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REVIEW

Potential Impact of Conjugate Pneumococcal Vaccines on Pediatric Pneumococcal Diseases

Katherine L. O'Brien and Mathuram Santosham

From the Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

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Children younger than age 2 years have the highest rates of invasive pneumococcal disease and play an important role in its transmission. In the United States, seven pneumococcal serotypes cause approximately 80% of invasive disease and represent approximately 60% of middle-ear isolates in children younger than age 2 years; the majority of penicillin-resistant strains are confined to these same few serogroups. Although unconjugated polysaccharide pneumococcal vaccines have demonstrated effectiveness in preventing invasive disease in adults, these vaccines fail to protect against otitis media or nasopharyngeal carriage and are poorly immunogenic in children younger than age 2 years. A new generation of pneumococcal vaccines has been developed, linking the capsular polysaccharide of seven to 11 serotypes to a protein carrier. The only pneumococcal vaccine approved to date for children younger than age 2 years is a seven-valent conjugate vaccine (PnCRM-7) (Prevnar; Wyeth Vaccines, Pearl River, New York), which contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. PnCRM-7 is more immunogenic than the polysaccharide pneumococcal vaccines and is 80–100% effective against vaccine-type invasive disease and 50–60% effective against vaccine-type pneumococcal otitis media. Routine immunization with pneumococcal conjugate vaccines should substantially reduce the morbidity, mortality, and costs associated with pneumococcal disease in children.

child; communicable diseases; immunization; pneumococcal diseases; *Streptococcus pneumoniae*

Abbreviations: CI, confidence interval; CRM, cross-reactive material; IPD, invasive pneumococcal disease; OR, odds ratio; PS-23, 23-valent pneumococcal polysaccharide.

Streptococcus pneumoniae (pneumococcus) has replaced *Haemophilus influenzae* type b as the leading cause of invasive disease among children in developed countries because of the *H. influenzae* type b conjugate vaccines. Pneumococcus colonizes the upper respiratory tract and causes invasive pneumococcal diseases (IPDs) and noninvasive diseases, particularly in children, the elderly, and those with certain underlying medical conditions (1). Pneumococcal diseases place a major burden on the US health care system. Acute otitis media accounts for 24 million pediatric office visits and $5 billion in costs annually (2, 3); 30–50 percent of bacterial acute otitis media episodes are caused by pneumococcus. IPD, although less common, is more severe and drives high treatment costs. Pneumococcal meningitis, for example, has a high case-fatality rate (14–30 percent) and long-term neurologic sequelae in 25–56 percent of cases (4–6).

The incidence of drug-resistant pneumococcal disease has increased dramatically, complicating treatment. Penicillin-nonsusceptible pneumococcal strains are now isolated in approximately 24 percent of IPD cases in the United States (2, 7–10). Infection with drug-resistant pneumococcal strains has resulted in treatment failures among children with otitis media and meningitis (11–13), largely because of the difficulty in achieving adequate antibacterial concentrations in the middle ear and cerebrospinal fluid (13–15).

Prevention tools include vaccination, judicious use of antibiotics, and infection control strategies in child-care settings.

Correspondence to Dr. Katherine L. O'Brien, Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, 621 North Washington Street, Baltimore, MD 21205 (e-mail: klobrien@jhsph.edu).

TABLE 1. Basis for increased risk of pediatric pneumococcal disease according to risk group

Risk group	Likely pathophysiology
Children <2 years of age	Lack of serotype-specific protective antibody
Children in day care	Increased exposure to pneumococcus
Ethnicity: American Indian, Alaska Native, African American	Multifactorial
Cerebrospinal fluid leak	Disruption of the central nervous system barrier
Functional asplenia (e.g., sickle cell disease) or anatomic asplenia (e.g., splenectomy)	Reduced bacterial clearance from blood and reduced production of immunoglobulin M
Human immunodeficiency virus infection	Multifactorial, including lack of functional serotype-specific antibody and possibly other immunologic defects
Congenital immunodeficiency	Defective serotype-specific antibody formation
Neoplastic: leukemia, lymphoma, myeloma, Hodgkin's disease	Multifactorial
Bone marrow transplantation	Lack of serotype-specific protective antibody
Nephrotic syndrome	Lack of sufficient amounts of protective antibody because of antibody loss in urine

The 23-valent pneumococcal polysaccharide (PS-23) vaccines are effective in children aged 2 years or older; however, they elicit a T-cell–*independent* response that makes them insufficiently immunogenic in children less than age 2 years. Thus, pneumococcal conjugate vaccines have been developed. These vaccines elicit a T-cell–*dependent* response, making them effective in children less than age 2 years.

