Review

Prevention of otitis media: Now a reality?

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ABSTRACT

Acute otitis media (AOM), one of the most common childhood diseases, is associated with a substantial medical, social and economic burden. Non-typeable Haemophilus influenzae (NTHi) and Streptococcus pneumoniae are the two main causes of bacterial OM. The 7-valent pneumococcal CRM_{197}-conjugate vaccine (7vCRM, Prevnar™/Prevenar™, Wyeth) demonstrated efficacy against AOM caused by vaccine pneumococcal serotypes. Protection against overall AOM was also observed with an 11-valent pneumococcal protein D-conjugate vaccine (11Pn-PD) in the Pneumococcal Otitis Efficacy Trial (POET). Following POET, an optimized 10-valent pneumococcal non-typeable H. influenzae protein D-conjugate vaccine (PHiD-CV; Synflorix™, GlaxoSmithKline Biologicals) was developed. This vaccine includes serotypes 1, 5, and 7F, in addition to those already included in 7vCRM, and was recently licensed in Europe for active immunization against invasive disease and AOM caused by S. pneumoniae in infants and children from 6 weeks up to 2 years of age. The use of protein D as carrier protein permits avoidance of possible interferences known to occur with some conjugate vaccines, and has the added potential benefit of providing protection against NTHi. This review seeks to highlight the recent advances in the field of OM vaccination, with a focus on data regarding the recently licensed PHiD-CV.

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Contents

1. Introduction

Acute otitis media (AOM) is one of the most frequent childhood diseases with the incidence peaking among children aged between 6 and 18 months [1]. Approximately three in four children will have developed at least one episode of AOM by the age of 3 years [2], with more than one-third of children experiencing recurrent infections (defined as three or more episodes within 6 months) [1]. Recurrent AOM has a considerable negative impact on the quality of life of children, and causes concern to their caregivers [3]. It is a common reason for both physician visits [4–6] and antibiotic prescriptions [7–9], resulting in a significant burden on healthcare systems.

The direct costs associated with AOM are substantial [10–12]. A Finnish study estimated that in total, each single attack of AOM cost $US228 when the children in the survey had 1.5 attacks of AOM per person year [10]. The majority of the economic burden of AOM stems from indirect costs primarily accounted for by parental time, averaging 84–90% of the total cost of the illness [13].

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Non-typeable *Haemophilus influenzae* (NTHi) and *Streptococcus pneumoniae* are the two main causes of bacterial OM [14–17], and the disease is a major cause of doctor consultations and antibiotic prescriptions [18,19] which are increasingly recognised as the main selective pressure driving antibiotic resistance [20]. The high prevalence of drug-resistant pathogens such as penicillin-resistant *S. pneumoniae* and β-lactamase producing or other ampicillin-resistant *H. influenzae* are complicating factors in OM management [21]. A study carried out in the US between 1992 and 2003 revealed that the proportion of β-lactamase producing *H. influenzae* isolates increased from 56% before, to 64% after 7vCRM introduction [22]. Increased resistance to penicillin, macrolides, cotrimoxazole, amoxicillin-clavulanate as well as multi-drug resistance were reported between 2000 and 2004 among non-vaccine serotypes of *S. pneumoniae* [23]. The clinical relevance of this phenomenon is still unknown, and debate continues as to whether increased resistance among pneumococci has been accompanied by an increased rate of treatment failure [24]. Preventing infectious diseases through vaccination may however reduce the need for antibiotics and the selective pressure exerted by their use on naso- and oropharyngeal bacterial pathogens [25].

The evolving etiology of OM also complicates treatment and case management. Since the introduction of the 7-valent pneumococcal conjugate vaccine (7vCRM, *Prevnar*™/*Prevenar*™, Wyeth), the relative proportion of AOM cases caused by NTHi has increased [16,22,26]. NTHi is a difficult-to-treat pathogen, more often associated with bilateral OM, treatment failure, recurrent episodes, spontaneous rupture of the tympanic membrane and acute mastoiditis [27–29].

In the last few years, progress has been made in the development of vaccines against OM pathogens. Given the large burden of OM (e.g. economic, societal, related to antibiotic consumption), prevention may be the best option for disease management. The objective of this review is to highlight the recent advances in the field of vaccination against AOM, with a special focus on a new 10-valent pneumococcal non-typeable *H. influenzae* protein D-conjugate vaccine (PHiD-CV; *Synflorix*™, GlaxoSmithKline Biologicals).

