Advances in Pneumococcal Disease Prevention: 13-Valent Pneumococcal Conjugate Vaccine for Infants and Children

Peter R. Paradiso
Pfizer Vaccines, Collegeville, Pennsylvania

A 13-valent pneumococcal conjugate vaccine (PCV13), developed with the same chemistry used for the 7-valent PCV vaccine (PCV7) and with the goal of expanding serotype coverage, was clinically evaluated in the United States and Europe and found to induce capsular-specific antibody responses comparable to those of PCV7 for the common serotypes, with robust responses to the 6 additional serotypes. In addition, PCV13 has a similar safety profile to PCV7 and can be given routinely to infants and children, ideally as a 3-dose primary series in the first year of life, with a booster dose in the second year. Children who have initiated their vaccination program with PCV7 can transition to PCV13 at any point in the schedule. Children aged ≥15 months who have been completely vaccinated with PCV7 can receive a single dose of PCV13 to induce immunity to the 6 additional serotypes.

The 7-valent pneumococcal conjugate vaccine (PCV7) was first licensed in the United States in 2000 and in Europe and much of the rest of the world in 2001 or later. PCV7 contained conjugate capsular polysaccharides directed at 7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) of the 91 pneumococcal serotypes causing disease [1]. At the time of licensure, these 7 conjugates covered ~80% of the serotypes causing invasive pneumococcal disease (IPD) in children in the United States and the majority of invasive disease around the world [2, 3]. Since 2000, >300 million doses of PCV7 have been administered worldwide, and >40 countries around the world have national immunization programs that include PCV7 as part of the routine vaccination schedule (Pfizer, data on file). The impact on pneumococcal disease has been dramatic in countries where the vaccine has been introduced. In the United States, within 3 years of introduction, there was a 94% decrease in the rate of IPD caused by vaccine serotypes in children <5 years of age and a 75% reduction in the overall IPD rate regardless of serotype [4], including an overall reduction in disease caused by antibiotic-resistant serotypes [5]. Through 2007 in the United States, there has been a nearly 100% reduction of invasive disease caused by vaccine serotypes in children <5 years of age [6]. The effectiveness of the vaccine against community-acquired pneumonia [7–10], otitis media (OM), and mortality [11–14] has also been reported. In addition, the effectiveness of PCV7 has been demonstrated in Canada [15], Europe [16, 17], and Australia [18]. The impact of PCV7 has recently been reviewed in the literature [19, 20].

Perhaps the most surprising outcome of routine infant vaccination with PCV7 was the indirect effects seen in the unvaccinated population. Again, within 3 years after vaccine introduction, the Centers for Disease Control and Prevention reported a dramatic reduction in the incidence rate of IPD among adults [4], suggesting that as many as 2 cases are prevented in adults for every case prevented in a vaccinated child. There have also been documented decreases in IPD among children too young to be vaccinated [21]. This indirect, or herd, effect has amplified both the public health and economic value of PCV7 vaccination.
programs [22]. Pilishvili et al [6] recently reported overall and PCV7-serotype IPD incidence rate decreases of 45% and 94%, respectively, for all age groups. However, in some regions, this impact has been blunted by increases in IPD caused by non-vaccine serotypes that may have occurred as a result of antibiotic pressure, normal secular trends, vaccine use, or some combination of these factors [23].

Although PCV7 has had an important impact in preventing pneumococcal disease, a second-generation vaccine containing 13 conjugate components (PCV13) has been developed to expand serotype coverage and to address the disease burden caused by emerging serotypes.

