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SPECIAL ARTICLE

The Future of Pneumococcal Conjugate Vaccines for Prevention of Pneumococcal Diseases in Infants and Children

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ABSTRACT. Seven-valent pneumococcal conjugate vaccine (PCV7) was licensed in February 2000. In June 2000, the Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommended the universal administration of pneumococcal conjugate vaccine for all children 23 months of age and younger and for children 24 to 59 months of age who are at high risk for serious pneumococcal disease. Since then, >23 million doses have been administered in the United States. Postlicensure surveillance of invasive pneumococcal disease (IPD) in the United States from the Active Bacterial Core Surveillance program at the Centers for Disease Control and Prevention and the Northern California Kaiser Permanente Vaccine Study Center has reported a decline in IPD and in pneumococcal disease incidence as a result of vaccine serotypes, respectively. During this period, issues critical to the long-term success of PCV7 have become more relevant: Will PCV7 be as effective in groups of children who are at high risk for IPD as in healthy children? Will nonvaccine types replace vaccine serotypes in the nasopharynx and in disease? Why are the results of the clinical trials different for IPD and for acute otitis media? How many doses of PCV7 and what concentrations of antibody are necessary for protection? Will universal administration of PCV7 to children younger than 2 years reduce antimicrobial drug resistance and alter prescribing patterns of physicians for febrile infants? Have there been unanticipated adverse events or benefits observed? The purpose of this report is to review the current data available to address these questions and to identify gaps that will require additional knowledge to determine the ultimate value of pneumococcal conjugate vaccines in reducing the burden of pneumococcal disease in infants and children. ***Pediatrics*** **2002;110:805–814;** ***pneumococcal disease, pneumococcal vaccine, conjugate vaccine, carriage, serotypes.***

ABBREVIATIONS. PCV, pneumococcal conjugate vaccine; IPD, invasive pneumococcal disease; NCKP, Northern California Kaiser Permanente; HIV, human immunodeficiency virus; NP, nasopharyngeal; PPV, pneumococcal polysaccharide vaccine; ELISA, enzyme-linked immunosorbent assay; OPA, opsonophagocytic activity; MnCC, meningococcal group C conjugate vaccine; Hib; *Haemophilus influenzae* type b; DTP, diphtheria-tetanus-pertussis.

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The first pneumococcal vaccine that is safe and effective in infants and toddlers was approved by the US Food and Drug Administration in February 2000. The introduction of the heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar; Wyeth, Radnar, PA) is the culmination of >100 years of pneumococcal vaccine development. In clinical trials, the PCV was demonstrated to be effective in prevention of serotype-specific invasive pneumococcal disease (IPD), pneumonia, and acute otitis media.[1,2] By December 2001, 23 million doses had been distributed throughout the United States (Frank Malinoski, Wyeth, personal communication). Postlicensure data from the Active Bacterial Core Surveillance program at the Centers for Disease Control and Prevention and the Northern California Kaiser Permanente (NCKP) Vaccine Study Center indicate a decline in IPD throughout the United States and in pneumococcal disease incidence for vaccine serotypes within the Kaiser Permanente System, respectively.[3,4] The reduction in IPD was predicted from the clinical trials previously reported; however, important questions have been raised about the long-term efficacy of the vaccine.[1,5] Will PCV7 be as effective in high-risk populations (eg, immunocompromised children [eg, human immunodeficiency virus (HIV), sickle cell disease]; premature infants; children of African American, Native American, and Alaskan Native descent) as in healthy populations? Will nonvaccine serotypes replace vaccine serotypes in nasopharyngeal (NP) carriage and disease, and why are the implications for otitis media different from IPD? How many doses of PCV7 and what concentrations of antibody are necessary for protection against IPD? Will there be unanticipated adverse events or benefits from immunization with PCV7? Finally, what evaluations should the physician undertake for the immunized child who has IPD? The purpose of this report is to summarize current data and suggest answers to these questions that will determine the ultimate value of conjugate vaccines in reducing the burden of pneumococcal diseases in infants and children.

WILL PCV7 BE EFFECTIVE IN POPULATIONS AT HIGHEST RISK FOR IPD?

The incidence and distribution of IPD in certain high-risk populations differ from those found in otherwise healthy children. For children with sickle cell disease, HIV infection, or humoral antibody defi-

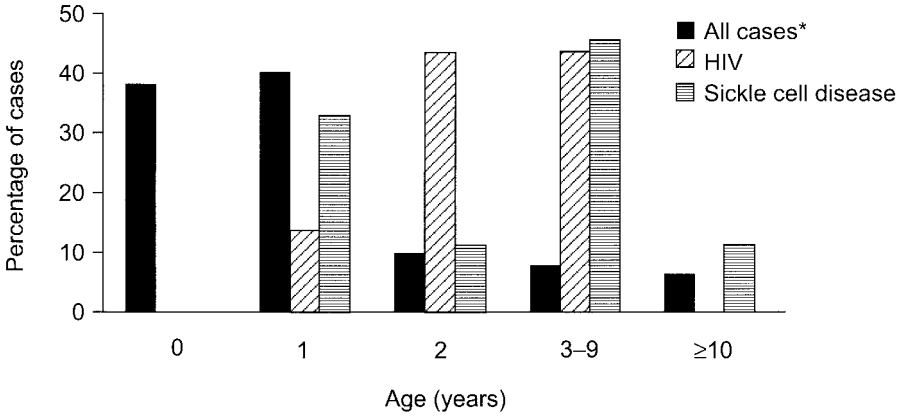

Fig 1. Age distribution of pneumococcal bacteremia in children with sickle cell disease or HIV and healthy children at Boston Medical Center, 1981–1998.[9] *All children with invasive pneumococcal disease at Boston Medical Center 1981–1998.

