

Effectiveness of the Heptavalent and Nonavalent Pneumococcal Vaccines in Severe Pneumococcal Pneumonia

a report by

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Streptococcus pneumoniae is, at present, the major cause of invasive diseases worldwide and is also the first pathogen in acute community-acquired bacterial pneumonia (CAP) in infants and young children.^{1,2} For a long time, patients older than two years who are at increased risk for invasive pneumococcal infections have been vaccinated with a polysaccharide 23-valent vaccine. However, the polysaccharide vaccine is not immunogenic in children younger than two years of age and it is known that, among the healthy population, children younger than two years and the elderly are at greatest risk for pneumococcal invasive diseases and pneumonia.²⁻⁴ Protein conjugate vaccines can induce immunity in very young infants and the production of conjugate pneumococcal vaccines has enabled the successful vaccination of infants from the age of two months.^{4,5} Until now the only conjugate pneumococcal vaccine that has been licensed is the heptavalent pneumococcal vaccine (7-valent PnV) Prevenar[®] (Wyeth), which contains the antigens of the following seven pneumococcal serotypes: SGT 4, SGT 6B, SGT 9V, SGT 14, SGT 18C, SGT 19F and SGT 23F. A nonavalent conjugate pneumococcal vaccine (9-valent PnV) (Wyeth), containing the antigens of the same serotypes plus SGT 1 and SGT 5, has also been produced and evaluated in clinical studies, but is not commercialized.^{6,7}

In the US, the licensing of the 7-valent PnV in 2000 and the vaccination of all children from the age of two months has led to a steep decline in incidence of invasive pneumococcal diseases in children.⁵ In the following years, the 7-valent PnV was also commercialized in Europe and other countries of the industrialized world. Although the 7-valent PnV has proven to have an excellent efficacy in the prevention of invasive diseases, the results for clinical diagnosed pneumonia were not convincing.⁵ On the other hand, recently some authors have described an increase in complicated pneumonia in the last five to 10 years.⁸⁻¹³

In this report, we aim to evaluate the theoretical efficacy of the 7-valent and 9-valent PnV in the prevention of severe childhood CAP, considering the reports published in the last 10 years.

Discussion

To be able to make an accurate evaluation of vaccine efficacy, it is necessary to have a single and specific endpoint and to know the true burden of disease.

Disease Burden

The true burden of pneumococcal disease is not known and is very difficult to assess. Estimates of the burden of pneumococcal disease differ from one region to another and from one population to another, varying from 166.9/100,000 child years in the US (children < two years) (before the universal vaccination with Prevenar) to 349/100,000 child years in South Africa (children < one year) for invasive pneumococcal disease only. The burden of non-invasive pneumococcal diseases such as non-bacteremic pneumonia is estimated to be two to ten times higher.¹⁴

Although everybody is convinced that *S. pneumoniae* is the leading pathogen in childhood CAP, its real contribution remains unknown.¹⁵ In childhood CAP, diagnostic practices are very different from one region and one setting to another.¹⁵ Blood cultures are not always routinely performed and lack sensitivity, as positive blood cultures are only found in 10–30% of pneumococcal pneumonia. Previous treatment with antibiotics or too small sample volumes often lead to false negative results.¹⁵ Samples of the lower respiratory airways are difficult to obtain in children. Children cannot expectorate their sputum and bronchoscopy with bronchoalveolar lavage (BAL) or diagnostic lung tap are not performed routinely in otherwise healthy children because these are invasive procedures.^{15,16}

However, it is not only necessary to establish the real burden of pneumococcal pneumonia but also the contribution of each single causative pneumococcal serotype.¹⁷ Serotyping has long been limited to positive culture cases, because the standard serotyping technique (Quellung reaction, Statens Seruminstitut Copenhagen) can only be performed starting from positive cultures. More recently, polymerase chain reaction (PCR) for the detection of pneumococcal DNA and capsular

Table 1: Overview of the Vaccine Efficacy for the 7- and 9- Valent PnV in Different Efficacy Studies for Different End-points of Pneumonia

