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Bacterial otitis media: A vaccine preventable disease?

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Abstract

Otitis media (OM) is the most common childhood illness for which medical advice is sought. Whilst the disease rarely results in death, there is a significant level of morbidity and economic burden on the community. Although the causes of OM are multifactorial, bacterial and viral infections are the single most important cause. Bacteria responsible for infections of the middle ear are predominantly, nontypeable Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis. Antibiotics have been widely used to treat children who present to a medical clinic with OM. However, given the high prevalence of this disease and the increasing incidence of microbial resistance to antibiotics, there is a need to develop alternative therapeutic strategies such as vaccination. Pneumococcal polysaccharide vaccination has produced disappointing results for effectiveness in preventing OM and there is evidence of an increased incidence of disease due to non-vaccine serotypes. An efficacious vaccine for bacterial OM would require combining protective protein antigens from all three causative bacteria. A combined bacterial-viral vaccine formulation would produce the most profound and sustained impact on reducing the global incidence of OM.

Keywords: otitis media, disease burden, risk factors, immunisation

Running Title: Otitis Media
1. Introduction

Otitis media (OM) is one of the most frequent childhood diseases, the primary reason for a child under the age of 3 years of age to visit a general practitioner [1] and the most common indication for the prescription of antibiotics [2]. In the mid 1990s, in the USA, it was estimated that there were 14 million episodes of OM per annum in children under the age of 5 and that the cost of treatment was in excess of $US85 billion [3]. Similar estimates are most likely to describe OM disease burden in other developed countries. In developing countries where the burden of respiratory disease is thought to be in the order of 10 times greater, compared with developed nations, the burden of suffering due to OM would be predictably higher and, without ready access to medical treatment, the serious and long term sequelae greater. The excessive use and indeed the necessity of antimicrobial therapy in OM remains controversial [2]. With the increase in the number of bacterial pathogens resistant to many antimicrobial agents there has been a corresponding increase in suppurative complications [4]. Over the past 30 years, there have been numerous studies examining the complex relationship of recurrent otitis media in early life to hearing loss and potential impact on language and academic achievement [5]. Because of the human and economic costs associated with OM, there is great interest in developing intervention strategies to manage this challenging disease. The burden of disease in many at risk cohorts meets the World Health Organisation’s (WHO) criteria as a massive public health problem [6].

2. Otitis media

OM is the general term for a continuum of related middle ear diseases. There are three main categories of OM of which, there is no accepted and standard definition
amongst health professionals. Acute otitis media (AOM) is generally defined as the presence of middle ear effusion accompanied with the rapid onset of one or more signs or symptoms of inflammation in the middle ear, such as otalgia, otorrhea, fever and irritability. Otitis media with effusion (OME) is a condition without signs or symptoms of acute ear infection manifested by the presence of middle ear fluid. There is no perforation of the tympanic membrane. Persistent middle ear fluid results in decreased mobility of the tympanic membrane and serves as a barrier to sound conduction. OME may occur independently because of poor Eustachian tube function or as an inflammatory response following AOM [7]. Chronic suppurative otitis media (CSOM) is a chronic inflammation of the middle ear and in which a non-intact tympanic membrane and discharge are present. There is no consensus on the duration of otorrhea to be termed chronic, however, on the basis of expert opinion it is generally accepted that otorrhea must be present for at least 6 weeks to 3 months for a diagnosis of CSOM [8].

3. The burden of suffering

3.1 Epidemiology

In the USA, approximately 80% of children have at least one episode of AOM by 3 years of age, with a peak incidence between 6 and 18 months [9,10]. Recurrent AOM is generally diagnosed when 3 or more episodes of AOM have occurred within a period of 6 months or 4 or more episodes in 12 months. It commonly affects 10 - 20% of children by 12 months of age. By 7 years of age, almost 40% of children have had 6 or more episodes of AOM [10]. By their first birthday, >50% of children have experienced OME. Recurrent OME occurs in 30 - 40% of children, and 5 - 10% of episodes last 12 months or longer [11].
Population-based studies in Finland and USA have estimated a rising trend in OM incidence of 68% [12] and 39% [13], respectively, over the past 10 - 20 years. In the US, the prevalence of early-onset OM and repeated OM in preschool children have increased, 11% and 18%, respectively [14].