ciency, the incidence of pneumococcal disease may exceed 6 cases per 100 patient-years compared with 0.02 to 0.06 cases per 100 patient-years reported in community-based studies of healthy children.[6–9] The risk for IPD in the general population begins after 3 months of age, peaks between 12 and 18 months, and then declines after 24 months of age. Children with HIV or sickle cell disease have attack rates for IPD that remain high throughout childhood (Fig 1).[9] Clinical manifestations in high-risk children often include a higher proportion of cases with pneumococcal meningitis as well as greater likelihood of relapse or reinfection. Studies of pneumococcal bacteremia in US children who have HIV infection do not indicate increased mortality or a greater risk of focal disease; however, studies in children with sickle cell disease identify increased mortality.[7,10,11]

The challenge of preventing pneumococcal disease in these high-risk groups is further complicated by the impaired immune function observed in children with these conditions. O'Brien et al[12] found responses to PCV7 in infants and toddlers with sickle cell disease comparable to those of healthy control subjects (Table 1).[12–16] Goldblatt et al[17] reported that a primary series of a 9-valent PCV (PCV9) administered at 6, 10, and 14 weeks to children with sickle cell disease resulted in high antibody concentrations at 7 months of age. The 23-valent pneumococcal polysaccharide vaccine (PPV23), given at 12 months of age to this cohort, elicited a booster response contrasted with the limited response to initial immunization with PPV23 at the same age. King et al[13] evaluated the immune response in children who had HIV infection and were younger than 2 years to a 5-valent PCV (PCV5). Seventy-eight percent of children who had HIV infection had >1 μg/mL of antibody to all 5 serotypes after 3 doses of vaccine. The response was comparable with a control group without HIV. Children with mild HIV disease were more likely to achieve antibody concentration >1 μg/mL than those with advanced disease. In a second study of older children who had HIV infection (aged 2–9 years), a single dose of PCV5 also elicited a greater antibody response than PPV23; however, when compared with healthy children, the response was significantly reduced.[18] The study suggests that immunogenicity to PCV5 may be limited in older children who have HIV infection presumably because of progressive immune dysfunction. These studies relied on measurement of antibody responses using an enzyme-linked immunosorbent assay (ELISA); however, when assays of functional activity have been used in adults with HIV infection, PPV23 has failed to elicit opsonophagocytic activity (OPA) to 4 of 5 serotypes evaluated.[19] Immunization with PCV7 in the same population resulted in increases in OPA to only 3 of 5 serotypes after 2 doses. Whether immune reconstitution after suppression of HIV replication, which results from antiretroviral therapy, restores the functional immune response to PCVs in children requires additional study.

It can be concluded from these studies that patients with sickle cell disease respond to PCV7 with functional antibody that seems to be adequate to

TABLE 1. Immune Response to PCVs in Special Populations

Investigator/Year/Reference	Vaccine	Population	No. of Doses	Time of Assessment (Months)	Proportion With Antibody Concentration 1 μg/mL by Serotype			
					6B	14	19F	23F
O'Brien (2000)[12]	PCV7	SCD (infants)	3	1 after third dose	~83	~95	~95	~90
		SCD (~1 y)	1	1 mo after dose	~55	~30	~60	~50
King (1997)[13]	PCV5	HIV (<2 y)	3	1 after third dose	63	94	81	63
Zielen (2000)[14]	PCV7	Nonresponders to PPV23 (3–18 y)	2	1 after second dose	25	65	70	50
Sorenson (1998)[15]	PCV7	Nonresponders to PPV23 (2–13 y)	1	4–6 wk postdose	~36*	~90*	~78*	~92*
Nachman (2001)[16]	PCV7	HIV (infants)	3	7 mo	80	92	92	84

SCD indicates sickle cell disease.
* Response defined as ≥1.3 μg/mL or a 4-fold rise in concentration.

prevent IPD. Additional studies on children who have HIV infection and are receiving highly active antiretroviral therapy will be necessary to identify whether children will elicit functional responses from such vaccination. Klugman[20] is completing a trial with PCV9 in children in South Africa, where PCV9 is being administered at 6, 10, and 14 weeks of age. PCV9 includes serotypes 1 and 5, thus better reflecting the serotype distribution for IPD in South Africa and Europe. Two important results are anticipated: 1) earlier administration of the vaccine will elicit protective responses before 7 months of age, and 2) children who have HIV infection and are not receiving highly active antiretroviral therapy (eg, those in South Africa, where availability is limited) will benefit from immunization with PCV9.

