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REVIEW

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Pneumococcal disease in western Europe: burden of disease, antibiotic resistance and management

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Abstract *Streptococcus pneumoniae*– the pneumococcus– affects children and adults worldwide. Invasive pneumococcal disease, including pneumonia, meningitis and bacteraemia, has been linked annually to the deaths of millions of children. The pneumococcus is also a significant contributor to mucosal infections such as acute otitis media and sinusitis. Though pneumococcal infections can occur at any age, persons at greatest risk include children younger than 2 years of age and adults aged 65 years or more. Rates of pneumococcal disease and the prevalence of pneumococcal serotypes vary by geographic location and patient age. Accurate ascertainment and sound epidemiological data are essential for the rational development of effective programmes for prevention and treatment. Pneumococcal resistance to penicillin and other antibiotics has emerged rapidly in recent years, highlighting the importance of vaccine development. Newer pneumococcal vaccines, such as those conjugated to protein carriers, can now overcome the limitations of older polysaccharide vaccines. Such conjugated vaccines induce excellent immune responses even in infants and young children and they may also reduce asymptomatic nasopharyngeal carriage of pneumococci. Pneumococcal 7-valent conjugated vaccine PNCRM7 contains common prevalent serotypes coupled to a nontoxic diphtheria variant (CRM_{197}). This vaccine has demonstrated high efficacy against invasive pneumococcal disease in clinical trials in infants and young children and is currently licensed for use in the United States and selected countries in Europe and Latin America. *Conclusion:* across Europe, pneumococcal infection is responsible for considerable morbidity and mortality, particularly in the very young and the elderly, groups whose members respond poorly to non-conjugated vaccines. The advent of new conjugated pneumococcal vaccines now offers an exciting opportunity in developed countries to reduce both the current burden of disease and the threat of rising antibiotic resistance. Rolling out the use of such vaccines across Europe must be accompanied by detailed ongoing surveillance in order to detect any changes that might occur in the pattern of pneumococcal serotypes.

Keywords Epidemiology · *Streptococcus pneumoniae* · Transmission · Vaccine

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Introduction

The pneumococcus is a bacterial pathogen that affects children and adults worldwide. It causes a wide spectrum of disease ranging from asymptomatic colonisation of the nasopharynx and other mucosal surfaces, through superficial infections including otitis media, sinusitis, and exacerbations of chronic bronchitis, to invasive infections including pneumonia, meningitis, and bacteraemia [9]. Children under 2 years of age are particularly susceptible [48,60], as are the elderly. In developing countries, the pneumococcus is the most common bacterial cause of mortality in young children [29] and pneumococcal disease has been linked annually to the deaths of over 1 million children worldwide [10,61].

Benzylpenicillin is the drug of first choice in the treatment of invasive pneumococcal infections, but in recent years, resistance to penicillin and other antibiotics has emerged. The reduced effectiveness of antibiotics against pneumococcal infections has highlighted the importance of the development of safe and effective vaccines [9,61]. It has been suggested that approximately 50% of the deaths caused by this bacterial pathogen could be prevented by vaccination [9]. Newer pneumococcal vaccines, in which capsular polysaccharides are conjugated to immunogenic proteins, can overcome the limitations of the older plain non-conjugated polysaccharide vaccines. These conjugated vaccines are capable

of inducing an immune response in young children (< 2 years of age) and reducing the rate of asymptomatic carriage of pneumococci [15]. They are also likely to offer a long duration of protection [11].

In this article, an overview is presented of the current burden of pneumococcal disease in European children (particularly the western countries), including the prevalence and consequences of antibiotic resistance, and current methods for the prevention of pneumococcal disease in young children are reviewed.

Rates of invasive pneumococcal disease in western Europe

Rates of invasive pneumococcal disease in Europe vary according to geographic location and patient age (Table1) [18, 20, 24, 32, 34, 43, 49, 55, 56, 60, 62]. Generally, the incidence is higher in young children (< 5 years of age) and the elderly (> 65 years of age) than in persons of other age groups. Children aged younger than 2 years exhibit the highest incidence of invasive pneumococcal disease [18, 20, 48, 60].

Pneumococcal capsular polysaccharide

The pneumococcus is a gram-positive encapsulated coccus [61]. The capsule surrounding the microbe is a critical virulence factor [35]. Extensive antigenic diversity in the pneumococcal polysaccharide capsule serves as the basis for serotyping [54]. At least 40 serogroups comprising 90 serotypes have been recognised to date, although only a fraction of these serotypes are commonly associated with invasive pneumococcal infection [35]. Knowledge of the distribution of pneumococcal serotypes causing invasive disease is important since it permits evaluation of the potential impact of vaccines containing specific serotypes. Although the distribution of serotypes associated with pneumococcal disease can vary according to geographic location and patient age [30, 33, 45,51], current indications are that 11 serotypes cause at least 75% of invasive disease in all regions [61].

The intact human immune system can generate opsonic antibodies to pneumococcal capsular polysaccharides that facilitate bacterial phagocytosis [35]. Pneumococcal polysaccharide antigens are type 2 T-cell-independent antigens and thus the generation of mature, antibody-secreting B-cells is accomplished independent of T-cell assistance. However, B-cells of young children (especially those aged less than 2 years) do not respond effectively to these polysaccharide antigens. Consequently, infants and young children do not develop an effective immune response to the bacterial capsule, nor do they respond adequately to pneumococcal polysaccharide vaccines.