2. Pneumococcal conjugate vaccines

2.1. 7vCRM, the first generation

7vCRM was the first pneumococcal conjugate vaccine (PCV) available and was introduced in the US in 2000. It contains the pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, each conjugated to CRM_{197} (a non-toxic, cross-reacting mutant of diphtheria toxin). 7vCRM has demonstrated noticeable efficacy against invasive pneumococcal disease (IPD) [30–32], but has some limitations. Firstly, whilst 7vCRM was estimated to cover 80–90% of serotypes responsible for IPD in young children in North America and Australia, its serotype coverage can be considerably lower in other parts of the world especially Africa, Latin America and Asia [33,34]. Secondly, since 7vCRM introduction in the US, non-vaccine serotypes, notably serotypes 1, 7F and 19A, have been increasingly found in children with IPD [35–40].

In the Finnish Otitis Media (FinOM) study, 7vCRM reduced the number of AOM episodes due to serotypes contained in the vaccine by 57% (95% CI: 44 to 67), and culture-confirmed pneumococcal episodes by 34% (95% CI: 21 to 45) [41]. The number of AOM episodes attributed to cross-reactive serotypes (i.e. 6A, 9N, 18B, 19A and 23A) was also reduced by 51% (95% CI: 27 to 67). However, these encouraging results in the prevention of AOM due to vaccine- or cross-reactive serotypes have been eroded by the apparent replacement of vaccine serotypes with non-vaccine serotypes, as well as by an increased incidence of AOM caused by otopathogens other than

S. pneumoniae [41]. Children in the 7vCRM group had 33% (95% CI: −1 to 80) more episodes of AOM caused by non-vaccine pneumococcal serotypes, 11% (95% CI: −34 to 8) more AOM episodes caused by *H. influenzae*. As a result, subjects receiving 7vCRM had only 6% (95% CI: −4 to 16) fewer episodes of AOM overall [41], a number that was very close to the 7% reduction of overall clinical AOM episodes observed in the large US efficacy trial (95% CI: 4.1 to 9.7) [42]. Interestingly, administration of another 7-valent prototype vaccine (7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine (PncOMPC; Merck)) to a third arm in the same study resulted in an apparent 27% (95% CI: −70 to 6, not significant) more episodes of AOM caused by non-vaccine serotypes, 9% (95% CI: −32 to 10, not significant) more AOM episodes due to *H. influenzae* and 16% (95% CI: −36 to 2, not significant) more AOM episodes caused by *M. catarrhalis* [43]. Overall, there was virtually no difference in term of occurrence of clinical AOM episodes of any cause between both groups (difference PncOMPC minus control group = 1% with 95% CI: −12 to 10) [43].

After widespread use of the 7vCRM vaccine, its effect on OM has been greater than expected [41,42,44–46]. Vaccination with 7vCRM was shown to reduce the number of outpatient visits for OM by 20% (95% CI: 2 to 38) in children aged < 2 years [45], to reduce the incidence of frequent OM (by 17% in Tennessee and 28% in New York children) and to reduce the incidence of pressure-equalizing tube insertions (by 16% in Tennessee and 23% in New York children) [46].

Another PCV including 13 serotypes also conjugated to CRM that contains the additional serotypes 3, 6A and 19A is currently under development.

2.2. 11Pn-PD, the prototype vaccine

Partially addressing the problem of emergence of pneumococcal strains not contained in the 7vCRM vaccine, expanded pneumococcal conjugate vaccine formulations were designed that include additional serotypes such as serotypes 1, 5 and 7F that are highly invasive [40,47–50]. An 11-valent pneumococcal NTHi protein D-conjugate vaccine (11Pn-PD), containing pneumococcal serotypes 1, 5 and 7F as well as serotype 3, in addition to the pneumococcal serotypes already included in 7vCRM was developed as the prototype of PHiD-CV. The serotypes 6A and 19A have not been included in the formulation because a cross-protection with 6B and 19F was expected. All serotype polysaccharides contained in the 11Pn-PD vaccine were conjugated to *H. influenzae* protein D. The rationale for using protein D as carrier protein was primarily to avoid possible carrier mediated suppression and bystander interference known to occur with some conjugate vaccines using either tetanus or diphtheria toxoids as carrier protein [51,52]. Additionally, it was also expected that the use of protein D would have the potential of providing protection against infections caused by NTHi, based on the positive experience with protein D containing vaccines in infants and in animal models [53,54]. This would have the advantage of addressing the problem of bacterial shift observed in the FinOM study [41,43].