The objectives of this paper are to 1) describe the epidemiology of and risk factors for pediatric pneumococcal infection and diseases in the United States and 2) review the potential impact of conjugate pneumococcal vaccines.

EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASES

S. pneumoniae is a major cause of morbidity and mortality in the United States, with the highest rates of disease occurring among young children and the elderly (1, 2, 16–18). Approximately 40,000 pneumococcal deaths occur annually in the United States, mostly among the elderly (1). However, pneumococcal diseases cause significant morbidity in the pediatric population, including otitis media, bacteremia, and pneumonia (2). Prior to the use of conjugate pneumococcal vaccine, the rate of IPD among children less than 2 years of age was 166.9/100,000 (18).

RISK FACTORS FOR INFECTION

Several demographic, health-related, socioeconomic, and environmental factors have been associated with an increased risk of pneumococcal infection. The pathophysiology of increased risk is multifactorial (table 1).

Age

Children less than age 5 years (especially those <2 years of age) and adults older than age 65 years are at increased risk of IPD compared with older children and young adults (figure 1) (19). Compared with those in other age groups, children less than age 2 years and the elderly are known to have lower antibody responses to the pure polysaccharide vaccines.

Race and ethnicity

The incidence of pneumococcal disease varies widely according to the race and ethnicity of the population (table 2) (19–21). The Active Bacterial Core Surveillance of the Centers for Disease Control and Prevention surveys all microbiology laboratories processing clinical specimens in geographically diverse areas of the United States, representing a total population of approximately 19 million persons. According to 2000 Active Bacterial Core Surveillance data, the annual incidence of IPD among persons of all ages is more than twice as high in the Black population (41.7/100,000) compared with the White (19.3/100,000) or

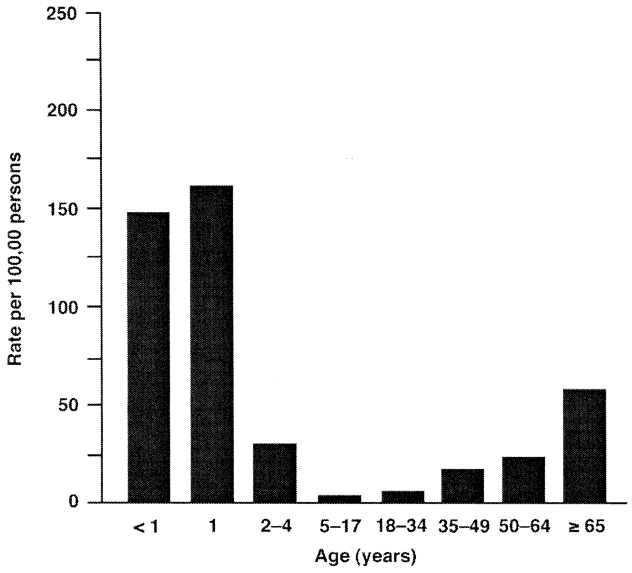

FIGURE 1. Incidence of invasive pneumococcal disease in the United States, by age, 2000.

TABLE 2. Incidence rates of invasive pneumococcal disease by race and ethnicity, United States, 1983–2000

Race or ethnicity	Annual incidence per 100,000 population (all ages)
White	18.8
Hispanic	16.3
Black	41.7
Alaska Native	74
White Mountain Apache	156

Hispanic (16.3/100,000) populations (19). Some Native American populations are at a high risk of IPD. Between 1986 and 1990, the age-adjusted annual incidence of IPD among Alaska Natives was 74/100,000 for persons of all ages and 624/100,000 for children less than 2 years of age (20). The highest rates for any US population were found among the White Mountain Apache Indians; the annual incidence of IPD between 1983 and 1990 was 207/100,000 for persons of all ages and 1,820/100,000 for children less than 2 years of age (21). The incidence of IPD was also found to be elevated among Navajo people, with an overall annual incidence from 1989 to 1996 of 63/100,000 for persons of all ages, 568/100,000 for children less than 12 months of age, and 537/100,000 for children less than age 24 months (22, 23). The reasons for high rates of disease among these Native American populations are not clear.

Underlying immunodeficiency

Persons with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy) are at higher risk of pneumococcal infection because of reduced clearance of encapsulated bacteria from the bloodstream (24, 25). IPD rates are also increased for persons with other immunosuppressive conditions (e.g., congenital immunodeficiency, human immunodeficiency virus infection, neoplastic diseases) or iatrogenic immunosuppression (e.g., organ/bone marrow transplantation, systemic corticosteroids) (26, 27).