Study	Conjugate PnV	Clinical CAP	X-ray + CAP	Culture + CAP	Serology + CAP
California ²²	7-valent PnV	4%	< 1 year: 32% < 2 years: 9.1%	87.5%	
South Africa ⁶	9-valent PnV	11%	17%	50%	
Gambia ⁷	9-valent PnV	7%	37%	70%	
California ⁴	7-valent nV	10.7%	35%		
Belgium ¹⁶	7-valent PnV			<2 years: 65.5% 2–5 years: 42.3% >5 years: 13.3%	
Belgium ¹⁶	9-valent PnV			<2 years: 68.9% 2–5 years: 69.2% >5 years: 86.6%	
Italy ¹⁷	7-valent PnV	16.8%			57.9%
Taiwan ¹¹	7-valent PnV			66%	
Uruguay ²	7-valent PnV			<2 years: 62% 2–5 years: 40%	
Uruguay ²	9-valent PnV			<2 years: 78% 2-5 years 84%	

serotype-specific antigen detection have been used to increase the accuracy of microbiologic diagnosis in negative culture cases of complicated pneumonia.^{13,17}

Efficacy Studies

In recent years, many efficacy studies of the conjugate pneumococcal vaccines have been published.^{5,6,18–21} However, as the end-points differed a lot between these efficacy studies, different results for vaccine efficacy were found. The first studies had as primary end-point the vaccine efficacy for invasive pneumococcal diseases in general and did not always differentiate between pneumonia and other infectious pneumococcal diseases (IPD).^{5,18} When pneumonia was differentiated from invasive pneumococcal diseases, a much lower efficacy was found in the prevention of pneumonia compared with the prevention of other invasive pneumococcal diseases.²² Moreover, when pneumonia was an end-point, definitions of pneumonia varied from one study to another (see *Table 1*).¹⁵ In some studies pneumonia was only diagnosed on clinical grounds or World Health Organization (WHO) criteria, whereas in other studies clinical and radiographic findings were used to establish the diagnosis of pneumonia (see *Table 1*). Some studies were not culture based, leading to a non-specific end-point and a possible false low efficacy, as neither clinical features nor radiographic findings are specific for *S. pneumoniae*, and do not even allow distinction between viral or bacterial origins (see *Table 1*).^{4,15} Most of the culture-based studies have only used blood culture and/or culture of pleural fluid and therefore give only information about invasive pneumococcal pneumonia

(see *Table 1*).^{2,6,7,11,22} In a Belgian study BAL cultures were additionally used to increase the microbiologic diagnosis of pneumococcal pneumonia and the investigators found some important differences in serotypes between invasive and non-invasive severe pneumococcal pneumonia.¹⁶ In this study SGT1 was only found in invasive pneumonia and never in non-invasive pneumonia, and the opposite was true for SGT 23 (with only one exception).¹⁶ This finding suggests that results of vaccine efficacy for invasive pneumococcal pneumonia cannot be simply extrapolated to pneumococcal pneumonia in general.

To the authors' knowledge, until now, only one vaccine efficacy study was serology based.¹⁷ In this study Esposito et al. found a moderate efficacy of the 7-valent PnV, which was in concordance with the culture based studies.¹⁷

Several authors have described a relationship between age cohort and causative serotypes.^{2,16,22} In pneumonia, as for other invasive pneumococcal diseases, the number of causative serotypes in the youngest age group is limited but a much greater diversity of serotypes is found in older children.^{16,23} All these authors found that vaccine efficacy of the 7-valent PnV was better in children < two years in comparison with older children (see *Table 1*).^{2,16,22} In children, in > two years, SGT1 was the predominant serotype especially in severe pneumococcal pneumonia.^{1,8,13,16,17,24–27} These data do explain the low efficacy of the 7-valent PnV and the much better efficacy of the 9-valent PnV in this age group, thanks to the incorporation of SGT1 antigen in the 9-valent PnV.