2.2.1. Protein D as an antigen candidate

Protein D has properties which makes it a good candidate for a carrier protein with antigenic properties. It is a highly conserved lipoprotein found in all *H. influenzae* strains [55–57], with limited drift observed in the encoding gene [58]. It is exposed on the cell surface [58,59], is a critical NTHi virulence factor in respiratory tract infections [56,57] and it plays a role in the pathogenesis of NTHi infection [59,60]. Mutants lacking the *hpd* gene which code for protein D are 100-fold less infectious than the wild type strain in a rat otitis model [59]. In addition, in a human nasopharyngeal tissue culture model, protein D caused a significant decrease in ciliary

beat frequency and increased loss of cilia [60]. Protein D expression was also shown to promote adherence and internalization of NTHi into human monocytic cells [61], but its exact role in adhesion and invasion remains to be determined.

2.2.2. Protective effect of NTHi protein D

Anti-protein D antibodies have shown protective efficacy in animal models of NTHi OM [54,62–64]. A pronounced activity of protein D antibodies has been observed in a chinchilla AOM model, which closely mimics human AOM infection [54,64]. Passive immunization by transfer of human serum from children vaccinated with two protein D-conjugated vaccine formulations (a 4-valent pneumococcal conjugate vaccine (4Pn-PD) or a Hib-TT-MenAC-PD combined conjugate vaccine) conferred approximately 34% protection against the development of OM due to NTHi [54]. Although the authors could not rule out the contribution of other antibodies contained within these human sera, the results indicated that the protection was largely attributable to vaccine induced anti-protein D antibodies present in the passively transferred serum [54].

The Pneumococcal Otitis Efficacy Trial (POET) evaluated the efficacy of 11Pn-PD in preventing AOM [65]. The POET trial was the first to show a protective efficacy against AOM episodes caused by NTHi. In addition, there was a remarkable similarity between the overall vaccine efficacy against AOM episodes caused by pneumococcal vaccine serotypes in POET (57.6%; 95% CI: 41.4 to 69.3) [65] and that of 7vCRM (57%; 95% CI: 44 to 67) [41] and 7v-PncOMPc (56%; 95% CI: 44 to 66) [43] in the FinOM trial. However, in POET no apparent increase in the incidence of AOM caused by pneumococcal serotypes not contained in the vaccine or other bacterial pathogens was recorded over the study period [65].

In POET, a highly significant protective efficacy of 11Pn-PD was shown against clinical AOM episodes (33.6%, 95% CI: 20.8 to 44.3), AOM episodes confirmed by aspiration of middle ear fluid (32.4%, 95% CI: 19.0 to 43.6), culture-confirmed bacterial AOM episodes (42.1%, 95% CI: 27.7 to 53.7) and culture-confirmed pneumococcal AOM episodes (51.5%, 95% CI: 36.8 to 62.9) [65]. The efficacy against the first episode of AOM (of any cause) persisted for at least 18 months (Fig. 1) [Prymula, personal communication, 2009]. Both vaccine serotype pneumococcal AOM episodes (57.6%; 95% CI: 41.4 to 69.3), and AOM episodes caused by vaccine-related cross-
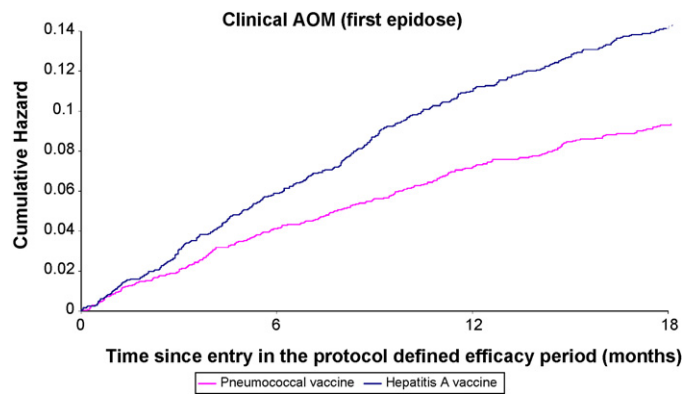
Fig. 1. Cumulative hazard curve for the first occurrence of acute otitis media (of any cause) during per protocol follow-up after administration of the 11-valent pneumococcal non-typeable *H. influenzae* protein D-conjugate vaccine (11Pn-PD) or hepatitis A vaccine in POET [Prymula, personal communication, 2009].

reactive pneumococcal serotypes including 6A and 19A (65.5%; 95% CI: 22.4 to 84.7) were also reduced [65].

