# Theories of otitis media pathogenesis, with a focus on Indigenous children

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## ABSTRACT

- Otitis media is a common childhood illness associated with hearing loss, social disadvantage and medical costs. Prevalence and severity are high among Indigenous children.
- Respiratory bacterial and viral pathogens ascend the eustachian tube from the nasopharynx to the middle ear, causing inflammation, fluid accumulation, and bulging of the tympanic membrane, with or without pain.
- Among Australian Indigenous children, ear disease commences earlier in life, and involves multiple strains of bacterial pathogens at high density that persist longer.
- Persistent nasal discharge, overcrowded living conditions (particularly exposure to many children) and poor facilities for washing children perpetuate a vicious cycle of transmission and infection.
- Risk factors include environmental tobacco smoke, season, lack of breastfeeding, younger age and immature immune system, and possibly genetic factors.
- The innate immune system is a critical first response to infection, particularly as passive maternal antibodies decline and during the maturation of the infant adaptive immune response. The relative contributions of innate factors to protection from otitis media are currently not well understood.
- A diversity of antibodies that target strain-specific and conserved antigens are generated in response to natural exposure to otitis media pathogens (or to vaccines). Deficiencies in these antibodies may explain susceptibility to recurrent infections.
- Incremental contributions from all these elements are likely to be important in otitis media susceptibility versus protection.
- Effective medical and social strategies to prevent early age of onset are urgently needed.


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Otitis media is a common disease that affects many children and their families across the globe. The burden of otitis media and the frequency and severity of infection varies among populations. In developed countries, acute otitis media (AOM) is the most common reason for antibiotic prescription, with possible links to rising rates of antibiotic-resistant bacterial pathogens. Estimates of the incidence of AOM from longitudinal birth cohort studies in developed countries range from 0.125 to 1.2 episodes per child-year.[1-3]

Australian Indigenous children experience a mean of five episodes of AOM or chronic suppurative otitis media (CSOM) per child-year.[4] In a Far North Queensland paediatric outreach program, CSOM was identified as the most common health problem among Aboriginal children.[5] A 2005 survey of 644 children aged 6 months to 2.5 years conducted by trained research personnel across 17 remote Northern Territory communities found that 20% of children had tympanic membrane perforation, and around 12% had bilaterally normal ears.[6]

The disease process of otitis media is a complex and dynamic continuum that is generally believed to commence with bacterial colonisation of the nasopharynx, with or without upper respiratory tract viral infection. Otitis media pathogens ascend the eustachian tube to the middle ear space, initiating an inflammatory response and accumulation of middle ear fluid, and causing bulging and possible redness of the tympanic membrane, pain and fever.

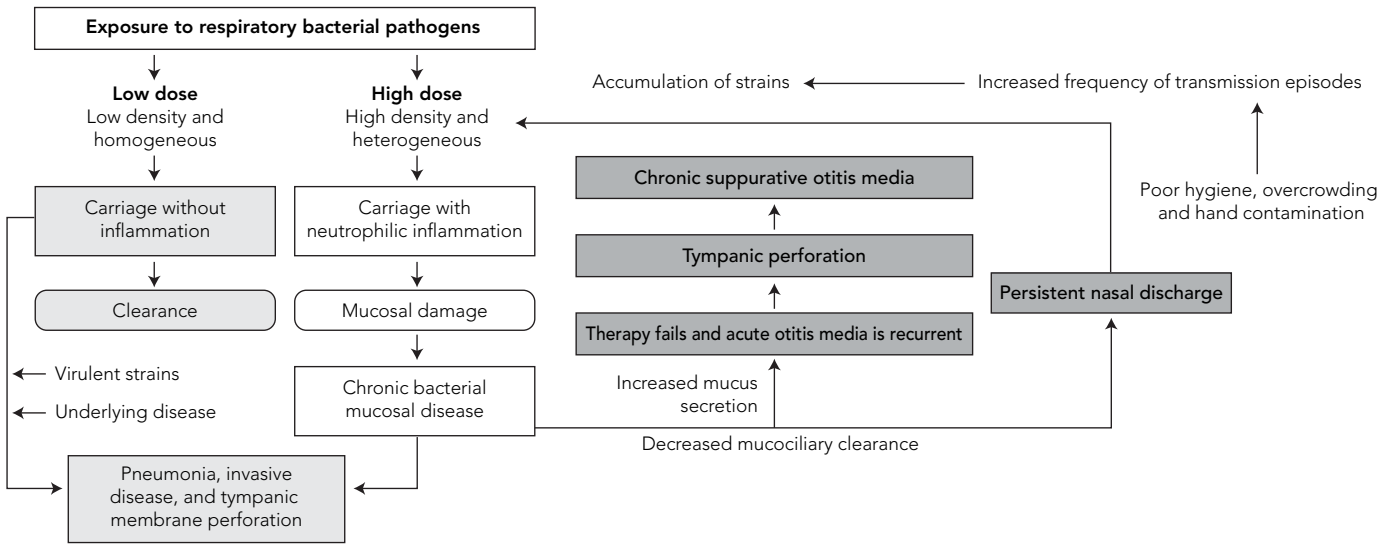
### Bacterial load and the role of viruses in otitis media