Other underlying illnesses

Children and adults with underlying illnesses—such as cardiac, pulmonary, or liver disease—are at high risk of pneumococcal disease (1, 28). In two separate case series of IPD, the proportion of children with an underlying illness increased with age: in the first case series, 11 percent (<1 year of age), 29 percent (aged 1–4 years), and 33 percent (≥5 years of age) (29); in the second case series, 15.9 percent (<2 years of age), 30.4 percent (aged 2–5 years), and 44.5 percent (>5 years of age) (30). Among children aged 2–59 months included in a case-control study, IPD was strongly associated with underlying disease, such as sickle cell disease, cancer, kidney disease, or asplenia (31).

Previous antibiotic therapy

Previous treatment with beta-lactam antibiotics predisposes for acute otitis media or IPD with a drug-resistant pneumococcal strain (32, 33). Among children aged 2–59 months in a case-control study, IPD caused by penicillin-resistant pneumococcal strains was independently associated with at least one course of antibiotics in the previous 3 months (31).

Socioeconomic status

By linking data from population-based surveillance for IPD with data from the 1990 US Census, rates of IPD were shown to be higher among persons residing in lower median income areas (34). However, the analysis also showed that White patients in areas with a higher median household income had a significantly higher risk of being infected with drug-resistant pneumococcal strains. The reason for this difference is not known but may result from higher antibiotic use in more affluent societies. By contrast, an association between socioeconomic status and risk of acute otitis media was not found in a large cohort of infants followed for up to 7 years (35). Therefore, increased socioeconomic status may result in fewer infections overall, but the infections that do occur are more likely to be caused by pneumococci that are nonsusceptible to various antimicrobial agents.

Day-care attendance

Among children aged 2–59 months included in a case-control study, IPD was strongly associated with day-care attendance (31). Day-care attendance is also a predisposing factor for infection with drug-resistant pneumococcal strains, both for otitis media and for IPD (31, 36, 37). Day-care centers, because of the close interactions between children, allow more efficient transmission of pneumococci from the nasopharynx of one child to another. Increased rates of disease (predominantly acute otitis media but also invasive disease) result in increased use of antibiotics, selecting for nonsusceptible pneumococci in the nasopharynx.

Lack of breastfeeding

Breastfeeding is associated with a decreased risk of both pneumococcal otitis media (35) and IPD (31, 38). According to a study by Teele et al. (35), a history of breastfeeding was independently associated with a decreased risk of otitis media during the first year (odds ratio (OR) = 0.64, 95 percent confidence interval (CI): 0.44, 0.91) and the first 3 years of life (OR = 0.48, 95 percent CI: 0.30, 0.76), as well as a decreased risk of frequent otitis media (≥3 episodes/year) during the first year of life (OR = 0.51, 95 percent CI: 0.30, 0.89). In case-control studies, breastfeeding was protective against IPD among both children aged 2–59 months (OR = 0.27, 95 percent CI: 0.08, 0.90) (31) and Alaska Native children younger than age 2 years (OR = 0.1, 95 percent CI: 0.0, 1.0) (38).

Exposure to tobacco smoke

In a cohort of 877 infants less than 1 year of age followed for at least a year, parental smoking was associated with an increased incidence of acute otitis media (261/410 (64

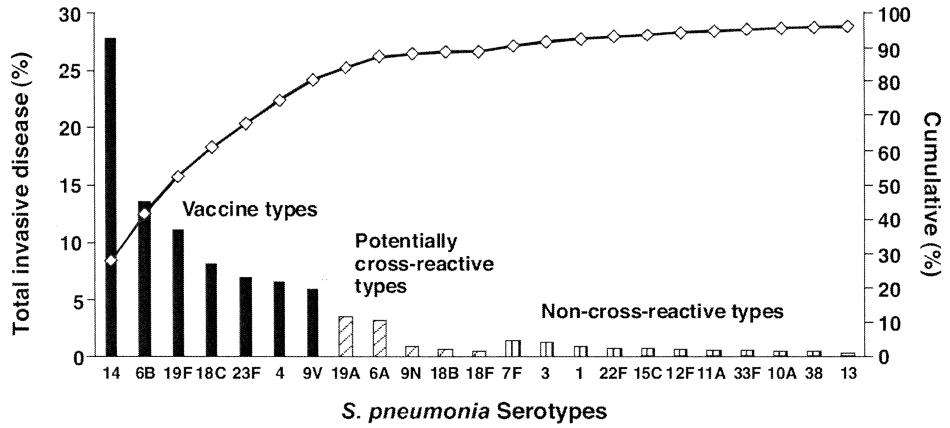

FIGURE 2. *Streptococcus pneumoniae* serotypes frequently associated with invasive pneumococcal disease in young children from North America, 1978–1998. Black bars, vaccine serotypes; diagonal hatch bars, potentially cross-reactive serotypes; vertical hatch bars, non-cross-reactive serotypes.

percent) for parental smoking vs. 263/467 (56 percent) for no parental smoking, $p < 0.05$) (35). In adults, IPD was associated with cigarette smoking (OR = 4.1, 95 percent CI: 2.4, 7.3) and with passive smoking (OR = 2.5, 95 percent CI: 1.2, 5.1) after adjustment for age and independent risk factors such as sex, race, chronic illness, level of education, and residing with young children attending day care (39).

