LEADING ARTICLE

Drugs 2002; 62 (10): 1441-1445
0012-6667/02/0010-1441/$30.00/0

Prevention of Otitis Media by Vaccination

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Abstract

Otitis media (OM) is one of the commonest infections in childhood and a frequent reason for prescribing antibacterials in infancy. However, the increase in prevalence of antibacterial-resistant respiratory bacterial pathogens has not been matched by the development of new antibacterial agents. Bacterial vaccine strategies aim to prevent OM directly and to reduce nasopharyngeal carriage of pneumococci, thereby reducing the likelihood of developing acute OM. Complete protection against OM would require an approach targeting both bacterial and viral agents.

Immunisation with a pneumococcal conjugate vaccine provides protection against acute OM caused by pneumococcal serotypes included in the vaccine, reduces serotype-specific pneumococcal carriage, and reduces carriage of penicillin-resistant pneumococci. However, an increase in non-vaccine serotype OM has been observed in vaccinated children, which may limit the overall effectiveness of this vaccine. New vaccines targeting non-typable *Haemophilus influenzae* and *Mycoplasma catarrhalis* are in the early stages of development. Efficacy studies with influenza vaccine have shown the most promising results to date in terms of overall reduction in OM episodes.

A more substantial reduction in the burden of OM in childhood would require a combination of vaccines that are effective against the bacterial and viral pathogens involved and that can be administered early in infancy.

Otitis media (OM) is one of the commonest infections in childhood. Long-term sequelae include hearing loss that may accompany acute and chronic OM. This in turn may result in language delay and subsequent difficulties in school.[1,2] OM is a common reason for prescribing antibacterials in infancy. However, the increase in prevalence of antibacterial-resistant respiratory bacterial pathogens has been accompanied by only modest gains in the development of new antibacterial agents.

Consequently, there is growing emphasis on the prevention of OM rather than treatment.[3] Potential bacterial vaccine strategies to prevent OM aim both to prevent disease directly and to reduce pneumococcal nasopharyngeal carriage, thereby reducing the likelihood of developing OM. Viral respiratory infections, such as influenzae and respiratory syncytial virus can alter eustachian tube function and thereby predispose to OM. Recent developments in respiratory viral vaccines, in particular the influenza vaccine, have shown promising results in terms of OM prevention.

1. Epidemiology

A recent study in the US found that 90% of children have experienced one or more episodes of

symptomatic or asymptomatic middle ear effusions by 2 years of age.[4,5] The peak incidence of OM is between 6 and 18 months of age. In the US, approximately 50% of infants experience their first episode by 6 months of age and recurrent episodes are common. Early onset of OM is associated with increased risk of recurrent OM and persistent middle ear effusions.

In developing countries where access to medical care is limited, untreated OM may lead to persistent perforation of the tympanic membrane (TM) and disarticulation of the ossicles which may lead to permanent conductive hearing loss.[6] A review of ten studies in developing countries indicates high rates of TM perforation, persistent otorrhoea and mastoiditis.[6] In Australian Aboriginal infants, OM develops in the first months of life and persists throughout childhood.[7] The timing of colonisation with respiratory pathogens was found to predict the onset of persistent OM.[7]

2. Aetiology

Fluid cultured from tympanocentesis has found a bacterial cause of acute OM (AOM) in 70% of episodes. *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Mycoplasma catarrhalis*, and *Streptococcus pyogenes* are the most common bacterial pathogens worldwide, with *S. pneumoniae* the commonest cause. *H. influenzae* type b (Hib) has been shown to cause OM but it is an infrequent cause.

Respiratory viruses have been considered primarily as cofactors in the pathogenesis of AOM, although they have been isolated alone from the middle ear fluid in children with this condition.[8] Respiratory syncytial virus (RSV), rhinovirus, influenza virus, adenovirus and parainfluenza virus are recovered frequently from either the middle ear or the nasopharynx in children with AOM.[8,9]

Viral infections have been shown to promote the development of bacterial OM. Influenza virus has been shown to cause disruption to eustachian tube function, impair recovery from infection and facilitate the attachment of bacterial pathogens to respiratory epithelial cells, supporting the commonly held view that viral infections precede bacterial OM.