The main pathogens associated with otitis media are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. We hypothesise that increased bacterial load in the nasopharynx is associated with perforation; this is supported by our recent study, which showed a greater probability of suppurative otitis media (AOM with or without perforation) as density of *S. pneumoniae, H. influenzae* and *M. catarrhalis* increases.[7] The probability of suppurative otitis media increased from 20% at a pathogen density of less than $10^5$/mL, to 40% at a pathogen density of $10^6$/mL, to 50% at a pathogen density of $10^7$/mL.[7] A much lower probability (10%) was associated with total bacterial density (commensal and pathogen density combined) of $10^6$/mL. *Alloiococcus otitidis* has been implicated by culture or polymerase chain reaction (PCR) in chronic otitis media with effusion (OME) in several studies, including one of Australian Indigenous and non-Indigenous children undergoing myringotomy.[8] The proportion of middle ear fluids positive for *A. otitidis* was far greater in these children than all other reported studies — cultures from 10 of 22 Indigenous and 10 of 28 non-Indigenous children tested positive.

The specific risk factors that lead to an increased density of otitis media pathogens are not known, but it is plausible that antecedent viral infection plays a role. The availability of improved detection methods has provided opportunities for exploring the role of respiratory viruses in otitis media.[9] In most regions and populations, winter peaks of AOM typically follow viral (particularly respiratory syncytial virus) epidemics,[10] but in the tropical regions of the NT, seasonality of AOM is not observed. Current studies are further investigating the role of viruses in otitis media and the potential effect of influenza vaccination[11] on otitis media prevention.

In a Western Australian study, the proportion of specimens positive for otitis media pathogens was higher among Aboriginal children than non-Aboriginal children (*S. pneumoniae*, 50% v 28%; *H. influenzae*, 42% v 13%; *M. catarrhalis*, 52% v 30%; adenovirus, 9% v 4%; and rhinovirus, 23% v 17%).[12] Rhinovirus infection was positively correlated with carriage of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, and adenovirus with *M. catarrhalis*. The increased frequency of severe otitis media among Indigenous children could be related to greater frequency of interaction between viral and bacterial pathogens.

**The extended vicious circle of inflammation hypothesis explaining high rates of otitis media and other respiratory infections among Indigenous infants and young children**




### Acute otitis media with and without perforation

Two large studies from Israel and Finland reported data on culture of middle ear fluid obtained by tympanocentesis at the time of acute infection. Both studies found that *S. pneumoniae*, non-typeable *H. influenzae* and *M. catarrhalis* were the commonest causes of AOM.[13,14] Interestingly, when Indigenous children in the NT are screened for middle ear infections, around 20% have AOM (with a bulging tympanic membrane) in the absence of symptoms (pain) or fever (Associate Professor Peter Morris, Deputy Leader, Child Health, Menzies School of Health Research, personal communication). In cases of AOM with perforation in this population (tympanocentesis has not been possible), *H. influenzae* could be cultured from 57% of ear discharge cultures, *S. pneumoniae* from 34% and *M. catarrhalis* from less than 10%.[15]

### Otitis media with effusion

Up to 73% of acute episodes of otitis media resolve clinically without antibiotic treatment, with no remaining pain and fever (middle ear effusion may persist), within 24 to 48 hours.[16] Asymptomatic OME may persist for several weeks (63%) or months (26% after 3 months) after an episode of AOM.[16] It is not known whether OME is an infectious process in itself or whether it is residual sterile fluid following AOM. The proportion of middle ear effusions of OME patients that are positive for pneumococci after PCR analysis (13%) has been found to be higher than after conventional culture (5%), but is still small. Antibiotic treatment of OME reduces the proportion of children with persistent OME by about 15% (95% CI, 7%–23%) at median time of 4 weeks.[16] In contrast, interventions such as antihistamines and decongestants do not effectively aid OME resolution (risk difference, 0; 95% CI, 7–7). This supports the hypothesis that OME is, in part, a bacterial infection.