There are few data on the effects of cigarette smoke on pneumococcal carriage. In a point-prevalence survey, passive smoking was not found to be independently associated with pneumococcal carriage among 1,723 Italian day-care attendees (40). However, a study of French children attending day-care centers indicated that tobacco smoke exposure increased colonization with antibiotic-resistant pneumococci (OR = 4.38, 95 percent CI: 1.10, 18.14) (41). The pathophysiology of the smoking-related risk may relate to alterations in the respiratory mucosa, thereby increasing pneumococcal binding to buccal cells (42).

CONTRIBUTION OF SEROTYPE TO PNEUMOCOCCAL DISEASE

The polysaccharide capsule of *S. pneumoniae* is an important virulence factor, protecting the organism against phagocytosis by granulocytes and macrophages in the absence of type-specific antibody. The capsular polysaccharide elicits a T-cell–*independent* immune response (43); evidence suggests that wild-type infection or nasopharyngeal carriage in adults may induce immunologic B-cell memory (44, 45). The T-cell–*independent* immune response is not fully developed in children less than 2 years of age, contributing to the high incidence of disease in this group (43).

Over 90 pneumococcal serotypes have been identified; the prevalence of these serotypes varies by age, geographic location, and type of disease (44). In the general US population, seven serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) cause approximately 80 percent of IPD in children less than 2 years of age (figure 2) (26, 46, 47); however, the proportion of IPD caused by these serotypes is lower among young children of some Alaska Native and American Indian populations (22, 48). These seven serotypes also represent 65–75 percent of middle-ear pneumococcal isolates from young children in the United States (46, 47, 49). Furthermore, according to 1998 surveillance data from eight US states, 80 percent of the 312 penicillin-nonsusceptible pneumococcal isolates collected from normally sterile sites among children less than 6 years of age were from these same seven serotypes (26). The serotype distribution of invasive isolates in other parts of the world including Europe, Asia, and Africa differs from that observed in the United States and Canada (46, 49); the proportion of isolates caused by serotypes contained in the seven-valent conjugate vaccines is lower in these areas of the world than in the United States. The threshold for obtaining blood cultures from febrile children is likely a major contributing factor to the observed differences.

CARRIAGE OF *S. PNEUMONIAE*

A significant number of persons are colonized with pneumococci in the respiratory tract (carriage) either intermittently or persistently for weeks to months (50–54). Although colonization of the nasopharynx with *S. pneumoniae* may or may not result in disease, the nasopharynx is the reservoir for transmission within families, day-care centers, and the community (41, 52–56).

Rates of carriage vary with age, living conditions (e.g., crowding, indoor air pollution), and the presence of upper respiratory tract infection. The distribution of pneumococcal serotypes associated with carriage is similar but not identical to that of isolates causing disease (57). Pneumococcal carriage rates are inversely related to age, with up to 65 percent in preschool children, 36 percent in primary school children, and 25 percent in high school children in the United States (58–60). As a consequence of their high and prolonged carriage rate and the method of transmission (respiratory droplets), young children play an important role in the transmission of pneumococcus, particularly in day-care settings, other crowded settings, and households. This

TABLE 3. Pneumococcal conjugate vaccines licensed or in development, United States

Conjugated vaccines	Manufacturer	Status
Seven-valent (4, 6B, 9V, 14, 18C, 19F, 23F)		
Pnc-CRM7 (polysaccharides conjugated to CRM_{197})	Wyeth Vaccines (Pearl River, New York)	Licensed
Pnc-OMP (polysaccharides conjugated to outer membrane protein of *Neisseria meningitidis* group B)*	Merck & Co. (Whitehouse Station, New Jersey)	Phase III (otitis media endpoint)
Nine-valent (seven-valent plus 1, and 5)		
Pnc-CRM9 (polysaccharides conjugated to CRM_{197})	Wyeth Vaccines	Phase III (invasive disease and pneumonia endpoints)
11-valent (nine-valent plus 3, and 7F)		
Pnc-D/T (polysaccharides conjugated to diphtheria toxoid and tetanus protein)†	Aventis Pasteur (Lyon, France)	Phase III (pneumonia endpoint)
Polysaccharides conjugated to protein D of nontypable *Haemophilus influenzae*	GlaxoSmithKline (Uxbridge, Middlesex, United Kingdom)	Phase II/III (otitis media endpoint)
Pnc-CRM11 (polysaccharides conjugated to CRM_{197})	Wyeth Vaccines	Preclinical

* This product is not being developed further by Merck & Co.