OME in developed countries is considered to be an important problem while in most developing regions, AOM and CSOM are reported to be more prevalent. In specific high risk populations; the Inuits of Alaska (30-40%), Australian Aborigines (12-33%), and some Native Americans (4-8%), AOM and CSOM are almost endemic [6]. It is thought that CSOM is prevalent in these communities because they share the socio-economic disadvantage seen in developing countries that predispose to early and persistent nasopharyngeal colonization such as overcrowding, large number of siblings in household, poor hygiene and malnutrition.

3.2 Complications and sequelae

AOM is painful. The pain is a result of pressure on the tympanic membrane by the expanding middle ear abscess. Fluid may persist in the middle ear for weeks to months causing some hearing loss, vertigo and tinnitus. Children may also experience systemic signs and symptoms such as anorexia, headache, diarrhoea, vomiting, conjunctivitis and nystagmus.

In developing countries, OM occurs at a higher rate and at a younger age, and contributes to increased mortality and severe disabilities. With limited access to medical facilities, perforation of the tympanic membrane, mastoiditis and otorrhea (consistent with CSOM) are common. Other OM complications include, septic shock, meningitis, thrombosis and brain abscess [15]. In 1993, the WHO reported that OM was responsible for the deaths of over 50,000 children under the age of 5 years each
year in developing countries [16]. In these communities chronic OM accounts for 60-80% of middle ear disease, of which, suppurative intracranial complications occurs in almost 10% of cases [17]. In the early 1990's, OM was estimated to result in 23.1 (x100,000) of disability-adjusted life years lost (DALYs, a measure of the combined loss of life from premature death with the loss of healthy life from disability) in developing countries. The significance of this figure is made more apparent when compared with other infectious diseases, such as meningitis (30.1 DALYs), syphilis (29.0 DALYs), trachoma (23.7 DALYs), and polio (19.9 DALYs), which are perceived to have greater morbidity outcomes than OM [16]. As the incidence of OM has continued to increase since then, comparative data, if available, could be predicted to demonstrate worsening statistics for OM.

Hearing impairment associated with OM is a major health problem in developing countries and compromises the quality of life in approximately one third of the population [15]. Children in these communities experience a form of necrotizing OM resulting in permanent perforation of the tympanic membrane, persistent suppurative drainage of the middle ear and destruction of the ossicular chain resulting in deafness. This phenomenon is typically seen in the Aboriginal people where the prevalence of conductive hearing loss in children is extraordinarily high (6 to 70%) with a loss of >25 dB (hearing aids may be required) [18]. On a comparative scale, in the US population the incidence of a 25 dB hearing loss in children has been reported as 5-7% of 5 to 8 year olds [19]. Inconsistencies of methodology and study criteria complicate the interpretation of data and make difficult the assessment of the causal relationship between OME in early childhood and its affect on communicative development [5]. In the majority of studies, hearing is the hypothesized factor accounting for developmental
sequelae. A recent meta-analysis has suggested at most a small negative association between temporary hearing loss associated with OME and other social factors and later speech and language development in otherwise healthy children [20]. However, children with prolonged periods of hearing loss, as is the case in developing countries and in lower socio-economic groups in developed countries, the sequelae is a particular concern because of the importance of comprehension of normal language for those who are uneducated.

4. Risk factors

An immature immune system and Eustachian tube is thought to account for the predisposition of infants and young children to OM. However, some children are at risk of severe and recurrent disease. It is important to identify risk factors for OM in these children as they can inform strategies for early prevention and intervention. To this end, much work has been done to understand the factors that have been associated with AOM, such as: microbial agents (bacterial and viral); anatomic factors (Eustachian tube dysfunction); host characteristics (young age, genetic predisposition, respiratory allergy) relating to an immature or defective immunologic status and environmental risk factors (older siblings, group day care, season of the year and smoking in the household) and social factors.

4.1 Eustachian tube dysfunction

The Eustachian tube plays an important role in maintaining a healthy middle-ear. In the event of a viral upper respiratory tract infection, the Eustachian tube and the nasopharynx may become overwhelmed with congestion, with impaired clearance mechanisms and pressure regulation, potential pathogens may be aspirated into the middle-ear provoking an inflammatory response and the onset of OM. Young children
are predisposed to OM because of an anatomically immature and consequently poorly functioning Eustachian tube. For those children prone to episodes of AOM and OME, anatomic abnormality of the Eustachian tube appears to be a contributing factor [21].