### Chronic suppurative otitis media

AOM with perforation generally requires a longer period of antibiotic therapy to resolve symptoms than AOM without perforation. Recurrent perforations may lead to CSOM (persistent discharge of at least 2–6 weeks) and a larger perforation size. The organisms involved in CSOM are dominantly opportunistic pathogens, particularly *Pseudomonas aeruginosa.* In most countries where studies have been conducted, *P. aeruginosa* is the predominant organism and is associated with around 20% to 50% of cases of CSOM; *Staphylococcus aureus* is also commonly isolated, but proportions of samples positive for *S. aureus* differ from study to study.[17-21] Among Aboriginal children, CSOM is also associated with non-typeable *H. influenzae* (22%), whereas *S. pneumoniae* is rarely cultured (3%).[17] Studies are needed to evaluate whether systemic antibiotics should be recommended in addition to topical antibiotics for young children with CSOM.

## Model to explain the high prevalence of chronic suppurative otitis media among Indigenous children

Among Australian Indigenous children, respiratory tract infections commence very early in life and involve a high density of multiple bacterial species and strains; these factors predict recurrent episodes of AOM and progression to CSOM.[7,22]

Indigenous infants whose nasopharynges were colonised with mixed infections and those involving *S. pneumoniae* and *H. influenzae* were at greater risk of otitis media (odds ratio, 33.6; 95% CI, 8–144) than those colonised with *M. catarrhalis* alone (odds ratio, 6.5; 95% CI, 2–29).[22] A study of cultures of ear discharge from acute perforations supports this mixed bacterial aetiology; 57% of cultures yielded *H. influenzae*, 34% contained *S. pneumoniae* and 21% yielded both pathogens.[15]

A vicious circle model of inflammation was developed to explain the pathogenesis of chronic suppurative lung disease in adults with bronchiectasis.[23] An extension of this model has been proposed to explain the high rates of otitis media and other respiratory infections, such as bronchiectasis, among Indigenous children (Box).[24,25] The density of these pathogens, their dominance among the nasopharyngeal flora, and the multiplicity of strains colonising simultaneously escalate during the first weeks of life[7] and are all

significantly associated with the presence and severity of current ear disease (no otitis media, OME, or suppurative otitis media).[26] A comparison of Aboriginal and non-Aboriginal children, all with a diagnosis of OME, demonstrated significantly higher nasopharyngeal loads of *S. pneumoniae* and *M. catarrhalis* in the Aboriginal group.[7] The increased bacterial load, despite similar clinical condition, could predict persistence of middle ear effusions and progression to suppurative otitis media in the Aboriginal population. Among adults, this dense and diverse colonisation causes neutrophilic infiltration, tissue damage, increased mucus secretion, and decreased mucociliary clearance, leading to chronic suppurative lung disease.[23] However, among infants, this cycle may also lead to CSOM and persistent nasal discharge.

The persistent nasal discharge perpetuates the vicious cycle, particularly where there is poor hygiene and overcrowding, by increasing opportunities for transmission among infants. This includes transmission via hand contamination (in a community-based survey, 40% of children were found to have pneumococcal hand contamination).[27] High rates of transmission events result in an accumulation of strains at a rate greater than can be cleared by the infant immune response or by damaged mucosa, and the vicious circle is repeated. For the middle ear, high density of organisms and damaged mucosa are also likely risk factors for failed therapy, recurrent AOM, and progression to perforation and CSOM.

## Risk factors for otitis media

Environmental risk factors for otitis media include season, respiratory viral infection, exposure to other children, environmental tobacco smoke exposure, lack of breastfeeding and dummy (pacifier) use. Most of these risk factors enhance opportunities for upper respiratory tract and nasopharyngeal colonisation by otitis media bacterial pathogens through increased exposure to multiple strains (from multiple children), increased transmission (due to crowding and aerosol spread in winter and during viral outbreaks), reduced clearance (from reduced mucociliary function due to environmental tobacco smoke, poor hygiene and lack of passive immunity). Swimming pools in remote communities, where pre-pool prevalence of infections was high, are associated with reduced rates of antibiotic prescription (45%), clinic attendance for middle ear infections (61%) and respiratory tract infections (52%).[28] Swimming pools may reduce these infections via chlorination or through more thorough physical removal of bacterial load in sores or the nasopharynx. Whether swimming in the absence of chlorination or increased frequency and duration of showering in the home would achieve similar reductions in otitis media is not clear, but this could be evaluated in appropriately designed trials.