WILL PCV7 PREVENT IPD IN PREMATURE INFANTS?

Shinefield et al[21] reported that premature infants are at an increased risk for IPD. Sufficient numbers of premature and low birth weight infants were enrolled in the NCKP Vaccine Trial to permit observations on both the frequency of disease and the efficacy of immunization in this cohort. Shinefield et al[21] identified an increased attack rate of IPD in premature infants and demonstrated the immunogenicity and efficacy of PCV7 in this neonatal population. Children who weighed <2500 g and/or were born before 37 weeks' gestation had a 2.6- and 1.6-fold increase, respectively, in the relative risk for IPD. All cases of IPD occurred in the cohort immunized with the control vaccine (meningococcal group C conjugate [MnCC]; Table 2).[21] PCV7 should prevent the increased incidence of IPD in premature infants.

WILL PCV7 PREVENT DISEASE IN RACIAL GROUPS AT HIGH RISK FOR IPD?

Higher rates of pneumococcal disease are seen in Apache and Navajo American Indians (10- to 30-fold), Alaskan Natives (5-fold), and black individuals (2- to 3-fold; Fig 2).[22–27] Genetic characteristics and variations in living conditions (eg, poverty, crowding, differences in smoking habits and breastfeeding practices, reliance on wood-burning stoves) all have been hypothesized as reasons for the observed increase in disease rate. The apparent persistence of increased risk in various ethnic groups, even when controlling for income, suggests a multifactorial cause. In the White Mountain Apache and Navajo communities, PCV7 has already been demonstrated to prevent IPD, affirming the immunologic capacity of these children to make protective antibody.[5] It seems likely that PCV7 will reduce disease in these high-risk ethnic groups before we understand all of the reasons for the racial disparities; however, whether the reduction in disease will be comparable to white children requires additional study.

TABLE 2. Invasive Pneumococcal Disease by Birth Weight and Gestational Age[21]

	Disease in Control Group (MnCC Vaccine)	Expected No.*	Relative Risk
Birth weight (g)			
<750	0	0	—
750–999	0	0	—
1000–1500	1	0.15	6.7
1501–<2500	5	2	2.4
≤2500† (total)	6	2.3	2.6
Gestational age (wk)			
<32	2	0.22	9.1
32–<36	1	1.5	0.67
36–<38	6	3.8	1.6
≤38‡ (total)	9	5.6	1.6

* Based on disease rate in term infants.
† $P < .03$.
‡ $P < .08$.

IS THE EFFECT OF PCV7 ON PREVENTION OF COLONIZATION IMPORTANT?

The pathophysiology of invasive and middle ear and sinus infection (referred to as mucosal surface infection) involves NP colonization with *Streptococcus pneumoniae* with concurrent viral respiratory infection in a preponderance of cases. Viral infection may impair host defenses such as ciliary clearance or phagocytic function and/or increase the density of NP colonization with selected bacterial pathogens. A reduction in NP colonization with *S pneumoniae* would likely result in a decrease in pneumococcal upper and lower respiratory tract infection as well as invasive disease.

In general, PCVs decrease the incidence of carriage attributable to serotypes in the vaccines but result in increased NP carriage of nonvaccine serotypes of *S pneumoniae* (Table 3).[28–31] Two studies reported the effect of a 3-dose regimen during the first 6 months of life on NP colonization at 7 and 9 months, respectively.[29,31] Both showed >50% reductions in NP colonization with vaccine serotypes. A third study demonstrated a 50% reduction with a 1- or 2-dose regimen in 12- to 18-month-old children.[28] These results suggest that immunization with PCV7 would likely decrease the incidence of respiratory disease caused by vaccine serotypes of *S pneumoniae*.

Haemophilus influenzae type b (Hib) conjugate vaccination demonstrated a dramatic reduction in colonization in immunized children as well as in the unimmunized community at large. A reduction of *S pneumoniae* in a significant proportion of the community (those vaccinated) has potential implications for protecting unimmunized children and adults within the community. O'Brien et al[32,33] used a randomized community design in the White Mountain Apache and Navajo Nation Indians that has provided preliminary information regarding herd immunity resulting from PCV7 immunization. The investigators have already reported a reduction in NP colonization with vaccine serotypes in unimmunized children living in the same household with immunized children. Additional data on changes in disease in unimmunized children in the household as well as changes in colonization and disease in adult household members will expand insight of the ability of PCV7 to achieve a herd effect and increase our knowledge of the role that children play as the source of exposure for pneumococcal disease in adults.