4.2 Microbiology

Three bacterial pathogens predominate as the cause of AOM - *Streptococcus pneumoniae* (25-50%), nontypeable *Haemophilus influenzae* (NTHi) (15-30%) and *Moraxella catarrhalis* (3-20%) [22]. During episodes of OM, colonization with these pathogens increases significantly, however, children prone to infection appear to be predisposed to a higher than normal carriage of NTHi [23]. It has been shown that a strong positive correlation exists between bacterial colonisation of the nasopharynx at an early age and the early onset of OM [24] that subsequently leads to increased risk of recurrent infections [23]. These factors are thought to contribute to the high prevalence of OM in Aboriginal people where virtually all infants have OM onset by 2 months of age, with the majority of cases progressing rapidly to chronic OM [25].

Heikkinen & Chonmaitree [26] have recently summarised the results of several studies of viral aetiology of AOM: respiratory viruses, alone, account for 30% of cases or with concurrent bacterial pathogens in approximately 15% of cases. The apparent low incidence of viral involvement may be a reflection of sensitivity and technical difficulties of culture and detection. Respiratory syncytial virus (RSV) is the most commonly detected virus in middle ear fluid. Other viral agents include rhinovirus, influenza virus and parainfluenza virus. Enterovirus and adenovirus are also occasionally reported. Interestingly, it has been shown that AOM caused by coinfection with bacteria and rhinovirus is associated with a high rate of antibiotic failure for treatment [27].
4.3 Immunology

The adenoid is a part of mucosa associated lymphoid tissue and plays an important role in local immune protection against bacteria and viruses. Locally produced secretory antibodies inhibit the uptake of antigens and block colonization of micro-organisms. A lack of sIgA [28], and increased adherence of NTHi and *S. pneumontiae* to nasopharyngeal cells [29] may be predisposing factors in the pathogenesis of OME in children prone to infection. With respect to systemic immunity, children prone to OM have been reported to have low immunoglobulin levels, specific IgG2 antibodies to polysaccharide antigens [30] and OMP P6 antibodies to NTHi [31].

Infants who have been breast-fed for at least 3 months have been found to have reduced risk of OM [32], most probably due to the component of breast milk such as lactoferrin, oligosaccharide and sIgA which serve to modulate bacterial colonization.

There is some speculation that high risk populations may be immunocompromised where early exposure to multiple pathogens before maturation of the immune system results in partial immune tolerance or suppression and prolonged bacterial carriage leads to persistent OM.

A successful immune response to bacterial or viral pathogens is dependent on a complex regulation of acute phase cytokines that induce proliferation and differentiation of T and B cells. TNFα, IL-1 and IL-8 are important in the inflammatory response in the middle ear in OME [33]. Children with recurrent OM may have a local defect in cytokine production and hence compromised immunity with low levels of IL-1β, IL-6 and TNFα following colonisation with NTHi [34].
4.4. Genetics

Twin studies have demonstrated that there is a strong genetic component in the predisposition of a child to recurrent episodes of OM [35]. The male gender and heredity for OM increases the risk for otitis-proneness [36] as does atopic status [37]. In addition, the HLA-A2 antigen is positively correlated with recurrent AOM [38].

4.5. Environment

A meta-analysis of OM risk factor studies confirmed that child care outside the home and parental smoking were the factors that most significantly increased the occurrence of AOM. AOM has a positive association with family OM history (RR = 2.6), day care (RR = 2.5), parental smoking (RR = 1.7) and pacifier use (RR = 1.2) and a negative association with breastfeeding for 3 or 6 months (RR = 0.87) [32].

5. Non-vaccine intervention strategies

5.1 Antibiotics and other chemotherapies

From a meta-analysis of 21 studies up until 1993, Williams and colleagues [39] concluded that antibiotic treatment had a beneficial but limited effect on recurrent OM and short term resolution on OME. A more recent Cochrane Review [40] of 10 trials concluded that antibiotics shortened the duration of AOM. Neither analysis provided evidence that antibiotic treatment altered the course of otitis disease in children. A recent Clinical Practice Guideline: Otitis Media with Effusion [11] also concludes that antimicrobials, as well as corticosteroids, do not have long-term efficacy for OME. The Guidelines also conclude that antihistamines and decongestants are ineffective for the treatment of OME. However, the use of these products and analgesics are important to control symptoms, when present, in children with OM.
High rates of spontaneous resolution of AOM (approximately 80% of cases resolve within 2-14 days) along with minimal benefits from antimicrobials [40] indicates that “watchful waiting” for a period of 48-72 hours prior to treating AOM with antibiotics can only be recommended in children 2 years and older when follow-up can be assured. For children less than 2 years there is no consensus for an observation period prior to antibiotic treatment. The benefit of antibiotic usage must be weighed against the possible adverse reactions of which the increased risk of carriage of potential respiratory pathogens and the emergence of resistant nasopharyngeal bacteria is of most concern [41].