In addition, several host risk factors contribute to the development of otitis media, one of these being young age. Most children (50%–85%) experience an otitis media episode in the first 3 years of life, with a peak incidence between 6 and 11 months of age.[2] This peak tends to coincide with the transition from breastfeeding and increased exposure to other children — either directly through daycare attendance or because of overcrowding. For Aboriginal children, disease starts early in life — within weeks of birth — and coincides with acquisition of otitis media pathogens.[22] Several birth cohort studies in different populations have shown that early age of nasopharyngeal acquisition of respiratory and otitis media pathogens was associated with increased risk of disease.[29-34] The mean age of pneumococcal acquisition was close to 30 days in the Gambia[34] and Papua New Guinea,[30] 60 days in Kilifi, Kenya,[29]and among Australian Indigenous children in the NT,[22] 6 months in Alabama[33] and 9 to 10 months in Costa Rica[31] and Buffalo, New York.[35]

Twin studies[36] and the fact that otitis media is more common in certain populations, such as Aboriginal Australian, Inuit and Native American people,[37,38] suggest that genetic factors play a role in otitis media susceptibility. Exactly which genes are involved in otitis media susceptibility needs to be established.

## The immune system in children with otitis media

Bacterial nasopharyngeal carriage in early infancy, when the immune system is still immature, is associated with subsequent recurrent and/or persistent infections, with relative risks depending on host and environmental risk factors.[39] Early bacterial carriage may also affect the development of long-term humoral and cellular immunity, resulting in less effective pathogen clearance. In addition, recurrent infections are more likely to occur because of a deficient innate and/or adaptive immune response.

The innate immune system is an evolutionary, ancient form of immunity, and offers the main resistance to microbial pathogens within the first minutes, hours or days of an infection. Innate immune responses provide critical defence in early life, as passive maternal antibody wanes and there is relative immaturity of adaptive immune responses. There might be a role for subtle deficiencies in innate immune responses in children with recurrent otitis media. Although there are publications on specific innate immune factors,[40] toll-like-receptors,[41,42] mannose-binding lectin[43-46] and soluble CD14,[47,48] further research is needed to elucidate which innate immune mechanisms are the most important, and how these innate systems interact and contribute to otitis media susceptibility.

Most data on the natural development of specific immunity against pneumococci and otitis media have focused on serum IgG antibodies against pneumococcal polysaccharides. Pneumococcal polysaccharide-specific mucosal IgA and serum IgG antibodies gradually increase in early childhood following exposure through carriage of the relevant serotypes.[49] IgG antibodies in serum appear to protect against the development of otitis media, but do not reduce nasopharyngeal carriage. Serotype-specific mucosal IgA antibodies reduce colonisation by the particular serotype; however, these antibodies do not protect against subsequent colonisation with other bacterial strains or serotypes. It is possible that children with recurrent AOM might produce serotype- and strain-specific antibodies, but fail to develop a broadly protective antibody response against conserved protein antigens. This subtle immunodeficiency might be a mechanism that makes certain children more susceptible to otitis media.[50]

In addition to antibody production, results of recent studies have suggested that CD4+ T-cell mediated mechanisms are required for optimal production of antibodies against pneumococcal proteins, for development of immunity to pneumococcal colonisation and for protection against mucosal infections due to non-typeable *H. influenzae* in murine models.[51-54] However, such studies have not examined high-risk populations, including children with recurrent otitis media, and it is not known whether these T-cell responses are altered in children with recurrent AOM.

It is unknown whether humoral or cellular immunity against bacterial antigens is more important in protection against otitis media. It is unlikely that a generalised immunodeficiency solely

underlies otitis media susceptibility (which does not mean that children with an immunodeficiency might not be more susceptible to otitis media). It is more likely that subtle differences in one or several immune pathways, together with additional host and environmental risk factors, make children more susceptible to otitis media.

## Conclusions

A detailed understanding of host colonisation and pathogen-specific innate and adaptive cellular and humoral immunity in young children, who are at greatest risk of disease, is required to facilitate the development of targeted interventions for recurrent and severe AOM to reduce the burden of disease.

For Indigenous children and others at increased risk of early age of otitis media onset and progression to tympanic membrane perforation, strategies to reduce exposure to high doses of multiple otitis media pathogens are urgently needed. Reduced crowding, improved household facilities for washing children and increased awareness of bacterial transmission among family members could contribute to delayed onset of otitis media. Maternal immunisation and vaccines with expanded bacterial protection and that can be commenced earlier in life are potential strategies. Long-term antibiotic therapy reduces the proportion of infants experiencing tympanic membrane perforation,[4] but these schedules are difficult for families. Alternative antibiotic regimens include single-dose azithromycin, which is not superior in resolving AOM compared with 7 days of amoxycillin, but is easier to administer.[55] Although there are some general indications that Indigenous child health has improved, such as increased birthweight and lower infant mortality, there is evidence to suggest that morbidity associated with infections, such as otitis media, has not changed over the past 30 years.[56]

## Competing interests

None identified.

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