Vaccine 27 (2009) 2877–2883

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

How to compare the efficacy of conjugate vaccines to prevent acute otitis media?

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ARTICLE INFO

Article history:
Received 30 September 2008
Received in revised form 23 February 2009
Accepted 24 February 2009
Available online 10 March 2009

Keywords:
Otitis
Conjugate vaccine
Randomized clinical trial
Pneumococcus

ABSTRACT

Although the currently available 7-valent pneumococcal conjugate vaccine (PCV7-CRM_{197}) has been primarily designed for the prevention of invasive pneumococcal disease, it has also demonstrated the potential to prevent acute otitis media (AOM) and its associated complications. A candidate 11-valent pneumococcal conjugate vaccine (PCV11-*Hi*D), which utilizes *Haemophilus influenzae* (*Hi*)-derived protein D as a carrier has demonstrated the ability to prevent AOM caused by not only vaccine serotypes of *Streptococcus pneumoniae* (*Sp*), but also those caused by *Hi*. The methodological, clinical, and epidemiological factors influencing results of vaccine trials for AOM prevention were reviewed and a model-based approach was developed, in order to assess the relative efficacy of different vaccine formulations. Six randomized trials having AOM as a measured outcome were identified. Vaccine efficacy (VE) ranged from −1% to 34% for all-cause AOM and between 56% and 64% for AOM caused by vaccine-type *Sp*. Using otopathogen-specific VE rates from the FinOM and POET trials and otopathogen distributions observed in three relatively unbiased studies, VE against all-cause AOM episodes under different scenarios was modeled. The most important factor explaining variation in VE estimates was bacterial replacement, which was present in the PCV7-CRM_{197} FinOM study but not in the PCV11-*Hi*D POET study. Another contributing factor was increased protection conferred against *Hi* AOM by protein D. Geographical variation in the distribution of otopathogens was a third factor explaining differences between trials. More studies on the current aetiology of AOM need to be performed to accurately predict the marginal benefit of a switch from PCV7-CRM_{197} to the newly licensed PCV10-*Hi*D-DiT or to the future PCV13-CRM_{197}.

1. Introduction

Acute otitis media (AOM) represents a substantial cause of morbidity and health services use in children and *Streptococcus pneumonia* (*Sp*) is the predominant causative pathogen [1]. In Canada, approximately 40% of health care costs associated with *Sp* infections are attributable to AOM and its complications [2]. Resistance to antimicrobial agents is a growing problem worldwide [3,4]. Although pneumococcal conjugate vaccines have been primarily designed for the prevention of invasive pneumococcal disease, they have the potential to prevent other pneumococcal infections, including AOM.

The first 7-valent pneumococcal conjugate vaccine using a non-toxic mutant of diphtheria toxin as carrier protein (PCV7-CRM_{197}) was licensed in the early 2000s [5], and a 13-valent product (PCV13-CRM_{197}) is currently under development [6]. Another 7-valent vaccine using an outer membrane protein complex of *Neisseria meningitidis* serogroup B as carrier protein (PCV7-*Nm*OMP) was also tested in a clinical trial [7], but the development of this vaccine was discontinued. Another approach for polysaccharide conjugation is to use as carrier a highly conserved surface lipoprotein found in both non-typable and typable *Haemophilus influenzae* (*Hi*) strains [8]. An 11-valent candidate vaccine (PCV11-*Hi*D) was tested in a clinical trial [9]. A more potent 10-valent derivative (PCV10-*Hi*D-DiT) was developed with a slightly different formulation: *Sp* serotype 3 was taken out, tetanus toxoid was selected as carrier for *Sp* serotype 18C, and diphtheria toxoid for *Sp* serotype 19F [10]. PCV10-*Hi*D-DiT has been licensed in several countries on the basis of immunogenicity data and no clinical data are available yet.

In a meta-analysis of four randomized controlled trials of pneumococcal conjugate vaccines, the authors concluded that vaccination resulted in a small and statistically non-significant 3% (95%CI: −8% to 13%) protection against all-cause AOM episodes [11]. However, a small reduction in the frequency of AOM could generate substantial savings for the health system, families and the society. Comparing the relative merits of different vaccines tested in differ-

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doi:10.1016/j.vaccine.2009.02.102

ent settings and using different methodologies is a real challenge. In a recent paper, Jahn-Eimermacher et al. [12] reviewed different approaches for analysing vaccine efficacy (VE) for the prevention of AOM, focusing on the selection of the main outcome and statistical methods. However, there are many other sources of variation that should be considered in comparing vaccine efficacy estimates observed in different trials. Head-to-head comparisons of different pneumococcal conjugate vaccines in randomized clinical trials are extremely difficult and new vaccines have been and will be licensed on the basis of immunogenicity data. A model-based approach is a solution for comparing the merits of different products in preventing AOM.

In the first part of this paper, results of trials assessing VE for AOM prevention are presented. In the second part, the possible effect of different methodological, clinical and epidemiologic factors in influencing VE estimates are reviewed. In Section 3, a model-based method is presented for assessing the relative efficacy of different vaccines to prevent AOM and is used to identify key factors explaining differences between the Finnish Otitis Media (FinOM) trial [13] and the Pneumococcal Otitis Efficacy Trial (POET) [9], as well as to predict the marginal efficacy of two new vaccines relative to their predecessors, respectively, PCV13-CRM_{197} vs. PCV7-CRM_{197} and PCV10-*Hi*D-DiT vs. PCV11-*Hi*D.

