day is often stated. A Cochrane review from 2013[21] identified 5 trials (1601 children in total) comparing amoxicillin with or without clavulanate administered once or twice daily to the same medication administered three or four times daily in children with acute ear pain and positive tympanocentesis or tympanogram. The clinical cure during and after therapy was similar between the groups, and the authors concluded that the two treatment strategies were comparable. However, small studies on a disease with a high spontaneous resolution rate may be difficult to interpret.

The adherence to guidelines has been investigated in several countries, and it has often been shown that guidelines are not followed. In the US, an initial decrease in antibiotic prescription rate after the publication of the first AAAP guidelines was followed by a return to pre-guideline levels. In addition, the use of broad-spectrum antibiotics increased despite the fact that treatment failures seemed to decrease[22]. At a GP practice in Surrey, UK, 93% of patients were given antibiotics for acute otitis media over a year. Only 52% of these antibiotics were given according to the NICE guideline criteria[23]. To improve the applicability of the guidelines, it has therefore been recommended that future guidelines should not only use a consistent grading system for quality of evidence and strength of recommendation, but also seek the preference of stake holders[24].

In patients where a complication is suspected or confirmed, oral antibiotics is not sufficient, but intraveneous treatment needs to be given, usually in combination with myringotomy, see below. If the causative agent is unknown, which is usually the case, broad spectrum antibiotics are given to start with, and when the results of a bacterial culture is known, the choice of antibiotic can be modified.

### *2.2 Myringotomy*

In the beginning of the 20$^{th}$ century, myringotomy was commonly performed as a treatment for AOM. Though much more rarely performed today, it should still be used in patients with complications, when antibiotic treatment has failed or in patients

with severe pain where analgesics are not sufficient.

## 3. Prevention

### *3.1 Modifiable risk factors*

There are several known risk factors for AOM, many of which cannot be modified, such as heredity[25-27] and having older siblings[28]. However, other risk factors can, to some extent, be influenced. One such example is day care, which has been associated with an increased risk of AOM[29, 30]. Multiple studies provide evidence that breastfeeding for at least 4-6 months reduces the number of AOM episodes and the risk of recurrent AOM[31, 32]. Eliminating exposure to passive smoking has been associated with a reduced incidence of AOM[33] as has a decreased use of pacifiers[34, 35]. The newly updated American guidelines on the management of AOM suggest that exclusive breastfeeding for 6 months and avoidance of tobacco smoking should be encouraged[36]

### *3.2 Non-surgical prevention*

#### *3.2.1 Non-pharmacological strategies*

One agent that has been suggested to be able to prevent AOM is xylitol, a polyalcohol often used as a sweetener. The effects of this substance on recurrent AOM were examined in a recent Cochrane review[37]. Based on the 4 studies included in the review, there was fair evidence that prophylactic administration of xylitol among healthy children attending day care centers reduced the occurrence of AOM by 25%. Chewing gum and lozenges containing xylitol appeared to be more effective than syrup, however, these formulas cannot be used safely in children below 2 years, ie those who are at the greatest risk of AOM. The authors did not find sufficient evidence that xylitol administered during a respiratory infection could prevent AOM. An even more recent randomized controlled trial comparing xylitol syrup to placebo found no effect on the number of AOM recurrences in otitis-prone children[38].

Vitamin D deficiency has been shown to be frequent in children with recurrent AOM, and low serum levels have been associated with an increased number of AOM episodes. Administration of vitamin D, and subsequent restoration of serum levels has, in turn, been associated with a significant reduction in the risk of uncomplicated AOM[39].

Pro- and prebiotics have been suggested to reduce the risk of AOM. One recent study was unable to show an effect of these substances in young, high-risk children[40], however, a simultaneously published systematic review (4 studies) of the effects of Lactobacillus rhamnosus, one of the components of the probiotics in the trial mentioned before, found that the bacterium had the potential to reduce the incidence of AOM, upper respiratory infections and antibiotic use in children[41]. Since children with recurrent AOM have been shown to have lower quantities of alpha-

haemolytic streptococci in their nasopharynges, and this bacterium is thought to be able to prevent nasopharyngeal growth of otopathogens, a nasal spray containing alpha-haemolytic streptococci was tested in two small Swedish trials as a means of preventing AOM. The somewhat larger study showed that treated children stayed healthy during the first 3 months of follow-up twice as often as the control children, however, in the smaller study, one was not able to show any differences between the groups.