† This product is not being developed further by Aventis Pasteur in part because of lower-than-expected immunogenicity of concomitantly administered acellular pertussis vaccine.

role is demonstrated by adult carriage rates of 18–29 percent in households with children compared with rates of 6 percent in households without children (58). Studies of children attending day care have demonstrated horizontal transmission of carriage (41, 52–55) and disease (56).

Recent antibiotic use is a significant risk factor for nasopharyngeal carriage of pneumococcus and, specifically, carriage of antibiotic-resistant strains (33, 61–64). Antibiograms and serotyping of nasopharyngeal pneumococcal isolates before and after treatment with various beta-lactam antibiotics have revealed that selection of resistant isolates occurs within 3 or 4 days of therapy initiation (65), most likely because of selection of preexisting resistant strains that constitute minor populations in the nasopharynx of children prior to treatment. Other risk factors for carriage of drug-resistant pneumococci include age less than 2 years and a recent history of upper respiratory tract infection, including otitis media (60).

PNEUMOCOCCAL VACCINES

The pneumococcal polysaccharide vaccines were first licensed in the United States in 1983, based predominantly on efficacy studies among South African adults (66). The efficacy against pneumonia of six- and 12-valent polysaccharide vaccines was 76 percent and 92 percent, respectively (66). Postlicensure observational effectiveness studies in the United States have estimated the efficacy against invasive disease to range from 0 percent to 81 percent. Vaccination with PS-23 vaccines is an established and important method of controlling pneumococcal disease in high-risk groups including the elderly (67, 68). However, the T-cell–*independent* response elicited by these vaccines results in limited immunogenicity and effectiveness in several important populations. More than 80 percent of healthy adults who receive PS-23 vaccines develop antibodies; however, older adults and persons with chronic illness or immunodeficiency may not respond as well (68).

Because the T-cell–*independent* immune response is not fully developed in children less than 2 years of age, the PS-23 vaccine is poorly immunogenic for important serotypes in this age group (1, 26). Furthermore, the immunologic response to pneumococcal serotypes 6A and 14 is decreased in children aged 2–5 years (69–71). Immunization with polysaccharide pneumococcal vaccines was shown to decrease mortality from acute lower respiratory tract infections by at least 50 percent ($p < 0.05$) in Papua New Guinean children vaccinated at 6 months to 4 years of age (72). To our knowledge, no other trials in developing countries have assessed the effect of polysaccharide vaccine on mortality; however, results of trials have shown no efficacy in infants and children against respiratory disease, hospitalizations, antibiotic use, or otitis media (1, 73–76). Although there are some data to the contrary (77), the preponderance of evidence shows that PS-23 vaccines do not protect against nasopharyngeal carriage (73). Therefore, pneumococcal polysaccharide vaccines have not been recommended for use among children less than 2 years of age (1).

Protein conjugate pneumococcal vaccines have been developed to address the limitations of the PS-23 vaccines, which involves covalently linking pneumococcal capsular polysaccharides to a protein carrier, resulting in enhanced serum antibody response and inducing a T-cell–*dependent* memory (booster) response. Several pneumococcal conjugate vaccines are in preclinical, clinical, or postlicensure phases; each uses a different protein carrier (table 3). One pneumococcal conjugate vaccine, the seven-valent vaccine (PnCRM-7) (Prevnar; Wyeth Vaccines, Pearl River, New York), is licensed for use in the United States and approximately 50 other countries.

TABLE 4. Immune response (μg/ml) following administration of pneumococcal conjugate vaccine in various infant populations, United States, 1995–1999