Recent Changes in the Epidemiology of Severe Pneumococcal Pneumonia

Recently some authors reported an important increase in parapneumonic empyema and necrotizing pneumonia in children.^{8–10,12,13,28} Absence of underlying disease and age >36 months were found to be significantly associated with an increased risk to develop complicated pneumococcal pneumonia.^{8,12,28}

In the US and the UK, the majority of the culture-positive cases were related to SGT1 disease, whereas in Taiwan a virulent clone of SGT14 was responsible for 30% of the culture positive cases.^{8–13,28} The authors warn of the invasive potential of SGT1 and other non-vaccine serotypes. Furthermore, Byington et al. have reported on a two-fold increase of empyema in childhood CAP since the universal vaccination with the 7-valent PnV. All of these cases were caused by non-vaccine serotypes, SGT1 being most prevalent and followed by SGT3 and SGT19, which seemed to be emerging.²⁸

Although Black et al. did not observe serotype replacement in invasive pneumococcal diseases after the universal use of the 7-valent PnV, other authors have reported on the emergence of SGT15 and SGT33 since the introduction of the 7-valent PnV.^{29–31} Following the data in parapneumonic empyema and complicated pneumonia, several authors warn of serotype replacement and recommend on-going surveillance of the serotype distribution in invasive pneumococcal disease and severe pneumococcal pneumonia.^{9–13,28,29}

Conclusions

From the literature it is clear that the real efficacy of the conjugate pneumococcal vaccines in the prevention of pneumococcal pneumonia remains unknown. Many authors have tried to estimate the vaccine efficacy but the use of different end-points and definitions have caused a huge variation in results from 4% to 90%, which has resulted in confusion about the vaccine efficacy for preventing pneumococcal pneumonia. However, some important conclusions can be drawn from the recent literature:

In children < two years, the theoretical coverage of the currently used 7-valent PnV and the 9-valent PnV is good and similar for the prevention of pneumococcal pneumonia.

In children > two years, the diversity of causative serotypes is greater and complicated pneumonia is more frequent. In this age group, SGT1 is predominant especially in invasive pneumonia, parapneumonic empyema and necrotizing pneumonia. Due to this predominance of SGT1, the efficacy of the 7-valent PnV is poor to moderate, but the efficacy of the 9-valent PnV is very good in this age group.

Serotype replacement has been reported and therefore continued clinical and epidemiological surveillance is necessary. Microbiologic diagnosis must be stimulated in clinical practice, to observe the influence of widespread pneumococcal vaccination on the serotypes causing pneumococcal pneumonia. ■

References

1. Zisis NP, Syriopoulou V, Kafetzis D et al., "Serotype distribution and antimicrobial susceptibility of Streptococcus pneumoniae causing invasive infections and acute otitis media in children", *Eur Pediatr* (2004);163 (7): pp. 364–368.
2. Camou T, Palacio R, Di Fabio JL et al., "Invasive pneumococcal diseases in Uruguayan children : comparison between serotype distribution and conjugate vaccine formulations", *Vaccine* (2003);21: pp. 2093–2096 .
3. Selman S, Diane H, Perin LA et al., "Pneumococcal conjugate vaccine for young children", *Managed Care* (2000) : pp. 49-62
4. Shinefield HR, Black S, "Efficacy of pneumococcal conjugate vaccines in large scale field trials", *Pediatr Infect Dis J* (2000);19: pp. 394–397.
5. Withney C, Farley M, Hadler J et al., "Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine", *N Engl J Med* (2003);348: pp. 1737–1746.
6. Klugman KP, Madhi SA, Huebner RE et al., "A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection", *N Engl J Med* (2003);349 (14): pp. 1341–1348.
7. Cutts FT, Zaman SMA, Enwere G et al., "Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial", *Lancet* (2005);365: pp. 1139–1146.
8. Byington CL, Spencer LY, Johnson TA et al., "An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations", *Clin Infect Dis* (2002);34 (4): pp. 434–440
9. Rees JH, Spencer DA, Parikh D et al., "Increase in incidence of childhood empyema in West Midlands, UK" *Lancet* (1997), 349: pp. 402.
10. Fletcher M, Leeming J, Cartwright K et al., "Childhood empyema: limited potential impact of 7-valent pneumococcal conjugate vaccine", *Pediatr Infect Dis J* (2006);25 (6): pp. 559–560.