Several studies have been conducted to determine the pneumococcal serotypes associated with invasive disease. Scott and associates [51] collated information from over 7,000 episodes of invasive pneumococcal disease from 13 different databases in Europe and the United States. They concluded that the 12 most common sero-

Table 1 Incidence of pneumococcal disease in selected European countries

Country	Year	Reference	Disease manifestation	Age group	Incidence/100,000 per year
Denmark	1981–1999	[34]	Invasive pneumococcal disease	< 1 year	39.4 (17.5–58.8)[b]
				< 2 years	34.9 (13.7–54.8)[b]
				2–6 years	5.5 (2.4–10.3)[b]
				< 7 years	13.9 (5.3–23.6)[b]
France	1987–1997	[24]	Invasive pneumococcal disease	All ages	9.5–10.5
			Meningitis	All ages	0.85–1.05
Finland	1985–1989	[20]	Invasive pneumococcal disease	Newborn–15 years	8.9 (< 16 years)
					24.2 (< 5 years)
					45.3 (< 2 years)
Germany	–	[62]	Meningitis	< 16 years	1.63
				< 1 year	10.74
			Bacteraemia	< 16 years	1.75
			Pneumonia	< 5 years	9.5
Greece	1995–1999	[56]	Invasive pneumococcal disease	< 14 years	44 (< 14 years)
					100 (< 5 years)
Italy	1994–1998	[49]	Meningitis	All ages	1.1 (Newborn–4 years)
The Netherlands	1990–1999	[55]	Meningitis	All ages	1.0–1.5
				< 5 years	8.2 (1999)
			Bacteraemia	< 5 years	2.7–5.8(1991–98)
Sweden	1981–1996	[18]	Bacteraemia and septicaemia	All ages[a]	5.2–15.2
	1991–1992	[32]		< 1 Month	3.6
Switzerland	1985–1994	[60]	Invasive pneumococcal disease	Newborn–17 years	2.7 (< 17 years)
					11 (< 2 years)
United Kingdom	1996–1998	[43]	Invasive pneumococcal disease	< 15 years	6.6 (39.7 < 1 year)
			Meningitis		1.6 (15.7 < 5 years)

[a]Age of children not specified in the reference
[b]Mean annual incidence (lowest rate to highest rate)

groups in these regions were (in rank order): 14, 6, 19, 3, 23, 1, 9, 4, 8, 18, 7, and 5 (Fig. 1). These 12 serotypes accounted for almost 81% of the pneumococcal strains in the study. There were differences in serogroup distribution based on age, gender, and geographic location. For example, serogroups 6, 9, 14, 18, 19, and 23 were most commonly observed in children from birth to 9 years of age. A study by Sniadack and colleagues [54] included data from 19 individual studies conducted in 16 developed countries. These workers found serogroups 14, 6, 19, 18, 9, 23, 7, 4, 1, and 15 (in rank order) to be the ten most commonly associated with invasive disease in children. A comparison of serogroup prevalence in the United States, Spain, Belgium, Finland, and Denmark demonstrated geographic differences (Table2) [54]. For example, Spain exhibited a high prevalence of serogroup 23 whereas Denmark exhibited a much lower prevalence of this serogroup. Serogroup 14 was uncommon in Spain but was quite common in other countries.

Geographic differences in serogroup distribution have also been observed between developed and developing countries [54]. In developing countries, the 11 most common serogroups were (in rank order): 6, 14, 8, 5, 1, 19, 9, 23, 18, 15, and 7. For example, the mean prevalence of serogroup 5 was 8.5% in developing countries but only 1.1% in developed countries, whereas the mean prevalence of serogroup 4 was 0.9% and 3.7%, respectively.

Hausdorff and associates [30] analysed geographic differences in serotype distribution. In this analysis, which included 72 worldwide data sets, results were stratified by continent rather than by socio-economic grouping. Because of the wide variation in age grouping in these studies, young children were defined as those with assumed protection from a diphtheria-pertussis-tetanus immunisation schedule. This definition most commonly included those aged 5 years and younger, but for some studies it included those aged up to 18 years. The analysis revealed that serogroups 4, 6, 14, 18, 19, and 23 were implicated in 70% to 88% of invasive pneumococcal disease in young children in North America, Oceania, Africa, and Europe, and more than 65% of invasive pneumococcal disease in Latin America and Asia. These six serogroups, together with serogroups 1 and 5, were responsible for 80% to 90% of invasive pneumococcal disease in every continent except Asia [30].

Invasive pneumococcal disease

Invasion of the lung parenchyma or direct dissemination of pneumococci into the bloodstream may be followed by pneumonia, meningitis, or bacteraemia [9] with particularly high rates of disease in young children (especially those younger than 2 years of age) [10, 57,61]. Other risk factors for invasive disease include male gender, a history of frequent otitis media, underlying immunodeficiency such as HIV infection, sickle-cell disease, or functional/anatomical asplenia [51]. Invasive pneumococcal disease can lead to death or serious neurological impairment including hearing loss [29,52].