The current experience with PCV7 demonstrates

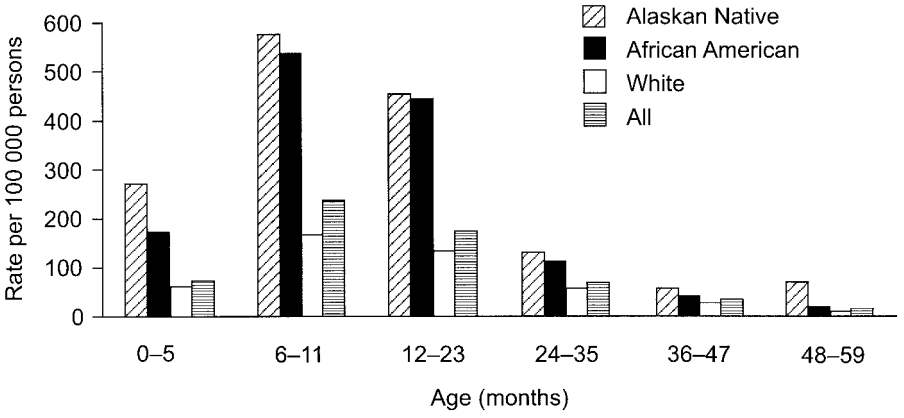

Fig 2. Age distribution of invasive pneumococcal disease for select racial/ethnic populations.[27]

TABLE 3. NP Carriage of Vaccine and Nonvaccine Serotypes of *S pneumoniae* in PCV and Control Infants and Toddlers

Investigator/Year	Age at Immunization	Interval Between Completion of Immunization and Culture	Vaccines		Controls	
			Vaccine Type (*n* [%])	Nonvaccine Type (*n* [%])	Vaccine Type (*n* [%])	Nonvaccine Type (*n* [%])
Dagan (1996)[28]	12 and 15 mo	12 mo	17 (13)*	—	14 (25)†	—
Obaro (1996)[29]	2, 3, 4, and 18 mo	~6 mo	13 (50)‡	20 (77)§	14 (90)‡	68 (43)§
Dagan (1997)[30]	2, 4, 6 and 12 mo	~1 mo	161 (17)‖	368 (38)	264 (27)‖	274 (28)
Mbelle (1999)[31]	6, 10 and 14 wk	~6 mo	43 (18)‡	87 (36)§	86 (36)‡	59 (25)§

* Control versus PCV for carriage of vaccine serotypes ($P < .065$).
† Control versus PCV for carriage of nonvaccine serotypes (P = not significant).
‡ Control versus PCV for carriage of vaccine serotypes ($P < .001$).
§ Control versus PVC for carriage of nonvaccine serotypes ($P < .007$).
‖ Control versus PCV for carriage of vaccine serotypes ($P = .034$).

approximately a 50% reduction in colonization with vaccine serotypes beginning 1 to 3 months after completion of the primary series; this may be insufficient to prevent exposure in immunocompromised children or to affect colonization and disease in adults. However, in these early studies, only a small proportion of the children in the community (30%–50%) received PCV7. It is possible that the universal administration of conjugate vaccine to young children in the community will result in a larger effect on NP colonization with vaccine serotypes than that observed during various clinical trials. In studies of PCV7 performed during the first year after introduction of vaccine in Massachusetts (between October 2000 and December 2001), the proportion of pneumococcal isolates from the nasopharynx that was 1 of the nonvaccine serotypes was 45% compared with 20% observed in historical controls.

WILL REPLACEMENT OF VACCINE SEROTYPES BY NONVACCINE SEROTYPES RESULT IN DIMINISHED EFFICACY OF PCV7?

Results from studies of NP colonization in PCV7-immunized children have demonstrated a decrease in the proportion of children colonized with vaccine pneumococcal serotypes and an increase in the recovery of nonvaccine serotypes from the nasopharynx.[29,31] The potential for disease caused by nonvaccine serotypes to increase seems to be dependent on whether invasive or mucosal surface infection is being considered. At the time of unblinding of the NCKP phase III trial of PCV7, 49 cases of IPD caused by vaccine serotypes had occurred in the control group and 3 cases in the PCV7 cohort in the intent-to-treat analysis (children who received ≥1 dose of vaccine). Of equal importance, the number of episodes caused by nonvaccine serotypes was similar between the PCV7 and control groups.

O'Brien et al[5] reported the results of a community-based randomized trial in Navajo and Apache children evaluating PCV7 versus a control vaccine (MnCC) for prevention of IPD. Communities were randomized, and infants younger than 2 years were offered 1 of the vaccines, depending on the community in which they resided. The investigators observed 8 cases of IPD caused by vaccine serotypes in the control group and 2 cases in the PCV7 group, indicating a point estimate of vaccine efficacy of 77%. An overall reduction in all cases of IPD (both vaccine and nonvaccine serotypes) of 50% was observed. The reduced efficacy for prevention of all IPD compared with the efficacy observed in the NCKP trial reflects a substantial number of cases caused by nonvaccine serotypes in this community. Disease caused by nonvaccine serotypes, especially serotype 12F, had increased in these Native American communities before the initiation of the conjugate vaccine study (Fig 3).[5] The results highlight the potential for nonvaccine serotypes to cause invasive disease, the need for ongoing surveillance within defined geographical regions, and potential need for reformulation of PCV7 in the future.

