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Conference report

Issues in pneumococcal disease and pneumococcal conjugate vaccines: Highlights of the 27th meeting of ESPID, Brussels, Belgium, June 9–13, 2009

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ABSTRACT

The 27th annual meeting of the European Society for Paediatric Infectious Diseases (ESPID), held in Brussels, Belgium, addressed serious bacterial infections. The scientific program included international experts who provided insights into and discussions on the epidemiology, diagnosis, prevention, treatment, and clinical presentation of important pediatric infectious diseases. This conference report offers highlights of presentations addressing pneumococcal disease and pneumococcal conjugate vaccines.

1. Introduction

Pneumococcal disease, which continues to be one of the leading causes of childhood respiratory tract disease and mortality worldwide, results in 700,000–1 million deaths annually in children <5 years of age [1]. Before the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2000, the 7 pneumococcal serotypes covered by this vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) were associated with 65–80% of invasive pneumococcal disease (IPD) cases among young children in western industrialized countries [1]. Protection against IPD caused by vaccine serotypes may even exceed 90% with PCV7; however, protection against acute otitis media (AOM) is much lower [1].

Clinical outcomes following the introduction of PCV7 into vaccination programs have surpassed initial expectations. In addition to reducing the incidence of vaccine-serotype IPD [2] and mortality associated with IPD, [3,4] documented clinical outcomes now include reductions in the incidence of pneumonia [5] and hospitalizations due to pneumonia, [6–9] reduction in rates of IPD caused by antibiotic-resistant strains, [10] reduction in nasopharyngeal colonization, [11,12] and protection of unvaccinated populations, including adults, through the phenomenon of indirect or herd immunity [13].

Epidemiologic surveillance conducted in the years following the introduction of PCV7 has revealed that the *Streptococcus pneumoniae* serotypes causing IPD have changed [14]. The emergence of nonvaccine serotypes––19A being the most common––has made the task of reducing the incidence of IPD more complex [15–17]. These changes in the serotypes implicated in pneumococcal disease underscore the need for development of the next generation of pneumococcal conjugate vaccines.

Using the accumulated data and clinical experiences of PCV7 and looking to the future of investigational PCVs studies addressing public health and the economic impact of PCV13 in Germany, the Netherlands, the United Kingdom, and the United States were presented at the 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), which was held June 9–13, 2009, in Brussels, Belgium. This publication reports the highlights of several of these presentations and their implications for the treatment and prevention of IPD.

2. Highlights of 4 recent publications on pneumococcal disease

Serotype 19A causes invasive disease, nasopharyngeal colonization, and AOM. It is the most common serotype causing IPD in the United States. In fact, by 2004–2005, >75% of penicillin-resistant strains were serotype 19A [15]. Although serotype 19A is a member of the same serogroup as the PCV7 serotype 19F, PCV7 does not provide cross-protection against serotype 19A [15]. Because serotype 19A was common prior to the introduction of PCV7, which is evidenced by the percentage of IPD cases caused by this serotype rather than other non-PCV7 serotypes, it was able to fill an "ecological niche" left by reduced numbers of PCV7 serotypes in the postvaccine era [15].

Keith Klugman, MD, PhD, Professor at the Hubert Department of Global Health, Rollins School of Public Health, Emory University, in Atlanta, Georgia, and Ron Dagan, MD, Director of the Pediatric Infectious Disease Unit, Department of Pediatrics, at Soroka University in Beer-Sheva, Israel, spoke of these and other findings in pneumococcal disease at the symposium, "The Pneumococcal Year in Review: Interactive Expert Review of Four Recent Publications," which took place on Wednesday, June 10, 2009, at the 27th Annual Meeting of ESPID.

Research by Moore et al, [15] which was discussed during the symposium, noted that the overall incidence of IPD in the United States decreased from 24.4 to 13.8 cases per 100,000 population between 1998 (prevaccine baseline) and 2005. However, the incidence of IPD due to serotype 19A increased from 0.8 to 2.5 cases per 100,000 population during the same period—an increase of 145% to 285%.

While there were dramatic reductions in the incidence of IPD following the introduction of PCV7 in 2000, this study, which employed the population-based Centers for Disease Control and

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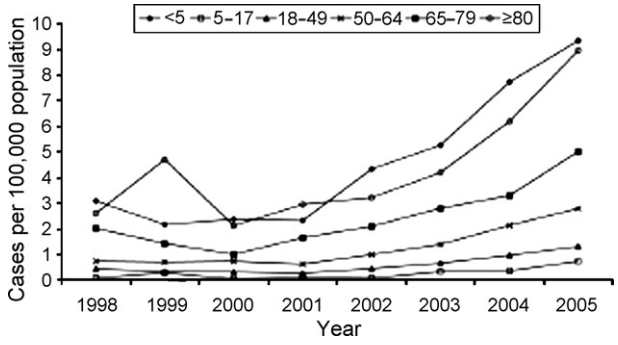

Fig. 1. Age-specific incidence of invasive pneumococcal disease caused by serotype 19A, 1998–2005. Reprinted from: Moore et al. [15], with permission.

Prevention Active Bacterial Core surveillance system, found that IPD caused by nonvaccine serotype 19A essentially increased on an annual basis thereafter (Fig. 1).