**RATIONALE FOR THE DEVELOPMENT OF A 13-VALENT CONJUGATE VACCINE**

Although the 7 conjugates in PCV7 cover the majority of disease in most regions of the world, in some countries, only 50% of the disease was covered by the serotypes in the vaccine [2, 3]. PCV13 contains, in addition to the conjugates in PCV7, conjugates to serotypes 1, 3, 5, 6A, 7F, and 19A. In many countries in Africa, the Southern Cone of South America, and certain parts of Asia, serotypes 1 and 5 are a significant cause of morbidity and mortality [24]. Serotypes 6A and 19A have long been important causes of invasive disease, and 19A in particular has been increasing in prevalence and antibiotic resistance over the past 10 years [25–27]. In the United States, Canada, and many European countries, serotype 19A is the predominant cause of IPD [28]. At the time that PCV7 was introduced, it was hoped that serogroup cross-protection would help control disease caused by serotypes 6A and 19A, based on the immune response elicited by the PCV7 serotype 6B and serotype 19F conjugates, respectively. In fact, although considerable cross-protection has been seen against serotype 6A [29], no clinically significant cross-protection has been seen against serotype 19A [30]. Lastly, serotypes 3 and 7F are significant causes of invasive disease in the United States and Europe [31], and both have been associated with high case-fatality rates [31–34], and infections due to serotype 3 are increasingly being reported, especially in older children and in association with severe pneumonia including empyema [35].

PCV7 and PCV13 use the same carrier protein, CRM197, for all the serotype-specific conjugates, and the saccharides, derived from the surface of the bacteria, are coupled to this carrier protein directly through reductive amination in both vaccines. A dose of PCV13 consists of 0.5 mL and contains aluminum phosphate as an adjuvant.

**CLINICAL DEVELOPMENT OF PCV13**

The efficacy of PCV7 was determined through randomized, placebo-controlled clinical trials in the United States [7, 36, 37] and Finland [38]. These trials demonstrated efficacy against IPD and OM, respectively. A 9-valent vaccine formulation that includes the conjugates from PCV7, but with the addition of conjugates against serotypes 1 and 5 using the same carrier protein, was tested in large clinical trials in South Africa [39] and the Gambia [40]. Both trials demonstrated efficacy against IPD and all-cause pneumonia. Of importance, in the Gambia, there was 16% (95% confidence interval, 3%–28%) efficacy against overall mortality [40].

Because of the proven efficacy and effectiveness that had been demonstrated for PCV7, it was not ethically feasible to conduct placebo-controlled trials for PCV13. Recognizing this fact, the World Health Organization (WHO) issued a technical report outlining the criteria to be used for the assessment of new pneumococcal conjugate vaccines [41]. It was determined that new vaccines should be tested against a vaccine with proven efficacy based on the immune response elicited in infants after a 3-dose primary series during the first year of life. Specifically, the report suggests comparisons based on the percentage of persons achieving an antibody threshold of 0.35 μg/mL of anticapsular antibody (measured using an enzyme-linked immunosorbert assay), the total anticapsular geometric mean antibody concentration (GMC), the functional opsonophagocytic antibody response (OPA), and the ability to induce a booster response during the second year of life. Demonstrating good total and functional antibody responses to each serotype is critical to ensure efficacy against not only invasive disease, but also mucosal infections, such as OM and pneumonia, which may require higher antibody titers to control.

The WHO criteria were used to assess PCV13 in clinical trials. In a pivotal trial in the United States [42], infants received PCV13 or PCV7 at 2, 4, 6, and 12–15 months of age with routine pediatric vaccinations. For the 7 common serotypes, 87%–98% of children achieved titers of ≥0.35 μg/mL after 3 doses of PCV13, and the immunoglobulin G (IgG) titers were non-inferior to those elicited by PCV7, although PCV13 titers were generally somewhat lower. For the 6 additional serotypes, >90% of children achieved IgG titers of ≥0.35 μg/mL except for serotype 3 (64%). All of the titers were boosted by the dose at 12–15 months, and there was good concordance between the IgG and OPA responses. A similar study was done in Germany using an accelerated primary series, with dosing at 2, 3, 4, and 11–12 months of age [43]. In this study, 78%–99% of the participants receiving PCV13 achieved IgG titers ≥0.35 μg/mL to the 7 common serotypes, and 92%–99% achieved that threshold against the 6 additional serotypes.