The postlicensure report from the NCKP Vaccine Study Center identified cases of IPD attributable to possibly cross-reacting serotypes and nonvaccine serotypes in addition to vaccine serotypes.[4] For non-

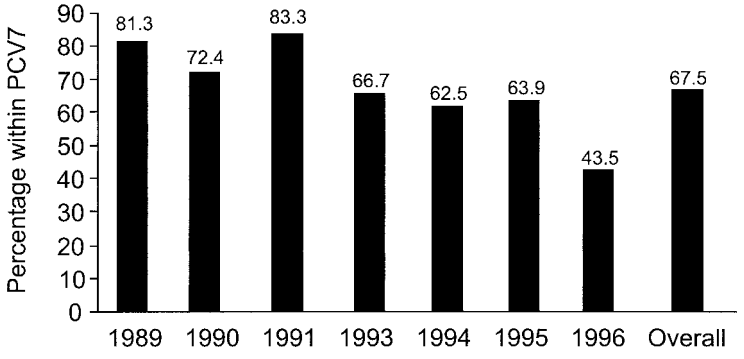

Fig 3. Proportion episodes of invasive pneumococcal disease caused by serotypes within PCV7 in Navajo and White River Junction Indians, 1989–1996.[5]

vaccine serotypes, a nonsignificant trend to fewer episodes was observed. Most important, no evidence for any increment in cases of IPD caused by nonvaccine serotypes was identified. For cross-reacting serotypes, there was a decline reported during the fourth quarter of 2000 to the third quarter of 2001; however, the percentage reduction appeared smaller than for vaccine serotypes.

An increase in episodes of otitis media caused by nonvaccine serotypes was observed in the Finnish otitis media trial.[2] It is hypothesized that after bacterial colonization, co-infection with respiratory viruses exposes new receptors in the nasopharynx and elicits cytokines critical to increasing the burden of bacterial colonization. If combined with immature eustachian tube dysfunction and naïve immunity, ascending infection may follow. The resultant otitis media is caused by *S pneumoniae*, nontypable *H influenzae*, or *Moraxella catarrhalis* present in the nasopharynx. Therefore, increased colonization with nonvaccine serotypes is likely to result in increased acute otitis media unless specific serotypes lack virulence factors that would enable them to invade the middle ear.

In part, these observations explain the difference in efficacy of PCV7 for acute otitis media and IPD. In the Finnish otitis media study, pneumococcal otitis media caused by the vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were reduced by 57%; overall episodes of pneumococcal otitis media were reduced by 34%.[2] The inability to achieve a reduction in pneumococcal otitis media similar to that reported for IPD seems to relate to replacement by nonvaccine serotypes and at least 2 additional issues. First, the number of serotypes recovered from cases of acute otitis media was larger than that seen with IPD; therefore, the proportion of disease caused by vaccine and vaccine-associated serotypes was smaller (Fig 4).[34] Second, protection against vaccine serotypes was substantially less for middle ear disease compared with IPD (57% vs 97%), probably as a result of the antibody concentration achieved in the middle ear. A recent report by Kilpi et al[35] (evaluating another 7-valent vaccine [PCV7OMP], containing the same serotypes as PCV7 but conjugated to the outer membrane of *Neisseria* meningitidis group B, administered at 2 and 4 months and boosted with PPV23 at 12 months) demonstrated increased protection against acute otitis media caused by serotype 19F with a vaccine regimen that achieves higher concentration of serum antibody. This observation suggests that greater immunogenicity may be necessary (at least for serotype 19F) for protection from middle ear infection.

HOW MANY DOSES OF PCV7 ARE REQUIRED FOR PROTECTION?

Several PCVs with unique carrier proteins are under clinical investigation. The carrier proteins include diphtheria toxoid, tetanus toxoid, CRM_{197} (a detoxified diphtheria toxoid), outer membrane of *Neisseria* meningitidis group B, and protein D. Those PCVs that have completed at least phase I studies have demonstrated immunogenicity and safety in healthy children and infants.[2,28,36–39] Multiple studies have demonstrated immune response to 3-dose regimens in infants and 1- and 2-dose regimens in

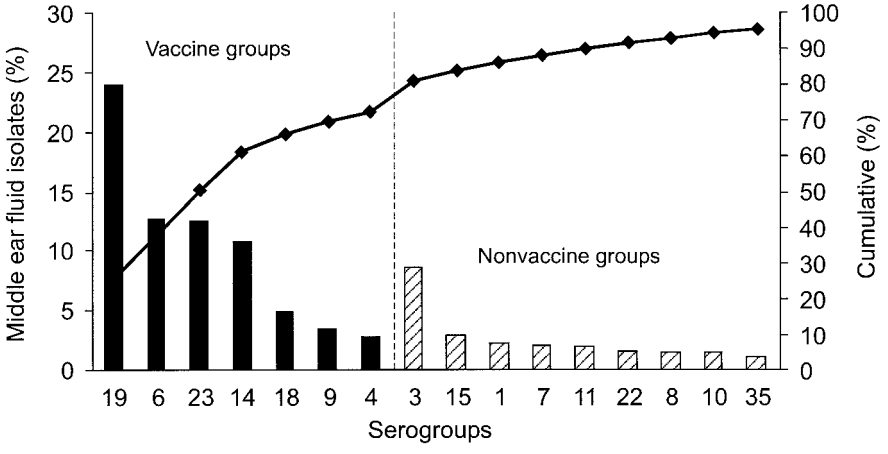

Fig 4. Serogroup of *S pneumoniae* recovered from middle ear fluid of North American children.[34]