Serotype	Patient population (immune response (ref. no.))						
	Healthy infants*				Otitis-prone children (85)† (*n* = 30)	Nonresponders to polysaccharide vaccine (86)‡ (*n* = 20)	Children with human immunodeficiency virus (87)§ (*n* = 17)
	(*n* = 90 (78))		(*n* = 75 (79))				
	GMC¶	95% CI¶	GMC	95% CI	GMC (25th, 75th percentile)	Median response (range)	GMC (range)
4	1.36	1.2, 1.6	1.365	NA¶		2.2 (0.1, 13)	
6B	1.37	0.97, 1.9	2.143	NA	1.19 (0.38, 2.83)	0.1 (0.1, 6.7)	2.74 (0.01, 64.12)
9V	0.98	0.83, 1.2	1.234	NA		1.2 (0.1, 17)	
14	3.48	2.7, 4.5	5.041	NA	2.10 (1.02, 3.75)	1.7 (0.3, 19)	6.59 (0.03, 57.60)
18C	1.24	1.0, 1.5	1.880	NA		0.6 (0.1, 8.4)	2.87 (0.005, 56.53)
19F	3.45	2.7, 4.4	1.524	NA	4.26 (1.82, 10.52)	3.1 (0.1, 165)	2.94 (0.01, 24.66)
23F	1.8	1.3, 2.5	1.207	NA	2.12 (0.54, 4.33)	0.7 (0.1, 14.3)	1.47 (0.01, 20.89)

* After the third of four doses of PnCRM-7 vaccine.
† After the only dose of PnCRM-7 vaccine.
‡ After the second of two doses of PnCRM-7 vaccine.
§ After the third of three doses of five-valent conjugate vaccine.
¶ GMC, geometric mean concentration; CI, confidence interval; NA, not applicable.

Safety and tolerability

Safety and tolerability data have been published for several pneumococcal conjugate vaccines, including those conjugated to diphtheria toxin cross-reactive material (CRM_{197}), diphtheria toxoid and tetanus protein, and meningococcal outer membrane protein (78–82). The most comprehensive safety data available are for the PnCRM-7 product, which has been administered to approximately 20,000 infants and children in controlled clinical trials (78, 79). Adverse reactions occurring when the vaccine is administered to infants and children have generally been transient, mild to moderate in severity, and comparable to those experienced by control groups or to those receiving other licensed infant vaccines.

In a large, double-blind trial of PnCRM-7, 37,868 healthy infant members of Northern California Kaiser Permanente were randomly assigned to immunization at 2, 4, and 6 months of age (primary series) and at 12–15 months of age (booster) with PnCRM-7 or meningococcal group C conjugate vaccine (control group) (79). Local reactions were generally mild, transient, and self-limited. Although there were some differences in the incidence of transient fever (≥38°C) and febrile seizures in subgroups of patients receiving PnCRM-7 and diphtheria-tetanus toxoid whole cell pertussis or diphtheria-tetanus toxoid acellular pertussis vaccines when compared with controls, no clear pattern of increased incidence was evident for children receiving the PnCRM-7 vaccine.

A study among Finnish and Israeli children evaluating the investigational 11-valent diphtheria-tetanus toxoid protein conjugated pneumococcal vaccine (seven serotypes plus 1, 3, 5, and 7; Aventis Pasteur, Lyon, France) found that the vaccine was safe and well tolerated, with no occurrences of serious adverse events (80). An investigational nine-valent CRM_{197} vaccine (seven serotypes plus 1 and 5) also demonstrated an excellent safety profile in a study of 500 South African infants, with no reports of systemic toxicity associated with the vaccine as compared with placebo (81).

Immunogenicity

Immunogenicity evaluations of pneumococcal conjugate vaccine products include the ability of the vaccine to induce serotype-specific antibodies, to induce T-cell memory, and to still allow an immune response to concomitantly administered vaccines. Immunogenicity data have been published for pneumococcal vaccines conjugated to CRM_{197}, diphtheria and tetanus toxoids, *H. influenzae* protein D, and outer membrane protein. Below is a brief summary of the key findings for each of the products.

The immunogenicity of the seven- and nine-valent CRM_{197} pneumococcal conjugate vaccines has been evaluated among healthy infants in two large trials in the United States (78, 79), The Gambia (83), and South Africa (81). In all settings, the vaccine induced high antibody concentrations following a three-dose primary series and, when it was given, a booster response to a fourth dose. These vaccines have also been evaluated among children with sickle cell disease (84), otitis-prone children (85), children with recurrent respiratory tract infections who failed to respond to PS-23 vaccine (86), American Indian children, and children with human immunodeficiency virus infection (87). In all of these settings, the CRM_{197} conjugate products induced a memory response and high concentrations of serotype-specific antibodies (table 4) (78, 79, 85–87).

The four- to 11-valent diphtheria-tetanus toxoid protein conjugated pneumococcal vaccines also induce high serotype-specific antibody concentrations with evidence of T-cell memory induction. Evaluation of these products when

given in combination with other routine vaccinations is ongoing (80, 88–90). Several studies have evaluated the immunogenicity of the seven-valent meningococcal outer membrane protein–conjugated vaccine (91–93). These studies, like those of the other conjugate products, have demonstrated induction of serotype-specific antibodies and evidence of a T-cell–*dependent* immune response, leading to a booster phenomenon. Immunogenicity results for the 11-valent protein D conjugate product have been presented in abstract form and are also promising (94).