3. Pneumococcal Vaccines

3.1 Pneumococcal Polysaccharide Vaccines

The pneumococcal polysaccharide (PS) vaccine produces a T-cell–independent antibody response, and is therefore poorly immunogenic in children less than 2 years old. Studies of pneumococcal PS vaccines indicate that antibodies provide some serotype-specific protection against OM, however, minimal reduction in overall episodes of AOM was seen.[10,11]

Maternal immunisation with the pneumococcal PS vaccine or with a conjugate vaccine has the potential to provide enhanced immunity for both mother and infant. This could result in protection from pneumococcal carriage and hence development of disease. Studies in Papua New Guinea, Bangladesh and The Gambia have demonstrated that maternal immunisation with the pneumococcal PS vaccine appears to have good safety and be immunogenic in pregnant women.[12-14] A short-lived increase in neonatal antibodies has been observed in the published trials, but the effects of maternal immunisation on the development of breast milk antibody, colonisation of the infant, and the development of OM have not been fully evaluated.[15]

3.2 Pneumococcal Conjugate Vaccines

The poor immunological response by infants to the pneumococcal PS vaccine led to the development of pneumococcal conjugate vaccines. Coupling a purified capsular PS with a protein 'carrier' increases the immunogenicity of the vaccine and creates a T-cell–dependent immune response. Pneumococcal serotypes included in the vaccine cover 60 to 95% of the serotypes that cause OM.

Recently two efficacy studies have demonstrated a reduction of OM with the use of vaccine serotypes of *S. pneumoniae*.[16,17] On the basis of these two studies, it is estimated that up to 1.2 mil-

lion of the 20 million yearly episodes of OM in the US could be prevented.[17] The 7-valent pneumococcal vaccine is now licensed in the US and Australia. However, the production of this vaccine is technically complex, limiting its mass production. In addition, the vaccine is very expensive and is unlikely to be affordable for universal use in most countries within the next 5 years.

The first efficacy trial of a pneumococcal conjugate vaccine was conducted in northern California.[16] That study evaluated the impact of four doses of the 7-valent pneumococcal conjugate vaccine given at 2, 4, 6 and 12 to 15 months of age on invasive pneumococcal disease and OM.[16] There was 97.4% vaccine efficacy for invasive disease and an 8.9% reduction in clinic visits for OM in the vaccine group. However, there was greater protection for bacteriologically confirmed vaccine serotype-specific pneumococcal OM (66.7% reduction in episodes of OM with perforation that were culture positive for vaccine serotypes), frequent episodes (22.8% reduction), and severe OM (20.1% reduction in ventilation tube placements). Among the children with spontaneously draining ears, all vaccine failures were caused by serotype 19F. This is the same serotype observed in the one fully vaccinated invasive disease vaccine failure.[16]

In a Finnish study, infants were vaccinated at 2, 4, 6 and 12 months of age with the 7-valent pneumococcal conjugate vaccine.[17] The vaccine reduced the overall number of episodes of OM by 6%, which is similar to the findings in the California study. Culture confirmed pneumococcal episodes were reduced by 34% (95% confidence interval [CI] 21 to 45%), and the number of episodes due to the serotypes contained in the vaccine was reduced by 57% (95% CI 44 to 67%).[17] The number of episodes attributed to serotypes that are cross reactive with those in the vaccine was reduced by 51% (95% CI 27 to 67%). However, the number of episodes due to all other serotypes increased by 33% (95% CI 1 to 80%). This indicates that vaccination may increase the likelihood of disease due to serotypes not included in the vaccine.[17]

The impact of pneumococcal conjugate vaccine on the development of OM for most children is therefore likely to be minimal for acute OM, but may be more substantial for severe or recurrent disease.

3.2.1 Nasopharyngeal Carriage of Pneumococci

There is a strong relationship between the acquisition and carriage of pneumococci and the development of OM.[18] Therefore, reduction in carriage rates in infancy can be expected to impact on OM rates. Furthermore, pneumococcal conjugate vaccines could reduce the circulation of pneumococcal strains that commonly cause disease and that are resistant to antibacterials. Antibacterial resistance in pneumococci is serotype specific, and most resistant strains belong to serotypes that are included in the 7-valent conjugate vaccine.[19] Thus, large-scale vaccine use should lead to reduced carriage of these serotypes in vaccinees and this in turn should reduce circulation of these serotypes in the community.

On the other hand, impact on carriage may also have some negative effects. It has already been demonstrated that reduction in carriage of vaccine-type pneumococci in recipients of conjugate vaccines is accompanied by an increase in the carriage of serotypes not included in the vaccine. A Gambian study in which infants were immunised with a 5-valent pneumococcal conjugate vaccine, then reimmunised with the 23-valent pneumococcal PS vaccine at the age of 2 years, showed a reduction in prevalence of nasopharyngeal carriage of pneumococci of the vaccine serotypes. However, replacement with pneumococci of non-vaccine serotypes occurred, so the overall prevalence of pneumococcal carriage in vaccinated children was little changed.[20] A second study of Gambian children 1 to 4 months after completion of the primary course of vaccination with the 9-valent conjugate vaccine in infancy showed a similar trend but the effect was smaller than in the initial study.[21] Studies from South Africa and Israel have shown similar effects.[22,23] As noted in section 3.2, serotype replacement has lead to a slight increase in OM due to non-vaccine serotypes, although the overall ef-

fect remained positive.[17] Concerns remain as to whether this phenomenon will affect rates of invasive disease.[20] This has not been observed in the US but it remains a possibility in developing countries and other communities with high carriage rates.[21]