### *3.2.2 Pharmacological strategies*

#### 3.2.2.1 Long-term antibiotics

In children with recurrent AOM, long-term antibiotics have been used at times, and in 2006, 16 studies on long-term antibiotics for AOM were analysed in a Cochrane review[42]. All studies concerned children who were at increased risk of AOM, and 7 of the studies focused on children with recurrent AOM. Long-term antibiotics were found to prevent 1.5 episodes of AOM per child per year, halving the number of AOM episodes during the period of treatment. Approximately five children needed to be treated to prevent one child from having an AOM episode whilst on treatment.

#### 3.2.2.2 Vaccination

One strategy in preventing AOM is vaccination, not only against the bacteria that cause most AOM, but also against viral infections that often precede AOM.

Polysaccharide vaccines against *S. pneumoniae* have existed for decades, however, these vaccines are not immunogenic in young children[43, 44]. Based on the successes of the conjugate vaccine against *H. influenzae* type B, conjugate vaccines against pneumococci were developed around the turn of the millennium, and found to be effective in young children. The first of these vaccines was heptavalent (PCV7) and conjugated to diphtheria toxoid, and was followed 10 years later by a 13-valent vaccine with the same conjugate and a 10-valent vaccine conjugated to protein D from *H. influenzae*. The main purpose of these vaccines is to protect from invasive pneumococcal disease, but the question was soon raised of whether the vaccines would protect against pneumococcal, and in the case of the protein D conjugate vaccine, also against *H. influenzae* AOM. A recently updated Cochrane review[45] analysed the effect of pneumococcal conjugate vaccines on AOM. Most of the included trials used PCV7, some included infants, some included older children and some focused on children with an increased risk of AOM. It seems that PCV7 has modest benefits in children with no increased risk of AOM, thus it does not seem to be justified to recommend vaccination with the sole purpose of preventing AOM. In older children with a previous history of AOM, no benefit has been observed with vaccination, however, infants at risk of developing recurrent AOM have still not been studied enough; neither have the more recently developed vaccines. The 10-valent protein D conjugate vaccine has been proposed to protect not only against pneumococcal AOM, but also against *H. influenzae* AOM. The first randomised trial of the protein D conjugate vaccine not only showed a decrease of one third of all-cause AOM, but also a similarly sized reduction in the number of *H. influenzae* AOM[46]. A recently published cluster-randomised trial in Finland showed

substantial absolute rate reductions of AOM among vaccinated children. The relative rate reductions were modest, but due to the high incidence of AOM, it was estimated that 12.000 episodes of AOM could be prevented in Finland every year in children below 2 years of age[47].

Observational studies, particularly in the US, have demonstrated a greater decline in AOM episodes than have been observed in clinical trials[48], however, the introduction of PCV7 coincided with the publication of new guidelines, offering the possibility of refraining from initial antibiotics, with the likely result of fewer doctors´ visits for AOM. A future challenge is that serotype replacement might reduce any long-term efficacy of vaccination.

Two of the most common viral infections to be complicated by AOM are influenza and respiratory syncythial virus (RSV). Vaccinations against these infections have therefore been postulated to have a potential protective effect also against AOM. In a recent review of the efficacy of live attenuated influenza vaccine on all-cause AOM[49], the results from 8 randomised trials suggested that influenza vaccination has a protective effect against AOM on a level similar to that of PCV7. During the first year after vaccination, 12.4% of all AOM episodes were prevented, compared to 6.2% during the second year after vaccination. There is presently no vaccine against RSV, however, it is estimated that such a vaccine should have an effect not only on RSV infections as such, but also on AOM[50].