toddlers. The concentrations of serotype-specific antibody needed for short- and long-term protection remain controversial. In fact, some investigators believe that the presence of T-cell memory after immunization is the critical feature and that circulating antibody is not the appropriate measure. Regardless, PCVs elicit high antibody concentrations in infants after a primary (3-dose) regimen, and most infants achieve ≥ 1 μg/mL antibody by 7 months of age. Most toddlers given a 1- or 2-dose regimen also achieve serum antibody concentrations >1 μg/mL 1 month after immunization.

In the United Kingdom, the Hib conjugate vaccine (HibTITER) is given as a 3-dose primary regimen without a booster compared with the 4-dose regimen in the United States. Both countries have observed virtual elimination of disease caused by Hib, although a recent report suggests waning immunity and increased disease in older toddlers and a potentially diminished efficacy for the 3-dose regimen.[40] Several investigators have followed an initial 3-dose regime of PCV7 with a booster dose of PPV23, and the studies have demonstrated excellent antibody responses both in healthy children and in special populations.[12,17,35] This regimen has the potential to offer 3 advantages: 1) protection against serotypes in the PPV23 not contained in the PCV7, 2) cost reduction, and 3) possibly greater postbooster serum antibody concentration of specific type antibody. Kilpi et al[35] reported that administration of PPV23 or PCV7OMP as the booster dose after a 2-dose primary series of PCV7OMP resulted in protection against acute otitis media. Enhanced efficacy against 19F was thought to result from the higher serum concentration of serotype 19F antibody observed after boosting with PPV23.[41]

In healthy children aged 2 years or older, the use of PPV23 rather than PCV7 has been proposed. Limited studies comparing the 2 vaccines in this pediatric population have been reported. Barnett et al[42] found that PCV7 was more immunogenic than PPV23 for all 4 serotypes studied (6B, 14, 19F, and 23F) in children prone to otitis media. In healthy children aged 2 to 6 years, there was a trend for higher antibody concentrations to these 4 serotypes measured by ELISA in children immunized with PCV7 compared with PPV23, but the differences were not statistically significant. Studies comparing functional antibody responses after immunization with PCV7 or PPV23 and the durability of antibody are currently in progress. Until additional studies clarify whether PPV23 is adequate as the booster dose, the current schedule using PCV7 for boosting as recommended by both the Advisory Committee on Immunization Practices of the Surgeon General and the Committee on Infectious Diseases of the American Academy of Pediatrics should be followed.[27,43]

CAN WE DEFINE THE IMMUNE CORRELATES OF PROTECTION?

Determination of antibody concentrations by ELISA has become the standard measurement of response to pneumococcal and other polysaccharide vaccines. However, in animal studies using serum selected for a spectrum of antibody concentrations and a disparity between antibody activity measured by ELISA and OPA for passive immunization, OPA correlated more strongly than antibody concentration with protection against IPD.[44] Several studies have evaluated OPA responses to PCV7 in selected populations. For healthy infants, the results of OPA and ELISA are strongly correlated.[45] In these children, antibody concentrations as measured by ELISA can be used as surrogates of protection against invasive disease. Serum concentrations of 0.15 μg/mL after immunization have been proposed as protective levels for Hib disease; that same level has been hypothesized as necessary for protection from IPD.[46,47] However, no specific concentration has been established from results of clinical trials, and a different concentration may be necessary for each serotype as well as for acute otitis media and pneumonia as opposed to what may be necessary for IPD.

In children with sickle cell disease and adults with HIV, PPV23 produced a significant increase in antibody concentrations to common pediatric serotypes as measured by ELISA but either failed to produce significant increases in OPA or elicited more modest increases compared with PCV7.[48,49] PCV7 elicited both increases in antibody concentration and increases in OPA to the common pediatric serotypes in children with sickle cell disease. In this population, OPA assays may be a better measure of protection.[50] Additional studies are necessary to determine what markers of immune status in children with HIV infection will correlate with the development of protective immunity after immunization with PCV7.

WILL WIDESPREAD IMMUNIZATION WITH PCV7 ALTER THE EXPANDING CONCERN ABOUT MULTIDRUG RESISTANCE AMONG *S PNEUMONIAE*?