Overall, 13 clinical trials were performed in >7000 persons (>4700 receiving PCV13 and the rest PCV7) and assessed a variety of schedules used around the world, along with various concomitantly administered vaccines (reviewed in Reinert et al
THE TRANSITION FROM PCV7 TO PCV13

The 7 conjugates in PCV7 are also present in PCV13. Because the immune responses and safety profiles are comparable between these 2 vaccines, switching from PCV7 to PCV13 at any point in the immunization schedule should have no impact on the response to the 7 PCV7 serotypes. In a study conducted in France [44], children received 3 doses of PCV7 in the first year of life and at 2, 3, and 4 months of age. The group was then randomized at 12 months of age to receive either a dose of PCV7 or a dose of PCV13. The responses to the 7 common serotypes after the booster dose in the second year of life were comparable in the 2 groups based on GMCs and percent responders. There were also good responses to the 6 additional serotypes after 1 dose of PCV13 at 12 months of age, with GMCs ranging from 1.1 to 5.3 lg/mL and 98%–100% of the subjects achieving OPA titers >1:8. It appears, therefore, that a single dose of PCV13 in children 12 months of age who received PCV7 in infancy is sufficient to induce immunity to all 13 serotypes in the majority of children.

There are, however, no data available on switching in the first year of life for the 6 additional serotypes. As discussed above, this is not an issue for the 7 common serotypes. For the 6 additional serotypes, there are data from the United Kingdom [47] and Italy [46] in children who received only 2 doses of PCV13 at either 2 and 4 months or 3 and 5 months of age, respectively. In the UK study [47], responses ≥0.35 lg/mL were seen in 79%–97% of children for the 6 additional serotypes, and >88% achieved OPA titers of >1:8 for all serotypes after 2 doses. The results in Italy [46] were similar, with 95%–100% of children achieving OPA titers >1:8 for the 6 additional serotypes after 2 doses. Therefore, in a transition regimen in which a child receives only 2 doses of PCV13 in the first year of life, the response to the 6 new serotypes is high. However, there are no data in children who received only 1 dose of PCV13 in the first year of life; consequently, the potential effectiveness for the 6 additional serotypes of a transition at the third dose and before the booster dose is unknown.

CATCH-UP IMMUNIZATION

Children who have been fully vaccinated with PCV7 remain at risk of disease caused by the 6 additional serotypes in PCV13. On the basis of Active Bacterial Core surveillance data, 68% of disease in children <5 years of age was caused by these additional serotypes during 2006–2007 [6]. Although the rate of disease decreases annually up to 5 years of age, there is still a substantial burden in these older children. The rate of IPD in US children is highest among those <12 months of age at ~40 cases/100,000 population but remains at ~10 cases/100,000 population among children 3–5 years of age [48]. It can, therefore, be calculated that ~13,000 cases of pneumococcal disease could be prevented over the next 10 years by vaccinating children 16–59 months of age with PCV13 (assuming all 13.2 million children in this age range were vaccinated) [48]. Because only 1 dose of PCV13 is required in these children, a substantial burden of disease could be prevented with a 1-time vaccination with PCV13 in children 16 months to 5 years of age who have been fully vaccinated with PCV7.

Rubin et al [48] and Messonnier et al [49] have developed economic models to consider the value of a transition from PCV7 to PCV13 and of a catch-up vaccination program in the United States in children up to 5 years of age. In both models, the primary transition to PCV13 in infants was found to be cost saving. The authors of the Messonnier model [49], considering only direct effects of the vaccine, concluded that a catch-up program in the United States would be cost effective at $16,125 per discounted quality-adjusted life-year. In the Rubin model [48], the potential for enhancing the herd effect in the population as a result of a catch-up program was also considered. The premise was that children 16 months to 5 years of age were still carrying the 6 additional serotypes and were an important factor in the spread of disease to the rest of the population. A catch-up immunization program, therefore, has the potential to enhance the speed with which a herd effect might be seen. With these assumptions, a catch-up program was considered to be cost saving.