Efficacy against pneumococcal nasopharyngeal carriage

Investigators have evaluated the effect of various pneumococcal conjugate vaccines on nasopharyngeal carriage among vaccinees (81, 95–103). All studies, regardless of the carrier protein used, found a reduction in vaccine-type colonization; most have shown a concomitant increase in nonvaccine-type colonization (81, 97, 100, 102, 103). The implications of this latter finding are as yet unknown; an increase in nonvaccine-type disease has been shown for otitis media only, as discussed below (82, 104).

Efficacy against IPD

Two large efficacy trials of the PnCRM-7 vaccine against IPD have been completed, one (individually randomized) among children in the Northern California Kaiser Permanente population (79) and one (group randomized) among American Indian children (105) enabling evaluation of indirect (herd) effects. Two IPD efficacy studies of nine-valent CRM vaccine, in The Gambia and in South Africa, are in progress or have been completed, respectively (106). Both the American Indian and the South African trials demonstrated clinically significant efficacy against serotype-specific IPD; however, in both trials, the point estimate of efficacy was somewhat lower than that of the Northern California Kaiser Permanente trial discussed here (79).

In the Northern California Kaiser Permanente study, the primary endpoint was efficacy against IPD caused by PnCRM-7 vaccine serotypes (79). Secondary analyses included efficacy against clinically diagnosed acute otitis media and pneumonia. PnCRM-7 was 97.4 percent (95 percent CI: 82.7, 99.9; $p < 0.001$) protective against vaccine serotype IPD (79). The overall impact of PnCRM-7 on IPD, regardless of the serotype and following at least one dose of vaccine, was 89.1 percent (95 percent CI: 73.7, 95.8; $p < 0.001$).

In a postlicensure study of children enrolled in the Kaiser Permanente health system, more than 150,000 doses of PnCRM-7 had been administered to almost 45,000 children by March 2001. Among children less than 12 months of age, the incidence of IPD before routine vaccine use was 51.52–98.15/100,000 person-years and fell to 9.35/100,000 person-years following routine use (107). Similarly, among those less than 2 years of age, the rate decreased from 81.67–113.80/100,000 person-years prior to licensure to 38.22/100,000 person-years after licensure (107). There was no increase in disease incidence from nonvaccine serotypes or from possibly cross-reacting serotypes.

Postlicensure data from 2001 for the general US population have shown a 69 percent decline in the rate of IPD among those less than 2 years of age compared with 1998 and 1999, a reduction in the rates of disease among adults (i.e., likely an indirect effect of conjugate vaccine use among children)—particularly those 20–39 years of age—and a 35 percent reduction in the proportion of isolates nonsusceptible to penicillin in 2001 compared with 1999 (108).

Reduction in disease rates among children too young to have received a full course of vaccine doses (i.e., children aged <6 months) has been observed. These reductions are likely due to partial protection from one or two doses of vaccine and indirect effects from use of vaccine among children community-wide. Further reductions in disease in this age group, particularly in developing-world settings where the burden of disease in this age group is higher, may depend on the success of vaccinating children at an earlier age (i.e., neonatal doses or 6-, 10-, 14-week schedules) or the use of maternal immunization programs. Most of these strategies are still under investigation.

Efficacy against otitis media

In the Northern California Kaiser Permanente study, PnCRM-7 was also shown to reduce the incidence of clinically diagnosed acute otitis media in the 1-year follow-up of fully vaccinated subjects (79). The vaccine reduced the overall rate of acute otitis media episodes by 7.0 percent (95 percent CI: 4.1, 9.7). PnCRM-7 efficacy was more pronounced for frequently recurrent infection, with an efficacy of 22.8 percent (95 percent CI: 6.7, 36.2) in subjects experiencing five episodes in 6 months or six episodes in 12 months. PnCRM-7 also decreased the number of physician visits for acute otitis media by 8.9 percent (95 percent CI: 5.8, 11.8) and reduced the rate of surgical intervention by 20.1 percent (95 percent CI: 1.5, 35.2) (79).