3.3 Pneumococcal Protein Vaccines

The rise in non-vaccine pneumococcal serotypes causing OM after immunisation with conjugate[17] may offset the clinical value of these vaccines.[20] Alternative potential vaccine strategies are being developed. The possibility of using immunity to pneumococcal surface proteins is currently being explored. Protein vaccines could have a definite advantage over PS-based vaccines because protection would be provided against all serotypes. In addition, proteins can be expressed in recombinant bacteria enabling large-scale production of vaccine antigens at a relatively low cost.

Initial results from animal studies appear promising. Pneumococcal Surface Protein A (PspA) has been found to provide protection against OM in rats.[24] Vaccination with a mixture of PspA and a second pneumococcal protein, Pneumococcal Surface Adhesin A (PsaA) has been observed to offer better protection against nasal carriage in mice, than vaccination with either protein alone.[25] PspA and the modified pneumococcal toxin, pneumolysoid, have been shown to elicit protection from invasive infections in animals.[26] A combination of these proteins may form a useful pneumococcal vaccine, or the inclusion of a few of these proteins into the pneumococcal conjugate vaccines might enhance their efficacy and might constitute a complete pneumococcal vaccine.[27]

4. Respiratory Syncytial Virus Vaccines

An effective RSV vaccine for infants and young children could markedly decrease the occurrence of OM. However, no successful vaccine has yet been developed for RSV infection. Subunit RSV vaccines based on the fusion protein (F protein) have been developed but their evaluation has been limited to previously infected persons. A live attenuated vaccine has been developed and evaluated in non-immune infants, but it resulted in respiratory symptoms. Its effectiveness is unknown.

The feasibility of RSV immunisation has been supported by the success of passive immunisation. In a double-blind, placebo-controlled trial involving 1502 high-risk infants, the protective efficacy of palivizumab, a RSV derived monoclonal antibody, demonstrated a reduction in lower respiratory disease; however, there was no reduction in the development of AOM.[28]

5. Influenza Vaccine

Prevention of OM by influenza vaccination has been demonstrated. A prospective cohort trial conducted within daycare centres of 168 children aged between 6 and 30 months documented a reduction in cases of influenza A. Half the participants received the trivalent subvirion influenza virus vaccine. There was a 31% decline (95% CI 2 to 51%) in OM in the daycare centres during a community outbreak of influenza.[29] In addition, there was a 25% reduction in OM with effusion; however, this was not statistically significant.[29]

A multicentre, double-blind, placebo-controlled trial of live attenuated, cold-adapted, trivalent influenza virus vaccine in children aged 15 to 71 months showed a similar reduction in episodes of febrile OM.[30] Culture-positive influenza was significantly less common in the vaccine group than the placebo group. The vaccine efficacy was 93% against culture-confirmed influenza. The vaccinated children had significantly fewer febrile illnesses, including 30% fewer episodes of febrile OM (95% CI 18 to 45%).[30]

The influenza virus vaccine is currently used in the US and indications for its use are changing. One indication for influenza virus vaccine is for children with recurrent AOM.

6. Conclusion

Prevention of OM by immunisation will require an approach targeting both bacterial and viral pathogens. The available data suggest that pneumococcal conjugate vaccines provide protection

against serotype-specific AOM in children, reduce serotype specific pneumococcal carriage, and reduce carriage of penicillin resistant pneumococci. However, an increase in non-vaccine serotype OM has been demonstrated in one study which may limit the overall effectiveness of the vaccine. The development of other candidate bacterial vaccines targeting non-typable *H. influenzae* and *M. catarrhalis* are in the early stages of identifying promising antigens that maybe immunogenic. The most promising vaccine in the prevention of OM to date has been influenza virus vaccine. A more substantial reduction in the burden of OM in childhood would require vaccines that are effective against the bacterial and viral pathogens beginning before 6 months of age.

Acknowledgements

No sources of funding were used in the preparation of this manuscript. There are no potential conflicts of interest.