Table 2 Differences in serogroup prevalence (% of pneumococcal disease) among some European countries and the United States. Reprinted with kind permission from [54]

Serogroup	Percentage of invasive pneumococcal disease				
	United States	Spain	Belgium	Denmark	Finland
14	27.3	2.6	28.6	13.4	21.5
6	17.1	17.4	7.8	20.1	18.4
19	14.2	17.4	15.6	10.4	17.4
18	9.3	4.8	9.1	16.5	7.6
9	7.2	4.8	9.0	6.7	6.0
23	7.1	15.0	5.2	2.4	7.3
7	1.6	3.0	6.5	6.7	8.5
4	6.7	2.4	2.6	1.8	6.0
1	1.1	3.0	5.2	6.7	0.0

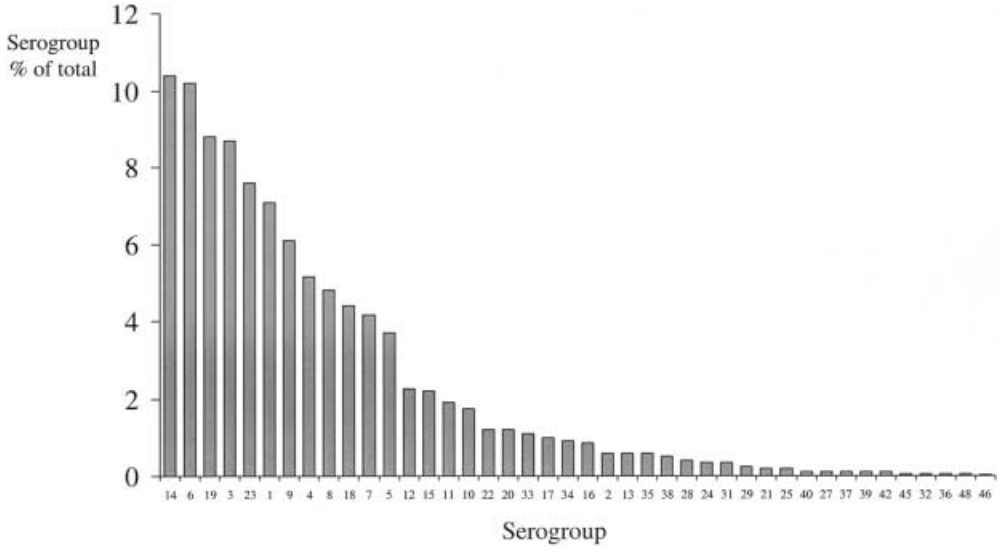

Fig. 1 Most common serogroups/types causing invasive pneumococcal disease in Europe and North America. Reprinted with permission [51]

Pneumococcal pneumonia

Pneumonia is the most common cause of pneumococcal death worldwide [61]. Most children diagnosed with pneumococcal pneumonia require hospitalisation [58]. Mortality rates attributable to pneumococcal pneumonia have been estimated to range from 10% to 20%, while rates may exceed 50% for high-risk groups such as young children and the elderly [61].

Pneumococcal meningitis

Pneumococcal meningitis is a serious disorder that is most frequent in children aged less than 24 months and adults aged 65 years or more [9]. Following the introduction of the *Haemophilus influenzae* type b conjugated vaccine and the subsequent reduction of *H. influenzae* meningitis, *S. pneumoniae* has become the most common cause of bacterial meningitis in the United States [53]. In developing countries, *S. pneumoniae* is associated with approximately 30% of cases of acute bacterial meningitis [44].

Pneumococcal otitis media

Pneumococci can induce acute otitis media and other upper respiratory tract infections [9]. In certain areas of the world, *S. pneumoniae* is a common cause of acute bacterial otitis media with upwards of 40% to 50% of cases attributed to this pathogen [25]. These infections are associated with considerable morbidity and health care costs due to the high number of physician visits and the extensive use (and overuse) of antibiotics. In the United States, 7 to 12 million cases of otitis media and more than 15 million physician visits are attributed to pneumococcal infections each year [59]. Sequelae may include hearing loss, and occasionally, untreated otitis media can lead on to serious complications such as meningitis, chronic otitis media, and lateral sinus thrombosis [47]. Chronic otitis media may require treatment with tympanostomy tube placement. In the United States, about 512,000 tympanostomy tubes are inserted each year [12]. Identified risk factors for otitis media include day care attendance, age younger than 2 years, and prior antibiotic treatment [25].

The incidence of *S. pneumoniae* infection varies somewhat across geographic regions. In a French study of 126 young children with acute otitis media who had failed on oral antibiotic therapy, *S. pneumoniae* constituted almost 40% of bacterial isolates [25]. In a study by Jacobs and associates [31], pathogens were isolated from the middle ear fluid of 917 children with acute otitis media from Eastern and Central Europe. *S. pneumoniae* was reported in 35% of the patients compared with 21% of isolates from patients in Israel and 26% from patients in the United States. When patients younger than 12 months were analysed separately, *S. pneumoniae* made up more than 60% of the isolates from Eastern and Central Europe, but about 25% of those from Israel and 30% of those from the United States [31]. Serogroups of *S. pneumoniae* that have been reported in European studies of bacterial isolates from children with otitis media include (in rank order) 6, 14, 19, and 23 [25].

Difficulties in disease management

The management of pneumococcal disease is complicated by several factors including control of disease transmission, the impact of antibiotic resistance, and the limitations of 23-valent plain non-conjugated polysaccharide vaccines.