Furthermore, a significant protective efficacy against AOM episodes caused by NTHi (35.3%; 95% CI: 1.8 to 57.4) was demonstrated in POET [65].

2.3. PHiD-CV

Following POET, the prototype 11Pn-PD vaccine formulation was refined and the final PHiD-CV formulation was developed. The PHiD-CV vaccine formulation includes serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (1, 5 and 7F in addition to those already included in 7vCRM). Serotype 3 was not maintained in the final vaccine formulation since clinical experience with 11Pn-PD generated unexpected results for this serotype compared to the other vaccine pneumococcal serotypes, in particular the lack of protection against AOM due to serotype 3 [65,66], and the generation of an atypical immune response [53,65,67]. All of the polysaccharides in PHiD-CV are conjugated to the NTHi-derived protein D carrier, with the exception of serotypes 18C and 19F, for which immunogenicity was improved by conjugation to tetanus and diphtheria toxoids, respectively [68,69].

Table 1
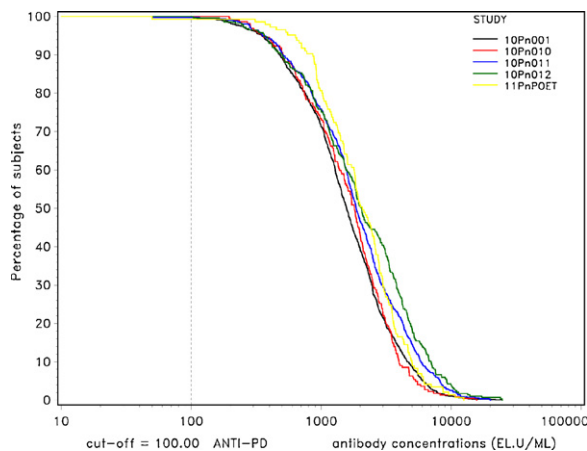Summary of studies which examined the immunogenicity of PHiD-CV or 11Pn-PD.

ID study number	Study groups included in reverse cumulative distribution curves	Vaccination schedule	Patient population	Country	Reference
Study 10Pn001 (10553/NCT00307554)	PHiD-CV + DTPa-HBV-IPV/Hib except for dose 2 in France (co-administered with IPV/Hib)	Three primary doses at 2, 3 and 4 months of age	Healthy infants aged 6–12 weeks at 1st vaccination	Finland, France and Poland	[69]
Study 10Pn010 (107017/NCT00370318)	PHiD-CV + DTPa-HBV-IPV/Hib + HRV without prophylactic antipyretic medication	Three primary doses at 3, 4 and 5 months of age	Healthy infants aged 9–16 weeks at 1st vaccination	Czech Republic	[70]
Study 10Pn011 (107005/NCT00334334)	PHiD-CV + DTPa-HBV-IPV/Hib + MenC-CRM PHiD-CV + DTPa-HBV-IPV/Hib + MenC-TT PHiD-CV + DTPa-HBV-IPV + Hib-MenC	Three primary doses at 2, 4 and 6 months of age	Healthy infants aged 6-16 weeks at 1st vaccination	Germany, Poland and Spain	[68]
Study 10Pn012 (107007/NCT00344318)	PHiD-CV + DTPw-HBV/Hib + IPV	Poland: three doses at 2, 4 and 6 months of age	Healthy infants aged 6–12 weeks at 1st vaccination	Poland	[71]
Study 11PnPOET (347414/NCT00119743)	11Pn-PD + DTPa-HBV-IPV/Hib	Three primary doses at 3, 4 and 5 months of age	Healthy infants aged 6 weeks–5 months at 1st vaccination	Czech and Slovak Republics	[65]