### *3.3 Surgical prevention*

#### *3.3.1 Ventilation tubes*

Transmyringeal ventilation tubes, or grommets, have been used for a long time, not only in children with otitis media with effusion and concomitant hearing loss, but also in children with recurrent AOM. Whereas the body of evidence for the former indication is clear, further research on the latter is still needed. A Cochrane review from 2008[51] found that only two studies met their inclusion criteria, being randomised controlled trials comparing grommet insertion with some sort of control treatment in children aged 0-16 years with recurrent AOM. One of the studies compared grommets to long-term antibiotics and the other to no treatment. The conclusion of this review was that, in children <3 years of age, grommets reduce the number of AOM episodes during the first six months after surgery. In the grommet group, more children were symptom-free during the six months following surgery. Though the effect size in terms of the total number of prevented episodes was small, both studies showed that over 50% of children were free of AOM after grommet insertion, compared to just a handful of the control children.

No surgical treatment is without risk, however, for grommets the risks are generally small. Apart from the inevitable peroperative anesthesiological risks, secretion from the grommets is commonly seen, but is usually easily treated with ear drops. Tympanosclerosis plaques are often seen in patients who have had grommets, however, it is not clear to which extent this is caused by the middle ear disease as such or by the tubes. The tympanosclerosis rarely affect hearing within the

frequencies usually tested. A persisting tympanic membrane perforation occurs in 2% of all patients with short-term tubes, and in 17% of patients with long-term tubes[52]. Misplacement of the tubes with extrusion into the middle ear is a rarely seen complication.

*3.3.2 Adenoidectomy*

Adenoidectomy has been widely used as a means of preventing recurrent AOM, the theory being that the adenoid causes mechanical obstruction as well as being a site of bacterial infestation. A Finnish study comparing adenoidectomy, with or without grommets, to antibiotic prophylaxis or placebo found that adenoidectomy did not reduce the number of AOM episodes[53]. One individual patient data meta-analysis found that children with recurrent AOM aged < 2 years are likely to benefit more than others from adenoidectomy. The proportion of children with recurrent AOM in this age group who still qualified as having recurrent AOM (ie had at least 4 AOM episodes in 12 months) one year after surgery was 16% in the adenoidectomy group and 27% in the control group. By contrast, children aged ≥ 2 years with recurrent AOM did not seem to benefit from adenoidectomy. In this age group 18% of the children in the adenoidectomy group still qualified as having recurrent AOM after 12 months compared to 3% of the control group[54]. Another, simultaneously published, systematic review compared the outcomes of children who had undergone grommet insertion and simultaneous adenoidectomy to children who had only had grommet insertion for middle ear disease. This review found that the combination of grommet insertion and adenoidectomy might be superior to grommet insertion only in reducing the risk of recurrent AOM or the risk of having to have a second set of grommets, however, limitations mentioned were heterogeneous studies, often using retrospective data[55].

## 4 Conclusion

During the last century, AOM has gone from being a disease that contributed substantially to child mortality, and that could not be treated in any other way than perhaps myringotomy for a subset of patients, still less be prevented; to an often self-healing disease where we, in most parts of the world, have the possibility to chose between different antibiotics if needed, and which we can also to some extent prevent. However, despite AOM being such a common infection, there are still many treatments that we use without having firm evidence for it. Further research is needed to answer the question of the effect of antibiotics through trials with strict inclusion and exclusion criteria and specific outcomes; we need to learn more about the effect of grommets and the preventive possibilities and long-term effects of various vaccinations, only to mention a few.