2. Trials assessing vaccine efficacy against AOM

Extending a search performed for a previous review [11], we identified five individually randomized clinical trials having AOM as a study outcome: two on PCV7-CRM_{197} [13–16], and one each on PCV9-CRM_{197} [17], PCV7-*Nm*OMP [7] and PCV11-*Hi*D [9]. Note that the same control group was used in the two FinOM studies [7,13]. A double-blind community-randomized trial on PCV7-CRM_{197} was also included [18]. A trial testing the administration of PCV-7 followed by a 23-valent polysaccharide vaccine was excluded because participants were children with recurrent otitis media and also because the effect of the two products could not be disentangled [19].

The main characteristics of the trials are shown in Table 1. The overall reported vaccine efficacy ranged from −1% to 34% for AOM, and between 56% and 64% for AOM caused by vaccine-type *Sp*. Overall, there was no major difference between vaccines for protection against AOM caused by vaccine-type *Sp*, whereas PCV11-*Hi*D conferred a much higher protection against all-cause AOM than all other vaccines.

Tympanocentesis and culture of middle ear fluid were routinely performed in the FinOM and POET trials, and pathogen- and serotype-specific VE rates could be estimated [7,9,13]. As shown in Table 2, confidence intervals of VE estimates were wide and inferences regarding vaccine or serotype differences should be made with care. The three vaccines provided a high level of protection against *Sp* serotype 6B, and the lowest efficacy estimates were against 19F. No consistent pattern was observed for cross-protection against the *Sp* serotypes related to those included in the vaccines. PCV11-*Hi*D provided significant protection against AOM caused by *Hi*, and this was mainly associated with protection against non-typable *Hi* representing the vast majority of *Hi* isolates [9].

All vaccines had a greatest impact on the most severe forms of AOM, reducing the risk of recurrence and complication. In the Northern California Kaiser Permanente (NCKP) trial, VE was 12% against recurrent AOM, compared with 6% against all AOM episodes in the intent-to-treat analysis [14]. In the PCV7-CRM_{197} FinOM trial, VE was 18% against recurrent AOM after 24 months of age and 8% against any AOM [16]. Reduction in the frequency of ventilatory tube placement was 20% (95%CI: 2–35%) in the per protocol analysis in the PCV7-CRM_{197} NCKP trial [14], 39% (95%CI: 4–61%) in the PCV7-CRM_{197} FinOM follow-up study [16], 22% (95%CI: −225% to 64%) in the per protocol analysis of the PCV7-CRM_{197} trial among American Indians [18], and 60% (95%CI: −27% to 88%) in the PCV11-*Hi*D POET study [9].

3. Factors influencing estimates of vaccine efficacy

The study design is the first factor that could influence VE estimates. Double-blind placebo-controlled randomized trials have the advantage of minimizing selection or information biases, but this is true for intention-to-treat analyses only. When a substantial number of participants are lost, as is often the case in extended follow-up studies [16], comparability of experimental and control groups is reduced. Community-randomized trials provide unbiased (although less precise) VE estimates when clustering is taken into account in statistical analysis [20]. In such trials, the comparison of AOM frequency between communities in which the vaccine was offered or not, provides an estimate the total direct plus indirect (herd) protection, while the comparison between vaccinated and unvaccinated children in communities in which the vaccine was offered provides an estimate of the direct protection, assuming that herd protection is equal in both groups.

Various immunization schedules have been used in PCV trials (Table 1). There has been no head-to-head efficacy comparison of an accelerated 2-, 3-, 4-month-schedule with an extended 2-, 4-, 6-month-schedule for the primary immunization series. In the United Kingdom, a group of infants received three primary PCV7-CRM_{197} doses, respectively, at 2, 4 and 6 months of age, and post-primary serotype-specific IgG geometric mean concentrations were similar to those measured in three studies in the United States where the same vaccine was administered at 2, 4 and 6 months of age [21]. It is thus unlikely that differences in immunization schedule could play an important role in explaining inter-trial variation in VE.

Another important issue is the precise definition of AOM in a given study. In the NCKP trial, the per-protocol VE was 8.9% for all AOM visits and 7.0% for AOM episodes defined as the first and any subsequent visit during a 21-day period [14]. A 30-day window was used for the definition of AOM episodes both in the FinOM and POET trials. Although there were slight differences in AOM case definitions between the two studies, this had a very small impact on results [22]. In a recent review of statistical methods [12], it was shown that VE estimates were substantially different depending on which models were employed. Specifically, estimates can be generated by comparing the risk of experiencing at least one episode, or the time to any episode (Andersen–Gill model), or the time to first episode (Cox model), or the event rate (Poisson regression). In the FinOM [7,13] and POET trials [9], the same analytical method (Cox model) was used to compute VE against AOM episodes, and differences in results could not be explained by this factor.

The size of the study population is also an important factor determining the precision of VE estimates. As shown in Table 2, confidence intervals were much narrower in the very large NCKP trial than in the other studies. Unfortunately, tympanocentesis was rarely performed in the NCKP trial and otopathogen-specific VE rates could not be measured [14].

Characteristics of the study population could also affect VE estimates. Geographical differences have been described in the prevalence of bacterial pathogens causing AOM [23,24]. For example, *Sp* was isolated from 38% of positive cultures in the control group in the PCV7-CRM_{197} FinOM trial [13], 62% in the POET study [9], and 33% in a multinational survey on AOM [25], while *Hi* was isolated, respectively, in 27%, 22% and 19% of cultures. Also, *Moxarella catarrhalis* was a very common pathogen in the PCV7-CRM_{197} FinOM trial (35% of positive cultures), but not in the POET