Disease transmission

S. pneumoniae is often identified in the normal nasopharyngeal flora of healthy individuals [5]. The organism may be carried for prolonged periods of time without evidence of pneumococcal disease. Asymptomatic carriers can transmit the organisms via respiratory droplets to other individuals [11]. Asymptomatic nasopharyngeal carriage of pneumococci is widely prevalent among young children and is an important factor in the development and transmission of pneumococcal disease [22]. Risk factors for pneumococcal nasopharyngeal carriage include young age, the presence of siblings younger than 2 years of age in a household, previous antibiotic consumption, male gender, and day care attendance [27, 40,42].

Pneumococcal carriage rates vary according to age and geographic region. Younger children are more likely to be asymptomatic carriers than their older counterparts [11]. Appelbaum and associates [6] found that approximately 30% of children from Central and Eastern European cities were asymptomatic carriers of pneumococcus. Most of these children were aged younger than 5 years and most were either hospitalised or attending outpatient clinics or day care centres. In a study by Lopez and colleagues [40] of healthy 6-year-old children in Northern Spain, 36% of children had positive cultures for *S. pneumoniae*. In an orphanage in Northeastern Romania, carriage rates were as high as 70% in HIV-negative and HIV-positive children aged 4 to 12 months [38]. In a study of children in eight day care centres in Israel, the overall pneumococcal carriage rate was almost 80% [27]. In a study that followed 82 children for the first 2 years of life, almost all of the children (96%) carried one or more types of pneumococci at some time during the observational period [28].

Antibiotic resistance

Pneumococcal antibiotic resistance presents a major challenge to the clinician. Rapid increases in the incidence of infection with penicillin-resistant *S. pneu-*

moniae have been reported worldwide (Fig. 2) [3, 8, 13, 14, 26, 37,39]. In France, penicillin resistance amongst pneumococcal strains increased during a 10-year period (1987–1997) from less than 4% to more than 48% [24]. Similarly in Spain, rates increased from 6% in 1979 to 44.3% in 1989 [23]. Conversely, low levels of resistance (< 5%) have been reported in several northern European countries (e.g. Germany, Denmark, Sweden, The Netherlands) [19, 34, 55,62]. The restricted use of antibiotics in those countries may account for this lower prevalence of resistance.

Pneumococcal strains that are resistant to penicillin are also more likely to be resistant to other classes of antimicrobial agents [7]. In addition, the effectiveness of β-lactam antibiotics in the treatment of infections due to penicillin-resistant pneumococci is limited by the inability of such drugs to achieve adequate levels in the central nervous system. This has grave implications for patients with invasive disease. Further, in countries and regions where penicillin-resistant pneumococci frequently cause meningitis, the empirical antibiotic treatment of all cases of suspected bacterial meningitis may need to be revised.

The proportion of pneumococcal isolates that are antibiotic resistant is generally highest among preschool-aged children [8]. Resistance has also been linked to overuse of antibiotics and day care attendance [25,27]. In Italy, samples collected from nasopharyngeal swabs of 3- to 5-year-old children in day care centres or outpatient hospital clinics showed a high prevalence of penicillin-resistant pneumococci (14%), erythromycin-resistant pneumococci (60%), and multiple antibiotic-resistant pneumococci (53%) [50].

Antibiotic resistance of pneumococci has important implications for the treatment of acute otitis media. In an evaluation of 170 isolates collected from middle ear fluid in 126 children in France with a history of recurrent otitis media, 77% of isolates exhibited reduced susceptibility to penicillin [25]. While the clinical significance of such reduced sensitivity has yet to be determined, the findings could explain the increase in the incidence of persistent acute otitis media, defined as an episode of acute otitis media evolving for longer than 3 weeks despite one or several courses of antibiotic treatment [41]. In France, a study of 475 children aged 3 months to 6 years was conducted to evaluate changes in the epidemiological features of persistent acute otitis media over 15 years and to compare these features with those of acute otitis media [41]. During the study period, among cultures with positive results, the prevalence of *S. pneumoniae* increased from 18% to 44% ($P < 0.001$) (Fig. 3) [41]. These pneumococcal strains became increasingly resistant to penicillin over time. No resistance was observed in cultures collected in 1989, but resistance was present in 76% of cultures collected in 1993 and in 97% of cultures collected in 1996 ($P = 0.01$). Pneumococcal otitis media is less likely than other bacterial ear infections to resolve without treatment. Pneumococcal

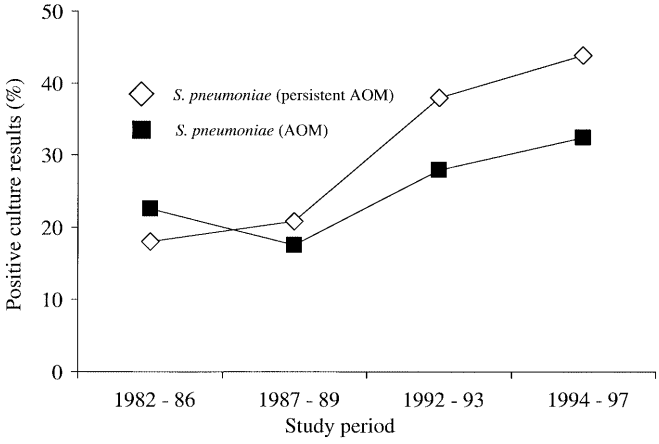

Fig. 3 Prevalence of *S. pneumoniae*-positive cultures in children with persistent acute otitis media and acute otitis media over a 15-year period in France. Adapted from [41] with permission. Note that during this same time period, *S. pneumoniae* cultures exhibiting resistance to penicillin in children with persistent acute otitis media increased from 0% (through 1989) to 100% (through 1996)