## 5 References

1. Klein JO. Epidemiology of otitis media. Pediatr Infect Dis J. 1989 Jan;8(1 Suppl):S9.

2. Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J Infect Dis. 1989 Jul;160(1):83-94.
3. Alho OP. How common is recurrent acute otitis media? Acta Otolaryngol Suppl. 1997;529:8-10.
4. Quesnel S, Nguyen M, Pierrot S, Contencin P, Manach Y, Couloigner V. Acute mastoiditis in children: a retrospective study of 188 patients. Int J Pediatr Otorhinolaryngol. 2010 Dec;74(12):1388-92.
5. Groth A, Enoksson F, Hultcrantz M, Stalfors J, Stenfeldt K, Hermansson A. Acute mastoiditis in children aged 0-16 years--a national study of 678 cases in Sweden comparing different age groups. Int J Pediatr Otorhinolaryngol. 2012 Oct;76(10):1494-500.
6. Appelman CLM BP, Dunk JHM,, Lisdonk EH dMR, van Weert, HCPM. NHG Standard Otitis Media Acuta
(Guideline on acute otitis media of the
Dutch College of General Practitioners). Huisarts Wet. 1990;33:242-5.
7. Priest P, Yudkin P, McNulty C, Mant D. Antibacterial prescribing and antibacterial resistance in English general practice: cross sectional study. BMJ. 2001 Nov 3;323(7320):1037-41.
8. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med. 1997 Aug 14;337(7):441-6.
9. EARS-net. Antimicrobial resistance interactive database 2013; Available from:
http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx.
10. Froom J, Culpepper L, Grob P, Bartelds A, Bowers P, Bridges-Webb C, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. BMJ. 1990 Mar 3;300(6724):582-6.
11. Siegel RM, Kiely M, Bien JP, Joseph EC, Davis JB, Mendel SG, et al. Treatment of otitis media with observation and a safety-net antibiotic prescription. Pediatrics. 2003 Sep;112(3 Pt 1):527-31.
12. Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. JAMA. 2006 Sep 13;296(10):1235-41.
13. Gisselsson-Solen M. The importance of being specific--a meta-analysis evaluating the effect of antibiotics in acute otitis media. Int J Pediatr Otorhinolaryngol. 2014 Aug;78(8):1221-7.
14. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2013;1:CD000219.
15. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006 Oct 21;368(9545):1429-35.
16. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United kingdom general practice research database. Pediatrics. 2009 Feb;123(2):424-30.
17. Sharland M, Kendall H, Yeates D, Randall A, Hughes G, Glasziou P, et al. Antibiotic prescribing in general practice and hospital admissions for peritonsillar

abscess, mastoiditis, and rheumatic fever in children: time trend analysis. BMJ. 2005 Aug 6;331(7512):328-9.
18. Molstad S, Erntell M, Hanberger H, Melander E, Norman C, Skoog G, et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. Lancet Infect Dis. 2008 Feb;8(2):125-32.
19. Läkemedelsverket. Diagnostik, behandling och uppföljning av
akut mediaotit (AOM)
– ny rekommendation
. 2010;21(5).
20. Subcommittee of Clinical Practice Guideline for D, Management of Acute Otitis Media in C. Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan. Auris Nasus Larynx. 2012 Feb;39(1):1-8.
21. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database Syst Rev. 2013;12:CD004975.
22. McGrath LJ, Becker-Dreps S, Pate V, Brookhart MA. Trends in antibiotic treatment of acute otitis media and treatment failure in children, 2000-2011. PLoS One. 2013;8(12):e81210.
23. Smith NS. Antibiotic treatment for acute otitis media. Int J Pediatr Otorhinolaryngol. 2013 May;77(5):873-4.
24. Zeng L, Zhang L, Hu Z, Ehle EA, Chen Y, Liu L, et al. Systematic review of evidence-based guidelines on medication therapy for upper respiratory tract infection in children with AGREE instrument. PLoS One. 2014;9(2):e87711.
25. Hafren L, Kentala E, Jarvinen TM, Leinonen E, Onkamo P, Kere J, et al. Genetic background and the risk of otitis media. Int J Pediatr Otorhinolaryngol. 2012 Jan;76(1):41-4.
26. Rovers M, Haggard M, Gannon M, Koeppen-Schomerus G, Plomin R. Heritability of symptom domains in otitis media: a longitudinal study of 1,373 twin pairs. Am J Epidemiol. 2002 May 15;155(10):958-64.
27. Casselbrant ML, Mandel EM, Fall PA, Rockette HE, Kurs-Lasky M, Bluestone CD, et al. The heritability of otitis media: a twin and triplet study. JAMA. 1999 Dec 8;282(22):2125-30.
28. Labout JA, Duijts L, Lebon A, de Groot R, Hofman A, Jaddoe VV, et al. Risk factors for otitis media in children with special emphasis on the role of colonization with bacterial airway pathogens: the Generation R study. Eur J Epidemiol. 2011 Jan;26(1):61-6.
29. Ladomenou F, Kafatos A, Tselentis Y, Galanakis E. Predisposing factors for acute otitis media in infancy. J Infect. 2010 Jul;61(1):49-53.
30. Bailie R, Stevens M, McDonald E, Brewster D, Guthridge S. Exploring cross-sectional associations between common childhood illness, housing and social conditions in remote Australian Aboriginal communities. BMC public health. 2010;10:147.
31. Sabirov A, Casey JR, Murphy TF, Pichichero ME. Breast-feeding is associated with a reduced frequency of acute otitis media and high serum antibody levels against NTHi and outer membrane protein vaccine antigen candidate P6. Pediatr Res. 2009 Nov;66(5):565-70.
32. Duncan B, Ey J, Holberg CJ, Wright AL, Martinez FD, Taussig LM. Exclusive breast-feeding for at least 4 months protects against otitis media. Pediatrics. 1993 May;91(5):867-72.