11. Yu-Chia H, Po-Ren H, Chun-Yi L et al., "Clinical manifestations and molecular epidemiology of necrotizing pneumonia and empyema caused by streptococcus pneumoniae in children in Taiwan", *Clin Infect Dis* (2004), 38: pp. 830-835
12. Yu-Chia H, Cheng-Hsiang H, Po-Nien T et al., "Necrotizing pneumococcal pneumonia in children: the role of pulmonary gangrene" *Ped Pul* (2006);41: pp. 623-629.
13. Ramphul N, Eastham KM, Freeman R et al., "Cavitary lung disease complicating empyema in children", *Ped Pul* (2006);41: pp. 750-753.
14. O'Brien KL, Moulton LH, Reid R et al., "Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial", *Lancet* (2003);362 (9381): pp. 355-361.
15. Obaro SK, Madhi SA, "Bacterial pneumonia vaccines and childhood pneumonia: are we winning, refining or redefining?" *Lancet Infect Dis* (2006);6: pp. 150-161.
16. De Schutter I, Malfroot A, Piérard D et al., "Pneumococcal serogroups and serotypes in severe pneumococcal pneumonia in Belgian children: theoretical coverage of the 7-valent and 9-valent pneumococcal conjugate vaccines", *Ped Pul* (2006);41: pp. 765-770.
17. Esposito S, Madore DV, Gironi S et al., "Theoretic coverage of heptavalent pneumococcal conjugate vaccine in the prevention of community-acquired pneumonia in children in Italy", *Vaccine* (2003);21: pp. 2704-2707.
18. Black S, Shinefield H, Fireman B et al., "Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children" *Pediatr Infect Dis J* (2000);19: p. 187-195.
19. Hortal M, Camou T, Palacio R et al., "Ten-year review of invasive pneumococcal diseases in children and adults from Uruguay: clinical spectrum, serotypes, and antimicrobial resistance", *Int J Infect Dis* (2000);4: pp. 91-95.
20. Levine MM, Lagos R, Levine OS et al., "Epidemiology of invasive pneumococcal infections in infants and young children in Metropolitan Santiago, Chile, a newly industrializing country", *Pediatr Infect Dis J* (1998);17: pp. 287-293.
21. Sniadack DH, Schwartz B, Lipman H et al., "Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children-implications for vaccine strategies" *Ped Infect Dis J* (1995);14 (6): pp. 503-510.
22. Black SB, Shinefield HR, Ling S et al., "Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia", *Pediatr Infect Dis J* (2002);21 (9): pp. 810-815.
23. Hausdorff WP, Bryant J, Kloek C et al., "The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, Part II", *Clin Infect Dis* (2000);30: pp. 122-140.
24. Clarke SC, Scott KJ, McClery SM, "Serotypes and sequence types of pneumococci causing invasive disease in Scotland prior to the introduction of pneumococcal conjugate polysaccharide vaccines", *J Clin Microbiol* (2004);42 (10): pp. 4449-4452.
25. Gendrel D, Raymond J, Moulin F et al., "Etiology and response to antibiotic therapy of community-acquired pneumonia in French children", *Eur J Clin Microbiol Infect Dis* (1997);16 (5): pp. 388-391.
26. Tan TQ, Mason EO, Wald ER, et al., "Clinical characteristics of children with complicated pneumonia caused by Streptococcus pneumoniae", *Pediatrics* (2002);110 (1): pp. 1-6.
27. Hausdorff WP, Feiklin DR, Klugman KP, "Epidemiological differences among pneumococcal serotypes", *Lancet Infect Dis* (2005);5: pp. 83-93.
28. Byington CL, Korgenski K, Daly J et al., "Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema", *Pediatr Infect Dis J* (2006);25 (3): pp. 250-254.
29. Byington CL, Samore MH, Stoddard GJ et al., "Temporal trends of invasive disease due to streptococcus pneumoniae among children in the intermountain west: emergence of nonvaccine serogroups", *Clin Infect Dis* (2005);41: pp. 21-29.
30. Black SB, Shinefield HR, Baxter R et al., "Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugated vaccine in the Northern California Kaiser permanente", *Pediatr Infect Dis J* (2004);23 (6): pp. 485-489.
31. Gonzalez BE, Hulten KG, Lamberth L et al., "Streptococcus pneumoniae serogroups 15 and 33. An increasing cause of pneumococcal infections in children in the United States after the introduction of the pneumococcal 7-valent conjugate vaccine", *Pediatr Infect Dis J* 25 (4): pp. 301-305.