The efficacy of PnCRM-7 against culture-proven pneumococcal acute otitis media has been investigated in a population of 1,662 infants in the Finnish otitis media study (104). Subjects were randomly assigned to receive either PnCRM-7 or a hepatitis B vaccine (control) at 2, 4, and 6 months of age, with a booster at 12 months of age. The rate of acute otitis media episodes caused by vaccine-specific serotypes was decreased by 57 percent (95 percent CI: 44, 67); by cross-reactive serogroups (6A, 9N, 18B, 19A, 23A), 51 percent (95 percent CI: 27, 67); and by any serotype, 34 percent (95 percent CI: 21, 45). Acute otitis media episodes, irrespective of etiology, decreased by 6 percent (95 percent CI: –4, 16). However, the rate of acute otitis media caused by pneumococcal serotypes other than those contained in, or cross-reactive to, the vaccine serotypes increased by 33 percent (i.e., vaccine efficacy = –33 percent, 95 percent CI: –80, 1) (i.e., replacement disease). Long-term follow-up data at 4–5 years of age (403 in the PnCRM-7 group, 353 in the control group) showed that 67 percent of PnCRM-7–immunized children and 73 percent of controls had had at least one acute otitis media episode after age 2 years (relative risk = 0.92, 95 percent CI: 0.84, 1.02) (109). The tympanos-

tomy surgery rate was 3.5/100 person-years in PnCRM-7 recipients versus 5.7/100 person-years in control vaccine recipients (vaccine efficacy = 39 percent (95 percent CI: 4, 61)) (109).

An increase in acute otitis media due to nonvaccine-type/non-cross-reactive pneumococci was also shown following vaccination with the seven-valent outer membrane protein–conjugated vaccine (82). It was found to protect against vaccine serotype disease (efficacy = 56 percent, 95 percent CI: 44, 66), but the overall efficacy against otitis media was 0 percent. The degree to which replacement disease will occur in other populations and for other disease syndromes (e.g., pneumonia, IPD) is unknown. Therefore, it is important to maintain active surveillance for disease in defined populations in which the vaccine has been introduced.

The efficacy of the investigational PnCRM-9 vaccine against otitis media was also evaluated in a double-blind study conducted among children aged 12–35 months at a day-care center in Israel (110). Subjects were randomly assigned to receive PnCRM-9 or the meningococcal group C conjugate vaccine. Children aged 12–17 months received two doses of the vaccine; those older than 17 months received one dose of the vaccine. During an average follow-up period of 21.3 months per child, pneumococcal vaccination was associated with a 17 percent (range, 2–33 percent) reduction in acute otitis media episodes and a 20 percent reduction in antibiotic use for acute otitis media.

Efficacy against pneumonia

The Northern California Kaiser Permanente study and the South Africa trial have published results of the efficacy of PnCRM-7 and PnCRM-9, respectively, against clinically diagnosed pneumonia (106, 111). Among children in the Northern California Kaiser Permanente study, there was a 20.5 percent reduction in the number of episodes of pneumonia with a positive chest radiograph, with the greatest impact seen among children less than 12 months of age (35.5 percent reduction), followed by those less than 24 months of age (23.4 percent reduction), and minimal impact among children older than 24 months of age (9.1 percent reduction) (111). In the South Africa trial, pneumonia episodes confirmed by chest radiograph were reduced by 25 percent among children uninfected with human immunodeficiency virus who were fully vaccinated and by 20 percent among those who had received at least a single dose of vaccine (106). Efficacy trials in The Gambia and the Philippines are also assessing the impact of PnCRM-9 and the "11-valent" diphtheria-tetanus toxoid protein conjugated pneumococcal vaccine, respectively, on pneumonias confirmed by chest radiograph. The results of these trials are expected in 2005–2006.

CONCLUSIONS

Pneumococcus continues to be the leading cause of invasive and noninvasive diseases in the pediatric population and asserts a high burden on the US population and health care system. In addition, treatment of some syndromes is becoming more challenging because of the rising prevalence of antibiotic-resistant strains. The licensure of the pneumococcal conjugate vaccine heralds a new era in the control of pneumococcal diseases.

Serotype-specific conjugate pneumococcal vaccines can potentially reduce the burden of IPD, pneumonia, and otitis media among young children. Through the effects of these vaccines on nasopharyngeal colonization, their widespread use may also confer protection against vaccine-type pneumococcal disease in adults, particularly the elderly. Careful, ongoing surveillance for incidence, serotype distribution, and antimicrobial susceptibility patterns among both invasive and colonizing pneumococci in vaccinated populations is critical to our understanding of the long-term effects of these vaccines. Several questions remain to be answered. How long will the protection from the pneumococcal conjugate vaccines last? How often should the booster dose be given? Will nonvaccine-type pneumonia or IPD emerge? The future directions of disease prevention may include the addition of serotypes to the conjugate vaccines, implementation of combined conjugate and polysaccharide pneumococcal vaccine schedules, and development of common protein pneumococcal vaccines. Each of these strategies holds promise for significantly impacting pneumococcal disease across the age spectrum.

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