References

1. Nelson WI, Kennedy DL, Lao CS, et al. Out-patient systemic anti-infective use by children in the United States: 1977 to 1986. Pediatr Infect Dis J 1988; 7: 505-9
2. Vernon-Feagans L. Impact of otitis media on speech, language, cognition, and behaviour. In: Rosenfeld RM, Bluestone CD, editors. Evidence-based otitis media. Hamilton (ON): Decker, 1999: 353-73
3. Gates G. Cost-effectiveness considerations in otitis media treatment. Otolaryngol Head Neck Surg 1996; 4: 525-30
4. Paradise JL, Rockette HE, Colborn DK, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. Pediatrics 1997; 99 (3): 318-33
5. Owen MJ, Baldwin CD, Swank PR, et al. Relation of infant feeding practices, cigarette smoke exposure, and group child care to the onset and duration of otitis media with effusion in the first two years of life. J Pediatr 1993; 123 (5): 702-11
6. Berman S. Otitis media in developing countries. Pediatrics 1995; 96: 126-31
7. Leach AJ, Boswell JB, Asche V, et al. Bacterial colonization of the nasopharynx predicts very early onset and persistence of otitis media in Australian aboriginal infants. Pediatr Infect Dis J 1994; 13 (11): 983-9
8. Giebink GS. The microbiology of otitis media. Pediatr Infect Dis J 1989; 8 (1 Suppl.): S18-20
9. Ruuskanen O, Arola M, Hekkinen T, et al. Viruses in acute otitis media: increasing evidence for clinical significance. Pediatr Infect Dis J 1991; 10 (6): 425-7
10. Teele DW, Klein JO, Bratton L, et al. Use of pneumococcal vaccine for prevention of recurrent acute otitis media in infants in Boston. The Greater Boston Collaborative Otitis Media Study Group. Rev Infect Dis 1981; 3 Suppl. 3: S113-8
11. Makela PH, Leinonen M, Pukander J, et al. A study of the pneumococcal vaccine in prevention of clinically acute atttacks of recurrent otitis media. Rev Infect Dis 1981; 3 Suppl. 3: S124-32
12. Shurin PA, Rehmus JM, Johnson CE, et al. Bacterial polysaccharide immune globulin for prophylaxis of acute otitis media in high-risk children. J Pediatr 1993; 123 (5): 801-10
13. Shahid NS, Steinhoff MC, Hoque SS, et al. Serum, breast milk, and infant antibody after maternal immunisation with pneumococcal vaccine. Lancet 1995; 346 (8985): 1252-7
14. O'Dempsey TJ, McArdle T, Ceesay SJ, et al. Immunization with a pneumococcal capsular polysaccharide vaccine during pregnancy. Vaccine 1996; 14 (10): 963-70
15. Englund JA, Glezen WP. Passive immunization for the prevention of otitis media. Vaccine 2000; 19 Suppl. 1: S116-21
16. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000; 3: 187-95
17. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; 344 (6): 403-9
18. Faden H, Duffy L, Wasielewski R, et al. Relationship between nasopharyngeal colonization and the development of otitis media in children. Tonawanda/Williamsville Pediatrics. J Infect Dis 1997; 175 (6): 1440-5
19. Klugman KP, Friedland IR. Antibiotic-resistant pneumococci in pediatric disease. Microb Drug Resist 1995; 1 (1): 5-8
20. Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? Lancet 2000; 356 (9237): 1210-1
21. Obaro SK, Adegbola RA, Banya WA, et al. Carriage of pneumococci after pneumococcal vaccination. Lancet 1996; 348 (9022): 271-2
22. Mbelle N, Huebner RE, Wasas AD, et al. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; 180 (4): 1171-6
23. Dagan R. Treatment of acute otitis media: challenges in the era of antibiotic resistance. Vaccine 2000; 19 Suppl. 1: S9-S16
24. White P, Hermansson A, Svanborg C, et al. Effects of active immunisation with a pneumococcal surface protein (PspA) and of locally applied antibodies in experimental otitis media. ORL J Otorhinolaryngol Relat Spec 1999; 61: 206-11
25. Briles DE, Hollingshead S, Brooks-Walter A, et al. The potential to use PspA and other pneumococcal proteins to elicit protection against pneumococcal infection. Vaccine 2000; 18 (16): 1707-11
26. Ogunniyi AD, Folland RL, Briles DE, et al. Immunization of mice with combinations of pneumococcal virulence proteins elicits enhanced protection against challenge with Streptococcus pneumoniae. Infect Immun 2000; 68 (5): 3028-33
27. Briles DE, Hollingshead SK, Nabors GS, et al. The potential for using protein vaccines to protect against otitis media caused by Streptococcus pneumoniae. Vaccine 2000; 19 Suppl. 1: S87-95
28. The Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102 (3 Pt 1): 531-7
29. Clements DA, Langdon L, Bland C, et al. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. Arch Pediatr Adolesc Med 1995; 149 (10): 1113-7
30. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. N Engl J Med 1998; 338 (20): 1405-12

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