33. Ilicali OC, Keles N, Deger K, Savas I. Relationship of passive cigarette smoking to otitis media. Arch Otolaryngol Head Neck Surg. 1999 Jul;125(7):758-62.
34. Niemela M, Pihakari O, Pokka T, Uhari M. Pacifier as a risk factor for acute otitis media: A randomized, controlled trial of parental counseling. Pediatrics. 2000 Sep;106(3):483-8.
35. Rovers MM, Numans ME, Langenbach E, Grobbee DE, Verheij TJ, Schilder AG. Is pacifier use a risk factor for acute otitis media? A dynamic cohort study. Fam Pract. 2008 Aug;25(4):233-6.
36. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964-e99.
37. Azarpazhooh A, Limeback H, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. Cochrane Database Syst Rev. 2011(11):CD007095.
38. Vernacchio L, Corwin MJ, Vezina RM, Pelton SI, Feldman HA, Coyne-Beasley T, et al. Xylitol syrup for the prevention of acute otitis media. Pediatrics. 2014 Feb;133(2):289-95.
39. Marchisio P, Consonni D, Baggi E, Zampiero A, Bianchini S, Terranova L, et al. Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. Pediatr Infect Dis J. 2013 Oct;32(10):1055-60.
40. Cohen R, Martin E, de La Rocque F, Thollot F, Pecquet S, Werner A, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized, double-blind, placebo-controlled study. Pediatr Infect Dis J. 2013 Aug;32(8):810-4.
41. Liu S, Hu P, Du X, Zhou T, Pei X. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. Indian Pediatr. 2013 Apr;50(4):377-81.
42. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Cochrane Database Syst Rev. 2006(4):CD004401.
43. Kalm O, Prellner K, Freijd A, Rynnel-Dagoo B. Antibody activity before and after pneumococcal vaccination of otitis-prone and non-otitis-prone children. Acta Otolaryngol. 1986 May-Jun;101(5-6):467-74.
44. Karma P, Pukander J, Sipila M, Timonen M, Pontynen S, Herva E, et al. Prevention of otitis media in children by pneumococcal vaccination. Am J Otolaryngol. 1985 May-Jun;6(3):173-84.
45. Fortanier AC, Venekamp RP, Boonacker CW, Hak E, Schilder AG, Sanders EA, et al. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane Database Syst Rev. 2014;4:CD001480.
46. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. Lancet. 2006 Mar 4;367(9512):740-8.
47. Palmu AA, Jokinen J, Nieminen H, Rinta-Kokko H, Ruokokoski E, Puumalainen T, et al. Effect of pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) on outpatient antimicrobial purchases: a double-blind, cluster randomised phase 3-4 trial. Lancet Infect Dis. 2014 Mar;14(3):205-12.