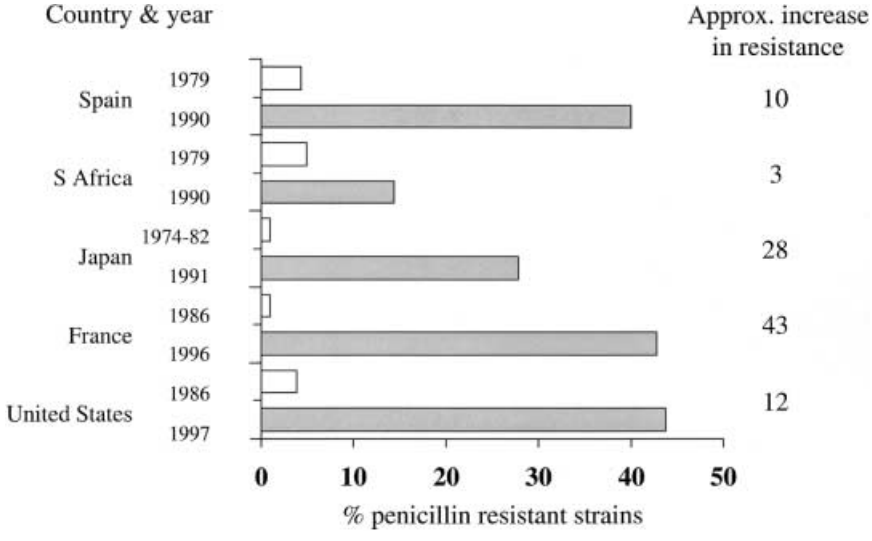

Fig. 2 Global escalation of penicillin-resistant *S. pneumoniae* [3, 14, 26, 37,39]

resistance to antibiotic treatment may compound difficulty in treating this condition successfully [25,31]. Strategies for reducing the morbidity associated with acute otitis media may need to take into account the impact of resistant pneumococci and the potential for disease prevention by vaccination [17].

Reducing the emergence of antibiotic resistant pneumococci can be achieved through more judicious use of antibiotics by clinicians, education of the public regarding the implications of needless or imprecise antibiotic usage, and prevention of pneumococcal disease through use of effective vaccines [16].

Limitations of the pneumococcal polysaccharide vaccines

Effective vaccines could reduce greatly the worldwide health care burden caused by pneumococci. Currently available non-conjugated polysaccharide vaccines contain 23 pneumococcal serotypes. They are ineffective in infants and young children, but have been used to prevent invasive pneumococcal disease in older children and adults. Since non-conjugated polysaccharides are T-cell-independent antigens, the antibody response is limited and memory B-lymphocytes are not generated. Infants and individuals with immature immune systems or immune deficiencies are unable to respond effectively to these vaccines. Additionally, these vaccines do not decrease nasopharyngeal carriage of pneumococci nor do they protect against otitis media [11,59]. In immunologically responsive individuals, non-conjugated polysaccharide vaccines are 60% to 70% effective in preventing invasive disease, but evidence that protection is limited can be found in a study that included 254 children of mean age 40.6 months with pneumococcal pneumonia [58]. Although these children had pneumococcal disease, 11% had received one or more doses of the 23-valent non-conjugated polysaccharide vaccine before their infection.

Future directions

Pneumococcal disease constitutes a major health care burden. Antibiotic treatments that were effective in the past have been impaired by the emergence of resistant pneumococci. More discriminating use of antibiotics by clinicians and better patient education regarding the implications of inappropriate and inaccurate use of antibiotic therapy in the development of resistance should help to control the current rapid emergence of resistant *S. pneumoniae*.

Vaccination against *S. pneumoniae* represents an important approach to controlling both invasive and non-invasive disease. Limitations of the current non-conjugated polysaccharide vaccines can be overcome by conjugating the capsular polysaccharides to protein carriers [35]. Conjugation improves the immunogenicity of pneumococcal vaccines by eliciting T-cell-dependent responses to the protein carrier. The protein is presented in association with the major histocompatibility complex class 2 molecules on the surface of antigen-presenting cells causing stimulation of T-helper cells that then stimulate B-cells to produce antibodies and to mature into memory cells. The T-cell-dependent nature of the immune response to such pneumococcal conjugated vaccines permits their effective use in young children (<2 years of age). Furthermore, by reducing the rate of carriage of the targeted bacterial pathogen, conjugated vaccines may also reduce pneumococcal transmission.

Pneumococcal 7-valent conjugated vaccine contains saccharides coupled to the non-toxic diphtheria variant CRM_{197}. A clinical trial of this conjugated vaccine in the Northern California Kaiser Permanente Healthcare System showed high efficacy rates against invasive pneumococcal disease (97% for serotypes inclusive of the vaccine; 89% regardless of serotype) [6]. This led to the approval of this vaccine by the United States Food and Drug Administration as prevention against invasive disease caused by *S. pneumoniae* and acceptance and incorporation into standard paediatric immunisation schedules by the Academy for Certification of Immunization Practices, the American Academy of Pediatrics, and the American Association of Family Practice [1, 2,59].