IMMUNOGENICITY OF REDUCED DOSING SCHEDULES

Effectiveness for IPD, pneumonia, and OM has been documented for PCV7 when administered in a dosing regimen in
which 2 doses are given in the first year of life, followed by a booster dose around the second year (known as a 2 + 1 schedule) [13, 15, 50]. As noted previously, PCV13 has been studied in a 2 + 1 dosing regimen [46, 47]. The immunogenicity of PCV7 has been well documented using such reduced dosing schedules [51]. With PCV7, the responses to serotypes 6B and 23F are consistently lower after 2 doses when compared with the other 5 serotypes or with a
3-dose primary regimen [51]. The same pattern was seen for PCV13. As noted previously, the responses to the 6 additional serotypes in these studies were quite good after 2 doses, and therefore, serotypes 6B and 23F remain the serotypes driving the need for a 3-dose primary series. However, after the booster dose in the second year of life, responses to 6B and 23F are comparable, regardless of whether 2 or 3 doses were received in the first year of life. In view of the comparable immunogenicity of PCV13 and PCV7 in a 2 + 1 schedule, this schedule has been approved for use in some countries.

**SAFETY OF PCV13**

PCV13 builds on the favorable safety profile of PCV7 that has been well studied and extensively documented [1, 52]. PCV13 was studied in >4700 infants who received a 2- or 3-dose primary series and in >2500 children who received a toddler dose [45]. There was uniform reporting of safety information across studies, and the results for PCV13 were compared with those for PCV7. Specific local (tenderness, redness, and swelling) and systemic (fever, irritability, decreased appetite, increased sleep, and decreased sleep) reactions were studied for 1–4 or 1–7 days after vaccination. Unsolicited adverse events and serious adverse events were also studied.

The data from published studies showed that the incidence of local and systemic reactions was comparable between PCV13 and PCV7 (Figures 1 and 2 [43]) [42, 43, 46, 53]. In addition, there was no indication of an increased risk of unsolicited adverse events or serious adverse events for PCV13 relative to PCV7.

**VACCINE USE RECOMMENDATIONS**

After licensure of PCV13 in the United States, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices [54] and the American Academy of Pediatric’s Committee on Infectious Diseases [55] issued recommendations for its use in US children. The main features of these recommendations are:

1. PCV13 is recommended for all children as a 4-dose series at 2, 4, 6, and 12–15 months of age.
2. Children <24 months of age who have received ≥1 dose of PCV7 should complete the immunization series with PCV13.
3. Children 14–59 months who are fully vaccinated with PCV7 should receive a single dose of PCV13.
4. Children with underlying medical conditions increasing susceptibility to pneumococcal infection who are fully vaccinated with PCV7 should receive a single dose of PCV13.

Similar recommendations for the transition to and routine use of PCV13 have now been adopted in many countries around the world.

**USE OF PCV13 IN DEVELOPING COUNTRIES**

Pneumococcal disease, particularly pneumonia, is reported to cause nearly 1 million deaths annually among children <5 years of age worldwide [3]. Many of these deaths occur in the poorest countries of the world, where access to new vaccines is a significant challenge. Recent advances in novel funding mechanisms have raised the prospect that access to pneumococcal conjugate vaccines will occur more quickly than in the past [56]. The serotypes covered in PCV13 account for ≥80% of the pneumococcal disease in most regions of the world [3], and the vaccine has recently been granted prequalification by the WHO for the prevention of IPD, OM, and pneumonia, thereby paving the way for early introductions in the countries with the greatest disease burden. Post-introduction effectiveness studies will be needed to determine the direct and indirect impact of vaccination in this setting [23].
CONCLUSIONS

The adoption of PCV7 into national immunization programs has dramatically decreased the pneumococcal burden of disease in those countries. However, IPD produced by non-PCV7 serotypes, particularly 19A, is increasingly important, along with the development of antibiotic-resistant, non-PCV7 serotypes. Studies conducted in many different countries in >4000 children have shown that PCV13 is comparable to PCV7 in producing immunogenic responses to all of the pneumococcal serotypes contained in the vaccine and that PCV13 exhibits a safety profile comparable to PCV7. Thus, incorporating PCV13 into national immunization programs may ameliorate the increasing emergence of antibiotic-resistant strains of serotype 19A and potentially decrease the pneumococcal burden of disease, particularly in countries where non-PCV7 serotypes are prevalent.

Acknowledgments

Financial support. Editorial support was provided by Elaine Santiago of Excerpta Medica and funded by Pfizer. Potential conflicts of interest. P. R. P. is an employee of Pfizer.

References