48. Pelton SI, Pettigrew MM, Barenkamp SJ, Godfroid F, Grijalva CG, Leach A, et al. Panel 6: Vaccines. Otolaryngol Head Neck Surg. 2013 Apr;148(4 Suppl):E90-101.
49. Heikkinen T, Block SL, Toback SL, Wu X, Ambrose CS. Effectiveness of intranasal live attenuated influenza vaccine against all-cause acute otitis media in children. Pediatr Infect Dis J. 2013 Jun;32(6):669-74.
50. Greenberg DP, Hoberman A. Vaccine prevention of acute otitis media. Curr Allergy Asthma Rep. 2001 Jul;1(4):358-63.
51. McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. Cochrane Database Syst Rev. 2008(4):CD004741.
52. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. Otolaryngol Head Neck Surg. 2001 Apr;124(4):374-80.
53. Koivunen P, Uhari M, Luotonen J, Kristo A, Raski R, Pokka T, et al. Adenoidectomy versus chemoprophylaxis and placebo for recurrent acute otitis media in children aged under 2 years: randomised controlled trial. BMJ. 2004 Feb 28;328(7438):487.
54. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton MJ. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. Health Technol Assess. 2014 Jan;18(5):1-118.
55. Mikals SJ, Brigger MT. Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. JAMA otolaryngology-- head & neck surgery. 2014 Feb;140(2):95-101.

**Highlighted references**

**14. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2013;1:CD000219.
*Recent systematic review and meta-analysis of the present evidence on the effect of antibiotics in AOM*

*36. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964-e99.
*The updated AAAP guidelines are likely to have a great impact in coming years*

**45. Fortanier AC, Venekamp RP, Boonacker CW, Hak E, Schilder AG, Sanders EA, et al. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane Database Syst Rev. 2014;4:CD001480.
*Recent systematic review and meta-analysis of the present evidence on the protective effect of pneumococcal vaccines for AOM*

*47. Palmu AA, Jokinen J, Nieminen H, Rinta-Kokko H, Ruokokoski E, Puumalainen T, et al. Effect of pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) on outpatient antimicrobial purchases: a double-blind, cluster randomised phase 3-4 trial. Lancet Infect Dis. 2014 Mar;14(3):205-12.
*Recent RCT evaluating the effects of the protein D conjugate pneumococcal vaccine on all-cause AOM*

*49. Heikkinen T, Block SL, Toback SL, Wu X, Ambrose CS. Effectiveness of intranasal live attenuated influenza vaccine against all-cause acute otitis media in children. Pediatr Infect Dis J. 2013 Jun;32(6):669-74.
*Evaluation of the effects of influenza vaccine on AOM*

*54. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton MJ. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. Health Technol Assess. 2014 Jan;18(5):1-118.
*Meta-analysis on the preventive effects of adenoidectomy and grommets in AOM*

*55. Mikals SJ, Brigger MT. Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. JAMA otolaryngology-- head & neck surgery. 2014 Feb;140(2):95-101.
*Meta-analysis on the preventive effects of adenoidectomy and grommets in AOM*

| Country | Finland | Holland | Israel | Scotland | Sweden | UK | USA |
|---|---|---|---|---|---|---|---|
| Watchful waiting for | Nobody with a reliable diagnosis of AOM | All but those who are "systemically ill" or those with risk factors for complications* | Children>6 months with non-severe symptoms and an uncertain diagnosis | Any child, irrespective of age | Children aged 1-12 without complicating factors* | All children* | Choice of watchful waiting in non-severe AOM in children>6 months** |

Table 1. Guidelines for AOM treatment in some countries

*Exception for children with otorrhea and children<2 with bilateral AOM

** Exception for children <2 with bilateral AOM even if symptoms are non-severe