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Review article

Impact of pneumococcal conjugate vaccines on otitis media: A review of measurement and interpretation challenges

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ABSTRACT

Acute otitis media (AOM) is among the most frequent childhood diseases and is caused by various bacterial and viral etiological agents. In this article, we provide an overview of published studies assessing the impact of higher-valent pneumococcal conjugate vaccines (PCVs) on AOM. In some instances, reports of PCV impact on complications of AOM have been included. While randomized controlled trials (RCTs) allow for the most precise assessment of vaccine efficacy against AOM, observational studies provide answers to questions regarding the public health value of these vaccines in real-life settings. We discuss the challenges that arise when measuring PCV impact on AOM in observational studies: the local variability of viral and bacterial etiology, differences in case ascertainment, care-seeking behavior, standards of care and diagnosis of AOM (e.g. use of incisions), as well as declining baseline AOM incidence that can already be in place before PCV introduction, and how these factors can impact the results and their interpretation.

Contents

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1. Introduction

Otitis media (OM) is among the most frequent childhood diseases. An assessment of its burden showed that in 2005, acute OM (AOM) had an estimated global incidence of almost 11%, with 51% of the cases occurring in children younger than 5 years of age [1]. A prospective cohort study in the US, conducted in the 1980s before the introduction of pneumococcal conjugate vaccines (PCVs), indicated that 80% of children had at least 1 AOM episode by the age of 3 years [2]. Another report shows that the incidence of OM-related visits in children younger than 2 years was 1.69 per child-year during the first year of using PCV in the US [3]. In Denmark, the cumulative pre-PCV incidence of otitis media in children younger than 7 years was 60.6% [4].

OM is also the leading cause of antibiotic prescriptions in children [5]. Evaluation of antibiotic prescription frequency in the US between 1995 and 2005 showed that, at the beginning of this period, almost 80% of pediatric patients (younger than 18 years) with AOM were prescribed antibiotics, and this proportion was generally maintained and even increased over time. However, decreasing AOM incidence that paralleled the introduction of the first commercially available PCV (PCV7) in the US in 2000 led to a decrease in overall antibiotic use [6].

Several viral and bacterial etiological agents play a role in OM. *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* (NTHi) have been described as the most common causes of bacterial AOM. Before the widespread use of PCVs, these pathogens were isolated from up to 61% of middle ear effusion samples [7–9]. Besides bacteria, viruses (e.g. influenza, rhinovirus, and others) are also involved in the pathogenesis of OM. Bacterial and viral co-infections have been observed in up to 70% of AOM cases and were associated with prolonged clinical illness [10].

Currently, there are two PCVs available on the market: the 10-valent pneumococcal NTHi protein D-conjugate vaccine (PHiD-CV) [11], in which protein D, isolated from NTHi, is used as a carrier for most of the antigens, and the 13-valent vaccine (13vCRM) [12], with CRM_{197} derived from *Corynebacterium diphtheriae* as carrier protein. These higher-valent vaccines have replaced the 7-valent CRM_{197}–conjugated PCV (PCV7 or 7vCRM), and were licensed in 2008 and 2009, respectively.

The impact of PCVs on OM has been researched and discussed since the time of their clinical development and introduction into routine immunization schedules, often with variable conclusions, typically showing a greater impact in observational studies as compared to controlled clinical trial settings. Different magnitudes of impact have also been observed in the methodologically diverse post-licensure impact/effectiveness trials. In this work, we aimed to review the outcome of recent randomized controlled trials (RCTs) and post-marketing surveillance (PMS) studies evaluating the impact of the higher-valent PCVs on OM and AOM. We also review some of the factors contributing to the differences between individual study observations that have to be considered during interpretation of these results.

2. Methodology

In this work, we aimed to identify articles and abstracts published in English language evaluating the impact of PCVs on OM and AOM in the pediatric population. We searched in 3 separate bibliographic databases: Embase/Medline, Scopus, and a Medmeme-powered database focused on conference abstracts. We selected publications reporting impact data on otitis-related endpoints between September 2010 and October 2015 (corresponding to the higher-valent PCV era) using the keywords “otitis-media”, “otitis”, or “middle-ear”. The following inclusion criteria were applied: 1) peer-reviewed original study; 2) assessment of PCV efficacy/effectiveness against all-cause AOM episodes, physician visits, or severity of OM; 3) a study population of children aged ≤5 years (Fig. 1). Additionally, relevant studies conducted on different pediatric age groups were added when necessary.

3. PCVs and their impact on AOM in RCTs

3.1. Systematic reviews of RCTs with previous generation PCVs

Since the development and implementation of PCVs, a growing body of evidence confirmed their impact on invasive pneumococcal disease (IPD) in clinical trial and post-licensure settings. However, their impact on AOM appeared to be less consistent, and the magnitude of impact varied between different efficacy and effectiveness studies [7,9,13–17]. Previously published systematic literature reviews have attempted to reconcile these outcomes and to describe the factors contributing to the different conclusions reached by these studies.

A systematic review by Taylor et al. [18] examined AOM efficacy and effectiveness in 18 studies published between January 1998 and September 2010. This paper covers results from 7vCRM, 7vOMPC (candidate vaccine conjugated to the outer membrane protein complex of *Neisseria meningitidis* serogroup B) and the 11-valent protein D-conjugated candidate vaccine (11Pn-PD; precursor of the licensed PHiD-CV). In the RCTs, 7vCRM efficacy against all-cause physician-reported AOM episodes or visits ranged between −0.1% and 9%, while the post-licensure studies showed a relatively higher effectiveness in the range of 17%–23%. These observations raised the question: why is the observed impact of 7vCRM on all-cause AOM higher in observational studies than in controlled trial settings? A possible explanation could be the decreasing incidence of AOM (mean change across studies of −15% [range: +14% to −24%]), which was observed in some countries/settings approximately 3–5 years before the introduction of PCVs [18]. Other factors may include introduction of seasonal influenza vaccination, changes to antibiotic policy such as introduction of wait-and-watch practice for AOM management aiming to reduce antibiotic use, and other non-vaccine factors. It is also important to keep in mind that RCTs analyze a relatively small sample size and are limited in time, which does not allow the effects of herd protection to be seen, and which thus hinders evaluation of the full benefit of PCVs against OM.

A more recent systematic review was published in 2014 under the aegis of the Cochrane Library [19], with the objective to assess the effect of PCVs in preventing AOM in children up to 12 years of age. The authors included 11 publications of 9 RCTs conducted in a total of 48,426 children: 7 studies with 7vCRM, one with 11Pn-PD and another one with 9vCRM. However, the results could not be pooled due to the clinical diversity between the studies in terms of study population, type of conjugate vaccine, and outcome measures. The interpretations therefore focused on the efficacy of 7vCRM, which, according to the authors' conclusion, had modest beneficial effects in healthy infants with a low baseline risk of AOM reflected by a relative risk reduction of 7% (95% confidence interval [CI]: 4%–9%). Furthermore, 7vCRM administration to high-risk infants after early infancy (first dose after 12 months of age) and in older children with a history of AOM appeared to have no benefit in preventing further episodes, with a relative risk reduction of −5% (95% CI: −25%–12%) [19].

None of these reviews included data from RCTs or post-licensure studies investigating the currently available higher-valent PCVs: PHiD-CV and 13vCRM (discussed below).