In Europe, six pneumococcal serogroups (6, 9, 14, 18, 19, and 23) were reported to be associated with more than 70% of invasive disease [30]. Due to geographic variation of serotype distribution, the coverage rate of a 7-valent conjugated vaccine could be less than 70% in some European countries. Recent epidemiological studies from Germany, Denmark, Greece, the United Kingdom, Spain, and southern Sweden have suggested that coverage rates for the 7-valent conjugate vaccine could range from 53% to 83% among children in these countries [19, 23, 34, 43, 56,62]. Approval by the European Commission (representing 16 European countries) has taken place and licensing is proceeding in many other countries worldwide. The inclusion of other pneumococcal serotypes (e.g. 1, 3, 5, and 7) in more extended conjugated formulations under clinical investigation may evoke additional interest in those European countries where these serotypes contribute materially to the burden of invasive disease.

Clinical trials with conjugated pneumococcal vaccines against bacterial otitis media have shown modest efficacy (6%—7%) [6] and this rate increased to 57% when analysis was focused on by episodes caused specifically by those serotypes included in the conjugated vaccine. Regarding the effect on nasopharyngeal carriage of the pneumococcus, recent preliminary analyses have also demonstrated that the 7-valent conjugated vaccine is effective in reducing carriage of vaccine-specific serotypes among two distinctly different paediatric populations: Finnish children [36] and children of native Americans (i.e. Navajo and Apache Indians) [46]. The phenomenon of carriage replacement with non-vaccine

pneumococcal serotypes was also observed in both these studies and also in the Kaiser Permanente trial [6]. At the present time the clinical significance of such serotype replacement is unclear; however, investigators have noted the potential pathogenic importance of such replacement [21]. Routine surveillance of carried as well as invasive serotypes may be warranted in ongoing and future trials with conjugated vaccines.

References

1. American Academy of Family Physicians (2000) Recommendation for pneumococcal conjugate immunization. American Academy of Family Physicians. Available from: http://www.aafp.org/policy/camp/24.html.
2. American Academy of Pediatrics Committee on Infectious Diseases (2000) Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics 106: 362–366
3. Appelbaum PC (1992) Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin Infect Dis 15: 77–83
4. Appelbaum PC, Gladkova C, Hryniewicz W, Kojouharov B, Kotulova D, Mihalcu F, Schindler J, Setchanova L, Semina N, Trupl J, Tyski S, Urbaskova P, Jacobs MR (1996) Carriage of antibiotic-resistant *Streptococcus pneumoniae* by children in eastern and central Europe: a multicenter study with use of standardized methods. Clin Infect Dis 23: 712–717
5. Austrian R (1986) Some aspects of the pneumococcal carrier state. J Antimicrob Chemother 18[Suppl A]: 35–45
6. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, Elvin L, Ensor KM, Hackell J, Siber G, Malinoski F, Madore D, Chang I, Kohberger R, Watson W, Austrian R, Edwards K (2000) Efficacy, safety, and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 19: 187–195
7. Butler JC, Hofmann J, Cetron MS, Elliott JA, Facklam RR, Breiman RF (1996) The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. J Infect Dis 174: 986–993
8. Butler JC, Dowell SF, Breiman RF (1998) Epidemiology of emerging pneumococcal drug resistance: implications for treatment and prevention. Vaccine 16: 1693–1697
9. Centers for Disease Control and Prevention (1997) Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 46: 1–24
10. Centers for Disease Control (2000) Pneumococcal disease In: Epidemiology and prevention of vaccine-preventable diseases, 6th edn. Centers for Disease Control, Atlanta, pp 249–263
11. Christenson B, Sylvan SP, Noreen B (1997) Carriage of multiresistant *Streptococcus pneumoniae* among children attending day-care centres in the Stockholm area. Scand J Infect Dis 29: 555–558