Surveillance programs in the United States have tracked susceptibility trends for the past decade. These programs reported an increasing trend in the resistance of *S pneumoniae* to β-lactams, macrolides, quinolones, and sulfonamides among isolates from the respiratory tract and sterile body sites of adults and children from all geographic regions.[51,52] Joloba et al[53] analyzed the association between pneumococcal serotype and antimicrobial resistance. More than 95% of amoxicillin-resistant pneumococcal isolates were vaccine or vaccine-associated serotypes. Thus, the reduction in colonization and disease caused by these serotypes should in the short term reduce the incidence of carriage and the frequency of disease caused by antibiotic-resistant pneumococci. This is likely to have its greatest impact on upper respiratory illness, where an increasing proportion of cases may be attributable to nonvaccine serotypes that are currently predominantly susceptible to antibiotics. In addition, the widespread use of PCV7 and the resultant decline in IPD are likely to reduce the number of prescriptions for antimicrobial agents used among the pediatric population, diminishing the selective pressure for emergence of resistance among the nonvaccine serotypes. Reduced antibiotic use for patients and the community should also decrease pres-

sure for selection of resistant pneumococcal strains. Ongoing surveillance of isolates from both the nasopharynx and sterile body sites is important, because changes in susceptibility patterns among nonvaccine serotypes are likely to evolve over time, and there will be an ongoing need to revisit recommendations for treatment of pneumococcal disease.

WILL EXPANDED USE OF PCV7 IDENTIFY UNANTICIPATED ADVERSE EVENTS OR BENEFITS?

Common adverse reactions to PCV7 include local swelling, pain, and decreased limb use.[54] Injection site reactions were reported in up to 40% of children. Reactions greater than a quarter in size (<2.4 cm) were seen in 4.9% to 6.1% of recipients in 1 study and in 2% of all recipients in another study.[36,38] These reactions were likely to limit leg movement. There is no observed increase in severity with subsequent doses, and in general, resolution of both local and systemic reactions occurred during a 2- to 3-day period.

Although local reactions can be adequately assessed even when a vaccine is studied in combination with currently licensed vaccines, systemic responses are more difficult to ascribe to a specific product when given with other vaccines. Systemic responses such as fever, irritability, lethargy, or diarrhea were seen in 22% to 38% of children receiving PCV7 concurrently with diphtheria-tetanus-pertussis (DTP), oral polio vaccine, and Hib conjugate vaccine.[37] Systemic reaction rates were greater in children who received PCV7 compared with the group that received MnCC. In a Finnish study, PCV7OMP was given to children at 2, 4, and 12 months of age without concurrent vaccine; fever >38°C was observed in 6% of vaccine recipients.[39] Prolonged crying was observed in 3% of children who received PCV7 in combination with DTP, oral polio vaccine, and Hib conjugate vaccine.[37] A transient hypotensive, hyporesponsive episode was observed in a single child (of 106 vaccinated with PCV7) in the same study.

More than 23 million doses of PCV7 have now been distributed in the United States. The Vaccine Adverse Event Reporting system provides some insights into possible associated adverse events, although it is unable to confirm causality. Concerns about a possible association of seizures and the administration of PCV7 have been raised. Current information available from prelicensure clinical trials identified a rate of seizure of approximately 1 per 7000 doses (Table 4; data on file, Wyeth). This rate is 4-fold lower than the rate of seizure after the administration of DTP vaccine and comparable to the rate of seizures with DTaP (containing acellular pertussis). To date, there have been 2 reports of adverse neurologic events (ie, encephalitis) after receipt of PCV7; however, no causal relationship has been established (data on file, Wyeth). No other unanticipated adverse reactions have been reported.

Two reports of a significant decrease in asthma diagnoses (asthma, asthmatic bronchitis, wheezy bronchitis, and bronchiolitis) and of nonspecific upper and lower respiratory illness in young children immunized with PCV7 compared with control regimens require additional evaluation of the potential mechanism and confirmation (Wyeth, data on file).[55] These data are consistent with the observed decline in pneumonia reported in the NCKP Vaccine Study. Lower respiratory disease was assessed by 4 different measures. For all 4 measures—clinical diagnosis of pneumonia, obtaining a chest radiograph for suspected pneumonia, abnormal chest radiograph, and lobar pneumonia—a reduction in the number of episodes was observed in the vaccine cohort.[56] A reduction of 35% of cases with any abnormality in radiograph and a 63% reduction in definite consolidation on radiograph were noted in children who received PCV7 compared with the control.[56] These observations suggest that the pneumococcus is responsible for more cases of radiographically identified pneumonia than had previously been assumed. These observations are consistent with studies using serologic techniques that have identified pneumococcus as the cause in an expanded number of cases of pneumonia.[57,58] Because respiratory infection is frequently a cofactor or trigger in reactive airway disease, it is possible that prevention of colonization and/or infection attributable to *S pneumoniae* reduces the severity of illness resulting in a lower respiratory tract infection that is milder and either does not trigger an asthma or bronchitis attack or results in an event so mild that it may not come to the attention of a physician.

TABLE 4. Seizures Within 3 Days of Vaccination Observed in the NCKP Vaccine Trial

Concurrent Vaccine	No. of Patients		
	PCV7	MnCC	*P* Value*
DTP	7	3	.23
DTaP	1	1	.99
Total	8	4	.27

Data on file, Wyeth, February 2000.
DTaP indicates diphtheria-tetanus-acellular pertussis.
* Two-sided exact binomial test.