The study also showed an increase in IPD due to penicillin-resistant serotype 19A of 6.7% to 35% between 1998 and 2005. Indeed, ~60% of 19A invasive isolates were found to be nonsusceptible to penicillin. To further their understanding of this increase and other changes in the 19A profile, Moore et al. characterized serotype 19A isolates recovered during the year 2005. Susceptibility testing and multilocus sequence typing were performed on 528 (95%) of 554 serotype 19A isolates. The researchers found a growing diversity of 19A serotype isolate strains. In 1999, clonal complex 199 and 3 minor clones were apparent among serotype 19A isolates. However, in 2005, clonal expansion and emergence were fully underway—11 multiple-isolate clonal sets were detected. Worldwide epidemiologic analysis of 19A suggests that the increase in 19A in invasive disease is related to several factors: high baseline prevalence, patterns of antibiotic use, pneumococcal transmission frequency, and virulent, multidrug-resistant pneumococcal clones of 19A—for example, CC320, which was detected at all 10 surveillance sites and is the fastest-growing 19A clonal complex in the United States.

Concern has been raised regarding the role of capsular switching in the emergence of non-PCV7 serotypes, particularly 19A. There is the possibility that 19F clones were co-transformed to the 19A serotype, conferring increased penicillin resistance. Because of the increase in the prevalence of serotype 19A in invasive disease, as well as its resistance to currently available treatments, the inclusion of this serotype in a second-generation vaccine is of great importance.

Results of a population-based surveillance study by Hsu et al. [18] on pneumococcal meningitis were also discussed during the symposium. The study investigated the effects of PCV7 on pneumococcal meningitis in the United States following the introduction of PCV7 and covered the period from 1998 to 1999 (prevaccination) to 2004 to 2005 (postvaccination). At the time of the study, the effect of PCV7 on IPD was known; however, its effect on pneumococcal meningitis was unclear.

This study found a 64% decrease in the incidence of meningitis in persons <2 years of age and a 30% reduction in persons of all ages. There was a 54% reduction in the incidence of meningitis in adults aged ≥65 years, probably due to an indirect herd effect. However, the incidence of nonvaccine serotype disease (primarily 19A, 22F, and 35B serotypes) increased by 60.5% during the study period. Furthermore, the incidence of meningitis due to serotype 19A increased significantly, from 0.02 to 0.08 case per 100,000 persons ($P < 0.001$) during the study period. This rate is consistent with the increased nonsusceptibility of 19A to antimicrobials.

A retrospective study by Zhou et al. [19] on AOM in US children was also reviewed. AOM is the most common cause of physician office visits among preschool-aged children in the United States, and *S pneumoniae* is the most common bacterial cause of AOM. This retrospective analysis used MarketScan databases and included >500,000 person-years of observations on the effect of PCV7 on the incidence of AOM in US children aged <2 years, comparing prevaccine baseline data (1997–1999) to postvaccine data (2004).

Over the study period, ambulatory visits for AOM were reduced by 42.7%, prescriptions per 1000 person-years were reduced by 41.9%, and total AOM-related costs were reduced by 32.3%. These reductions coincided with increased vaccine coverage during the study period. It is possible that indirect herd effects offered a benefit to unvaccinated and partially vaccinated children through reduced carriage and transmission of vaccine serotypes. Direct medical costs for AOM were estimated to be reduced by $460 million annually compared with costs in the prevaccine era. It is likely that if indirect costs (e.g., parents' lost work time) were also considered, further reductions in total costs could be calculated.

A study by Vestrheim et al. [20] on the incidence of IPD and the effectiveness of the 2 + 1 PCV7 dosing schedule (2 primary doses plus booster at 3, 5, and 12 months, respectively) was conducted at the Norwegian Institute of Public Health. Data from the Norwegian Surveillance System for Communicable Diseases (Norwegian National Vaccination Register) included IPD incidence, serotype distribution, and rates of vaccine coverage and status. According to assessment data, there was an estimated 74% effectiveness rate (95% CI, 57–85%) for the 2 + 1 dosing schedule. This was similar to the effectiveness rate found in the United States with the 3 + 1 dosing schedule [13].

Results from the Norwegian study [20] showed that vaccine coverage rates for PCV7 reached high levels soon after its introduction in July 2006. The incidence of IPD declined rapidly in the target population of children <1 year of age, and the decline in incidence observed in children 2–3 years of age was possibly due to an indirect herd effect. There was an increase in IPD due to clonal expansion of the macrolide-resistant serotype 14 during the prevaccine era, while IPD caused by serotype 14 declined following the introduction of PCV7.

Estimated serotype coverage of PCV7 was found to be slightly lower in Norway than in the United States (78.5% vs 83.1%).

Preliminary evidence suggests that indirect herd effects, reduced nasopharyngeal carriage, and reduced transmission all may play a role in the beneficial effects of the 2 + 1 vs the 3 + 1 dosing schedule. With fewer doses being administered, there are also implications for cost savings.

3. Predominance of serotype 19A *S pneumoniae* infections in West Paris

Implementation of PCV7 programs have helped to reduce the incidence of *S pneumoniae* infections caused by the serotypes covered in the vaccine; however, serotype 19A, which is not covered in this first-generation vaccine, has now emerged as a predominant serotype. In 2007, Dortet et al. [21] investigated the causative isolates in 457 cases of invasive *S pneumoniae* infection in adults and children living in the west area of Paris. The most frequently isolated serotype in both adults and children was found to be 19A. Overall, serotype 19A was found to be the causative isolate in 34.7% of cases. In adults, 19A was found in 12.8% of cases, while in children, it was found in 27% of cases.

Interestingly, serotype19A was isolated in 5 out of 10 pleural fluids from children and 4 out of 12 from adults. Among the 173 isolates found in AOM, 110 (63.6%) were 19A. In this study, the researchers found no difference in antibiotic resistance patterns between adults and children with *S pneumoniae* infections. However, strains isolated from AOM were less susceptible to β-lactams and erythromycin, and this decreased susceptibility was correlated