12. Consensus statement: establishing reimbursement guidelines for Pnc7, a new pediatric vaccine for *Streptococcus pneumoniae* (1999) Am J Manag Care 5: S965–S984
13. Davies T, Goering RV, Lovgren M, Talbot JA, Jacobs MR, Appelbaum PC (1999) Molecular epidemiological survey of penicillin-resistant *Streptococcus pneumoniae* from Asia, Europe, and North America. Diagn Microbiol Infect Dis 34: 7–12
14. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN (1998) Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. Clin Infect Dis 27: 764–770
15. Douglas RM, Paton JC, Duncan SJ, Hansman DJ (1983) Antibody response to pneumococcal vaccination in children younger than five years of age. J Infect Dis 148: 131–137
16. Dowell SF, Schwartz B (1997) Resistant pneumococci: protecting patients through judicious use of antibiotics. Am Fam Physician 55: 1647–1648
17. Dowell SF, Butler JC, Giebink GS, Jacobs MR, Jernigan D, Musher DM, Rakowsky A, Schwartz B (1999) Acute otitis media: management and surveillance in an era of pneumococcal resistance–a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. Pediatr Infect Dis J 18: 1–9
18. Ekdahl K, Martensson A, Kamme C (1998) Bacteraemic pneumococcal infections in Southern Sweden 1981–96: trends in incidence, mortality, age-distribution, serogroups, and penicillin-resistance. Scand J Infect Dis 30: 257–262
19. Eriksson M, Henriques B, Ekdahl K (2000) Epidemiology of pneumococcal infections in Swedish children. Acta Paediatr Suppl 89: 35–39
20. Eskola J, Takala AK, Kela E, Pekkanen E, Kalliokoski R, Leinonen M (1992) Epidemiology of invasive pneumococcal infections in children in Finland. JAMA 268: 3323–3327
21. Eskola J, Kilpi T, Palmu A, Jokinen J, Eerola M, Haapakoski J, Herva E, Takala A, Kayhty H, Karma P, Kohberger R, Lockhart S, Siber G, Mäkelä H (2001) Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 344: 403–409
22. Fedson DS, Musher DM (1994) Pneumococcal vaccine. In: Plotkin SA, Mortimer E Jr (eds) Vaccines, 2nd edn. Saunders, Philadelphia, pp 517–564
23. Fenoll A, Jado I, Vicioso D, Berron S, Yuste JE, Casal J (2000) *Streptococcus pneumoniae* in children in Spain: 1990–1999. Acta Paediatr Suppl 89: 44–50
24. Gaudelus J, Cohen R, Reinert P (2000) Epidemiology of pneumococcal infections in French children. Acta Paediatr Suppl 89: 27–29
25. Gehanno P, N'Guyen L, Derriennic M, Pichon F, Goehrs JM, Berche P (1998) Pathogens isolated during treatment failures in otitis. Pediatr Infect Dis J 17: 885–890
26. Geslin P, Fremaux A, Sissia G, Spicq C (1998) *Streptococcus pneumoniae*: serotypes, invasive and antibiotic resistant strains: The current situation in France (in French). Presse Med 27[Suppl 1]: 21–27
27. Givon-Lavi N, Dagan R, Fraser D, Yagupsky P, Porat N (1999) Marked differences in pneumococcal carriage and resistance patterns between day care centers located within a small area. Clin Infect Dis 29: 1274–1280
28. Gray BM, Converse GM III, Dillon HC Jr (1980) Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis 142: 923–933
29. Greenwood B (1999) The epidemiology of pneumococcal infection in children in the developing world. Philos Trans R Soc Lond B Biol Sci 354: 777–785
30. Hausdorff WP, Bryant J, Paradiso PR, Siber GR (2000) Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 30: 100–121
31. Jacobs MR, Dagan R, Appelbaum PC, Burch DJ (1998) Prevalence of antimicrobial-resistant pathogens in middle ear fluid: multinational study of 917 children with acute otitis media. Antimicrob Agents Chemother 42: 589–595
32. Johnsson H, Ewald U (1994) The incidence of neonatal pneumococcal septicemia in Sweden 1991–92. The result of a national survey. Ups J Med Sci 99: 161–165
33. Kalima P, Emmanuel FX, Riordan T (1999) Epidemiology of *Streptococcus pneumoniae* infections at the Edinburgh City Hospital: 1980–95. Epidemiol Infect 122: 251–257
34. Kaltoft, Zeuthen N, Konradsen HB (2000) Epidemiology of invasive pneumococcal infections in children aged 0–6 years in Denmark: a 19-year nationwide surveillance study. Acta Paediatr Suppl 89: 3–10