Evidence-based recommendations, on managing OME in children who are otherwise healthy, are observation for 3 months or longer before intervention is considered. This recommendation is based on the self-limiting nature of most OME (60% of newly detected OME resolve within 3 months) [11] and the beneficial although short-term effect of antimicrobial therapy [39].

Access to primary health care facilities for follow up is a major problem in developing countries and in developed countries particularly in areas of lower socio-economic status where there are significant medical workforce shortages, and where additional financial burden is associated with a return visit to the medical practitioner.

5.2 Surgery

If drug therapy is inadequate to clear effusion from the middle ear, tympanostomy tube insertion is the preferred initial procedure, whilst adenoidectomy should only be performed if a distinct indication exists. Both procedures have demonstrated to reduce OME prevalence. However, a benefits over harms assessment must be made when considering surgery, taking into account the relatively high OME relapse rate (20-50%)
after tube extrusion, the high risks associated with invasive surgery such as adenoidectomy and the transient improvement in hearing levels [11]. Outcomes from surgery are highly variable and would appear to be very dependent upon the selection criteria for the child and the appropriateness of the surgical procedure.

6. Vaccination

OM is a polymicrobial disease in which complex relationships between the different bacteria and viruses have been described and hypothesised. In fact the complex nature of these interactions are poorly understood. With this background and the large number of predisposing risk factors the concept of developing a successful vaccine to protect children against OM is indeed a challenge.

For a vaccine formulation to be efficacious for OM it must: contain one or more antigens from each of the responsible pathogens; induce appropriate immune responses in young children to clear the pathogens from the middle ear and reduce colonization load in the nasopharynx and finally, program the inflammatory response towards resolution of the infection without causing immune mediated damage in the middle ear [42]. A vaccine to cover the primary infectious microbes would need to include antigens from \textit{S. pneumoniae}, NTHi, \textit{M. catarrhalis}, RSV, parainfluenza and influenza. However, there is little likelihood that such a combined bacterial-viral vaccine could be developed in the medium term for widespread use in children.

Given that there is evidence of bacterial presence in approximately 70\% of samples of middle ear fluid taken from children with acute OM [26], a vaccine formulation consisting of antigens from \textit{S. pneumoniae}, NTHi and \textit{M. catarrhalis} would seem a logical place to start. Furthermore, a number of lead protein antigens for all 3 bacteria have now been identified [42, 43]. These antigens have the potential to protect across
the range of serotypes and strains responsible for disease. Preliminary studies in an animal model of acute lung infection [42] have demonstrated that mucosal immunisation with a tribacterial (\textit{S. pneumoniae}, NTHi and \textit{M. catarrhalis}) whole killed cell vaccine was able to significantly enhance clearance of each organism from the middle ear when challenged with live bacteria. Combination challenges were not conducted.

6.1 \textit{Streptococcus pneumoniae}

Immunisation of children with either pneumococcal or polysaccharide vaccines has not had a significant impact on the prevention of OM [44]. Whilst the efficacy statistics improve when adjusted for factors such as disease due to vaccine serotype and risk factors, they remain relatively unimpressive.

Evidence is emerging that the incidence of disease due to non-vaccine serotypes is increasing [45]. In addition, an increase in \textit{Staphylococcus aureus}-related acute OM as well as a possible disturbance in the ecological balance between \textit{S. pneumoniae} vaccine serotype and \textit{S. aureus} in the nasopharynx has been reported [46, 47]. This highlights the need to consider the impact on the balance of the respiratory tract microbial flora when introducing vaccines targeted at bacteria that also exist as commensals. It is not unreasonable to conclude that the current vaccination strategy based on inducing protection against pneumococcal OM with a restricted number of serotypes is flawed and an approach, which includes protein antigens that are conserved across the serotypes and reduces the nasopharyngeal bacterial load broadly, may be more likely to be successful.
6.2 *Haemophilus influenzae*

Virtually all OM due to *H. influenzae* is caused by non typeable strains. Therefore the widespread use of conjugated *H. influenzae* type b vaccines has had no observable effect on the prevalence of OM due to *H. influenzae*. Other potential NTHi immunisation approaches, such as a lipooligosaccharide-tetanus conjugate vaccine [48] and a whole killed cell vaccine [49], have been conducted in adults but have not been trialed for efficacy against OM in children. Both approaches have delivered promising results in animal models of otitis.