PHiD-CV: 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (Synflorix™, GlaxoSmithKline Biologicals).
11Pn-PD: 11-valent pneumococcal vaccine conjugated to protein D (GlaxoSmithKline Biologicals).
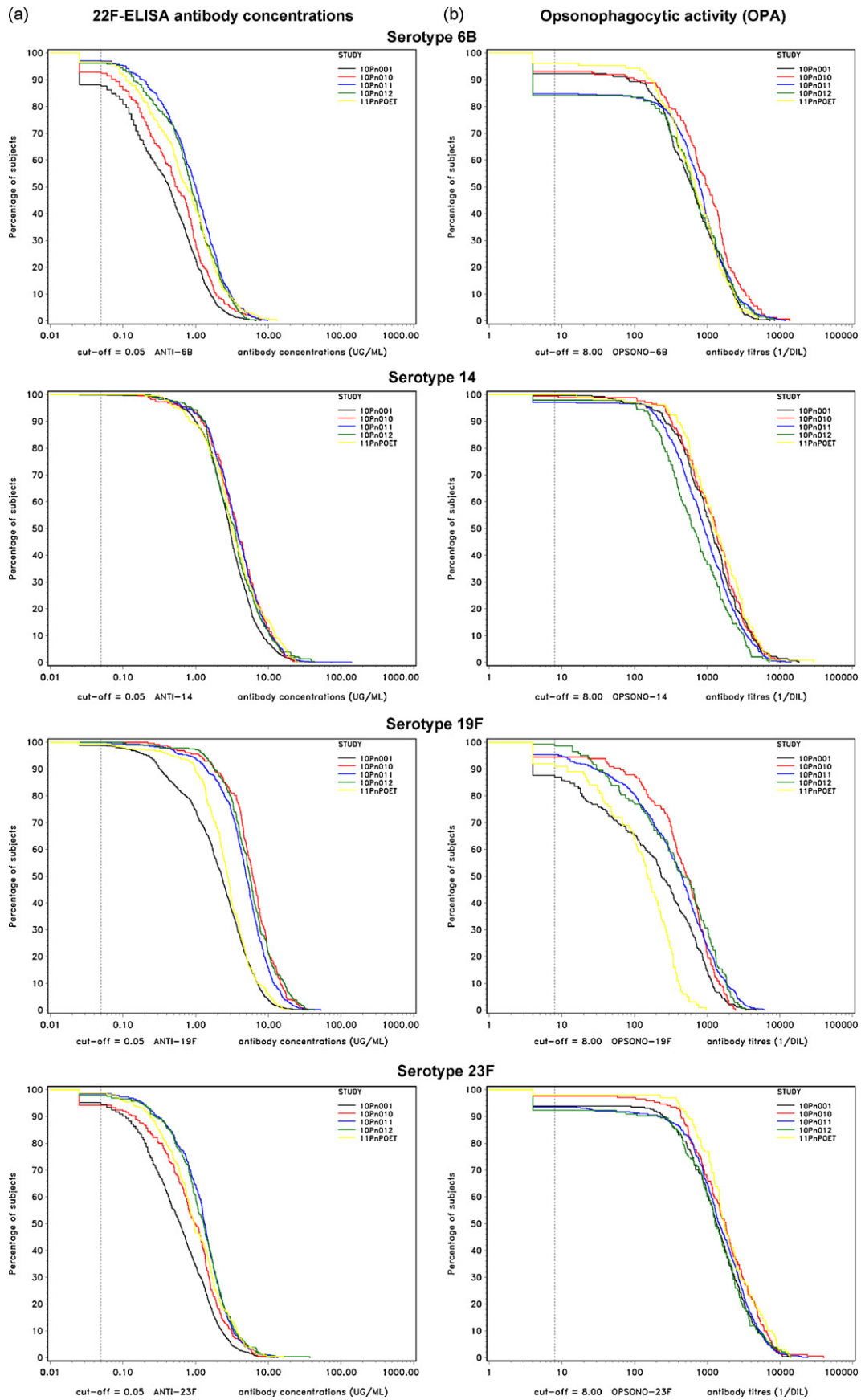
Fig. 2. Reverse cumulative distribution curve for (a) pneumococcal serotype concentrations (μg/ml) and (b) OPA titres of pneumococcal serotypes 6B, 14, 19F and 23F, 1 month after 3 primary 10-valent pneumococcal non-typeable *H. influenzae* protein D-conjugate vaccine (PHiD-CV) doses in the European studies 10Pn001, 10Pn010 (non-antipyretic group only), 10Pn011 and 10Pn012 (Polish patients only), or following 3-doses of 11-valent pneumococcal non-typeable *H. influenzae* protein D-conjugate vaccine (11Pn-PD) priming in POET.

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