35. Kayhty H, Eskola J (1996) New vaccines for the prevention of pneumococcal infections. Emerg Infect Dis 2: 289–298
36. Kilpi TM, Syrjänen R, Palmu A, Herva E, Eskola J, Mäkelä PH, Fin S (2001) Parallel evaluation of the effect of a 7-valent pneumococcal conjugate vaccine (PNCCRM) on pneumococcal (PNC) carriage and acute otitis media (AOM) (abstr). 19th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), March 26–28, Istanbul, Turkey
37. Koornhof HJ, Wasas A, Klugman K (1992) Antimicrobial resistance in *Streptococcus pneumoniae*: a South African perspective. Clin Infect Dis 15: 84–94
38. Leibovitz E, Dragomir C, Sfartz S, Porat N, Yagupsky P, Jica S, Floreschu L, Dagan R (1999) Nasopharyngeal carriage of multidrug-resistant *Streptococcus pneumoniae* in institutionalized HIV-infected and HIV-negative children in northeastern Romania. Int J Infect Dis 3: 211–215
39. Linares J, Pallares R, Alonso T, Perez JL, Ayats J, Gudiol F, Viladrich PF, Martin R (1992) Trends in antimicrobial resistance of clinical isolates of *Streptococcus pneumoniae* in Bellvitge Hospital, Barcelona, Spain (1979–1990). Clin Infect Dis 15: 99–105
40. Lopez B, Cima MD, Vazquez F, Fenoll A, Gutierrez J, Fidalgo L, Caicoya M, Mendez FJ (1999) Epidemiological study of *Streptococcus pneumoniae* carriers in healthy primary-school children. Eur J Clin Microbiol Infect Dis 18: 771–776
41. Loundon N, Roger G, Vu Thien H, Begue P, Garabedian EN (1999) Evolution of the bacteriologic features of persistent acute otitis media compared with acute otitis media: a 15-year study. Arch Otolaryngol Head Neck Surg 125: 1134–1140
42. Melander E, Molstad S, Persson K, Hansson HB, Soderstrom M, Ekdahl K (1998) Previous antibiotic consumption and other risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae* in children. Eur J Clin Microbiol Infect Dis 17: 834–838
43. Miller E, Waight P, Efstratiou A, Brisson M, Johnson A, George R (2000) Epidemiology of invasive and other pneumococcal disease in children in England and Wales 1996–1998. Acta Paediatr Suppl 89: 11–16
44. Molyneaux E, Walsh A, Phiri A, Molyneux A (1998) Acute bacterial meningitis in children admitted to the Queen Elizabeth Central Hospital, Blantyre, Malawi in 1996–1997. Trop Med Int Health 3: 610–618
45. Muller-Graf CD, Whatmore AM, King SJ, Trzcinski K, Pickerill AP, Doherty N, Paul J, Griffiths D, Crook D, Dowson CG (1999) Population biology of *Streptococcus pneumoniae* isolated from oropharyngeal carriage and invasive disease. Microbiology 145: 3283–3293
46. O'Brien KL, Bronsdon MA, Carlone GM, Facklam RR, Schwartz B, Reid RR, Santosham M (2001) Effect of a 7-valent pneumococcal conjugate vaccine on nasopharyngeal (NP) carriage among Navajo and White Mountain Apache (N/WMA) infants (abstr). 19th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), March 26–28 2001, Istanbul, Turkey
47. Paradise JL (1998) Otitis media and child development: should we worry? Pediatr Infect Dis J 17: 1076–1083
48. Pedersen FK, Henrichsen J (1983) Pneumococcal meningitis and bacteraemia in Danish children 1969–1978. Serotypes, incidence, and outcome. Acta Pathol Microbiol Immunol Scand 91: 129–134
49. Principi N, Marchisio P (2000) Epidemiology of *Streptococcus pneumoniae* in Italian children. Acta Paediatr Suppl 89: 40–43
50. Ronchetti MP, Guglielmi F, Latini L, Merolla R, Lorusso G, Bajaksouzian S, Villa MP, Catania S, Jacobs MR, Ronchetti R (1999) Resistance patterns of *Streptococcus pneumoniae* from children in central Italy. Eur J Clin Microbiol Infect Dis 18: 376–379
51. Scott JAG, Hall AJ, Dagan, R, Dixon JM, Eykyn SJ, Fenoll A, Hortal M, Jette LP, Jorgensen JH, Lamothe F, Latorre C, Macfarlane JT, Schlaes DM, Smart LE, Taunay A (1996) Serogroup-specific epidemiology of *Streptococcus pneumoniae*: associations with age, sex, and geography in 7,000 episodes of invasive disease. Clin Infect Dis 22: 973–981
52. Shackley F, Knox K, Morris JB, Crook D, Griffiths D, Mayon-White R, George R, Willocks L, Moxon E (2000) Outcome of invasive pneumococcal disease: a UK based study. Oxford Pneumococcal Surveillance Group. Arch Dis Child 83: 231–233
53. Short WR, Tunkel AR (2000) Changing epidemiology of bacterial meningitis in the United States. Curr Infect Dis Rep 2: 327–331
54. Sniadack DH, Schwartz B, Lipman H, Bogaerts J, Bulter JC, Dagan R, Echaniz-Aviles G, Llyod-Evans N, Fenoll A, Girgis NI, Henrichsen J, Klugman K, Lehmann D, Takala AK, Vandepitte J, Gove S, Breiman RF (1995) 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. Pediatr Infect Dis J 4: 503–510
55. Spanjaard L, van der Ende A, Rumke H, Dankert J, van Alphen L (2000) Epidemiology of meningitis and bacteraemia due to *Streptococcus pneumoniae* in The Netherlands. Acta Paediatr Suppl 89: 22–26
56. Syriopoulou V, Daikos GL, Soulis K, Michos A, Alexandrou H, Pagali IPA, Hadjichristodoulou C, Theodoridou M (2000) Epidemiology of invasive childhood pneumococcal infections in Greece. Acta Paediatr Suppl 89: 30–34
57. Takala AK, Jero J, Kela E, Ronnberg PR, Koskenniemi E, Eskola J (1995) Risk factors for primary invasive pneumococcal disease among children in Finland. JAMA 273: 859–864
58. Tan TQ, Mason EO Jr, Barson WJ, Wald ER, Schutze GE, Bradley JS, Arditi M, Givner LB, Yogev R, Kim KS, Kaplan SL (1998) Clinical characteristics and outcome of children with pneumonia attributable to penicillin-susceptible and penicillin-nonsusceptible *Streptococcus pneumoniae*. Pediatrics 102: 1269–1375
59. Van Beneden CA, Whitney CG, Levine OS (2000) Preventing pneumococcal disease among infants and young children. MMWR 49: 1–38
60. Venetz I, Schopfer K, Muhlemann K (1998) Paediatric invasive pneumococcal disease in Switzerland, 1985–1994. Swiss Pneumococcal Study Group. Int J Epidemiol 27: 1101–1104
61. World Health Organization (1999) Pneumococcal vaccines. WHO position paper. Weekly Epidemiol Rec 74: 177–183
62. Ziebold C, von Kries R, Siedler A, Schmitt HJ (2000) Epidemiology of pneumococcal disease in children in Germany. Acta Paediatr Suppl 89: 17–21