6.3 *Moraxella catarrhalis*

No human studies have been undertaken to examine the possibility of immunising against OM caused by *M. catarrhalis*.

6.4 *Influenza, RSV and parainfluenza*

Different trial designs and risk cohorts studied as well as a failure to take into account low incidence of influenza infections in the community during the trial period, has resulted in confusion with respect to the effectiveness of influenza vaccination in prevention of OM. The current evidence indicates that influenza vaccination may have a significant impact on reducing the incidence of AOM in high risk cohorts during periods of influenza activity in the community. Given the need to review the active constituents of an influenza vaccine annually it is not practical to include influenza in a polymicrobial otitis vaccine. Opinion now seems to favour the immunisation of children for influenza to prevent systemic disease and, if formulations are developed,
will also prevent OM. This would be an added benefit for a scheduled annual immunisation.

There have been substantial efforts over the past decade towards producing a vaccine for RSV infection in children, primarily to prevent pneumonia and bronchiolitis. Despite a number of formulations being trialed in humans the development of a safe effective vaccine has yet to be registered and no studies on the impact of these formulations on OM have been reported.

A phase 2 trial of a live attenuated parainfluenza type 3-cold passage mutant vaccine (PIV-cp45) was recently conducted in healthy children 6-18 months of age [50]. Whilst the vaccine was safe and immunogenic it did not alter the incidence of acute or serious OM. Clearly further studies are required at this stage.

Viral antigens are detected in at least one third of middle ear fluids tested and as viral infections may precede bacterial otitis, it is essential that development of vaccines for RSV and parainfluenza virus continue despite the lack of positive results thus far. Given that both viruses and bacteria can be detected in the middle ear fluid of approximately 15% of children with AOM [26] the development of a combined bacterial-viral vaccine formulation for OM must remain the long-term objective.

6.5 *Passive immunisation*

Administration of hyperimmune globulin or monoclonal antibodies is not a feasible strategy for either treatment or prevention of OM. Early studies have suggested that maternal immunisation as a means of preventing OM as well as other respiratory infections in the first few months of life is worthy of further study [51]. If antibodies of the IgG1 isotype for placentental transport and IgA antibodies with breast milk can be induced then these maternally derived antibodies might not only be able to provide
passive protection against disease, but also alter the nasopharyngeal colonization load in favour of the infant host.

7. Relief from the misery of otitis media

Millions of children are afflicted with the misery of OM across the globe. The disease is complex and multifactorial in aetiology. Interventions include widespread use of antibiotics, invasive surgical procedures, and risk reduction strategies. However, none of these interventions are likely to result in a sustained global reduction in the incidence of OM. The most successful intervention strategy for controlling infectious diseases has been immunisation. Whilst immunisation against what are normally commensal microbes is not without challenge, it is feasible [52].

A recent "Washington Otitis Vaccine Workshop" was held at which representatives from leading research centres, the National Institute of Health, the Food and Drug Administration and nine vaccine companies attended. This workshop was precipitated by frustration in academic research centres with the lack of progress being made in the development and trialing of vaccines to prevent OM. This frustration was largely brought about by the failure of industry partners to progress a number of highly characterized protein antigens, either singularly or in combination formulations, into phase I clinical trials [53]. The workshop concluded that the major obstacles to progress were several fold but the major impediments to progress were structural in the manner in which programs were prioritised within any given company’s product development portfolio and the financial burden of development being entirely borne by the industry. The workshop proposed a number of alternative partnership models between government agencies, industry and research institutions which, if pursued, would bring key lead antigens to clinical trial rapidly [11].
Whilst it is never wise to predict with certainty the outcomes of such trials, it would be disappointing if from the 3-4 lead candidate antigens for each bacteria a successful combination formulation for bacterial OM was not possible, particularly given the substantial pre-clinical data that exists for these antigens. Clinical trials of RSV and parainfluenza are progressing. If trials for lead protein antigens e.g. *S. pneumoniae*, NTHi and *M. catarrhalis* can be advanced similarly, then a combined bacterial-viral vaccine may also be feasible. This approach is by far the most promising to deliver a sustained reduction in the burden of OM in children globally – a polymicrobial vaccine.
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