WILL ADVERSE EVENTS BE MORE COMMON IN CHILDREN PREVIOUSLY IMMUNIZED WITH PPV23?

Zielen et al[14] observed reduced movement of the vaccinated extremity in 17% of children after the first dose of PCV7 and 9% of children after the second dose in a small cohort of children previously immunized with PPV23. The rate of reduced movement was comparable to that observed in a control cohort not previously immunized with PPV23. Injection site inflammation and swelling were more frequent in those previously immunized with PPV23. Vernacchio et al[48] reported a similar rate of systemic and local reactions in children with sickle cell disease previously immunized with PPV23 and reimmunized with either PCV7 or PPV23. There is limited experience with revaccination of children with sickle cell disease or HIV using the suggested schedule (PCV7/PCV7/PPV23 for all children older than 2

years). The major concern is increased local reactions (possibly associated with high concentrations of humeral antibody to some serotypes present at the time of reimmunization).

WHAT APPROACH IS NEEDED FOR CHILDREN WHO HAVE AN EPISODE OF IPD DESPITE IMMUNIZATION WITH PCV7?

IPD will occur in the community despite extensive PCV7 use, because pneumococcal disease will continue to occur as a result of nonvaccine serotypes; some cases of IPD caused by vaccine serotypes will represent vaccine failure. In addition, failure to vaccinate because of parent choice, lack of funding, or physician error will likely represent an additional cause of continuing episodes of IPD.

Efforts to determine the reason for an episode of IPD should begin with serotyping the causative pneumococcal isolate (available at the Centers for Disease Control and Prevention through local state health departments or from well-established laboratories). This will permit initial classification of the case as attributable to a vaccine or nonvaccine serotype. The child's immunization status should be reviewed to determine the number of doses received and the interval between immunization and disease. Hib infection in children immunized with the conjugate vaccine has been associated with identification of immunodeficiency.[59,60] Heath et al[59] evaluated such children in the United Kingdom and found a substantial frequency of immunoglobulin A and immunoglobulin G subclass deficiency. Speculating that a similar spectrum of immunologic abnormalities may be found in children with IPD, we suggest an evaluation that includes measurement of total immunoglobulins, immunoglobulin G subclasses, complement, determination of T- and B-cell subsets, a smear for Howell-Jolly bodies, and HIV testing.

Blood should be obtained for acute and convalescent serology—an initial sample to determine the presence of naturally acquired or vaccine-acquired antibody and a second sample to determine the response to the invasive serotypes. Measurement of antibody to vaccine serotypes may uncover specific defects in response to polysaccharides even when presented as conjugates. Preliminary data suggest that PCV7 will elicit antibody responses in children who failed to respond to PPV23.[14,15]

In some children, detailed history may suggest potential alternative concerns such as a cerebrospinal fluid leak in a child with head trauma; additional diagnostic tests will be indicated. Careful evaluation of children who develop IPD in communities that have begun programs of immunization with PCV7 will permit recognition of increased disease caused by nonvaccine serotypes. It will also identify limitations in the current vaccine program that may require alternative schedules such as earlier administration of the primary series (6, 10, and 14 weeks) or maternal immunization.

In children who have documented IPD and have not had a complete course of PCV7, we recommend that additional doses be administered to complete the schedule. In addition, in children older than 2 years, use of the PPV23 both as a booster and to broaden coverage should be considered, in our opinion.

WILL UNIVERSAL ADMINISTRATION OF PCV7 TO CHILDREN YOUNGER THAN 2 YEARS ALTER THE PRACTICE OF PEDIATRICS?

Pneumococcal disease is primarily an illness of infants and toddlers within the pediatric population. Kaplan et al[61] described the spectrum of disease observed in a 3-year prospective study at 8 children's hospitals. Thirty-six percent of cases occurred within the first year of life, and two thirds of cases occurred before 24 months of age. Only 13% of cases occurred in children older than 5 years, demonstrating the propensity for IPD to occur early in life.[61] Bacteremia without a focus was the clinical manifestation in >57% of cases. It represented a far greater proportion of cases in children younger than 2 years (>60%) compared with children older than 5 years (<40%).

The evaluation and treatment of highly febrile infants and toddlers currently includes consideration of the likelihood of occult bacteremia.[62] The pneumococcus is responsible for approximately 90% of cases of occult bacteremia. Often, especially in hospital settings, complete blood cell count, blood culture, and presumptive therapy are frequently used. If the predicted efficacy of PCV7 of nearly 90% is realized, then the risk of bacteremia in febrile infants and toddlers will decline from approximately 3% to 0.3%.[63,64] Although cases of nonvaccine-type IPD and meningococcal bacteremia would continue to occur, as well as uncommon bacteremias, the total incidence of invasive episodes would be decreased. How would this alter the use of laboratory tests and antimicrobial agents for this syndrome? Would physicians be more likely to observe rather than treat the child who has high fever and was not toxic? We believe that febrile infants with fever without a source and a white blood cell count $\geq 15\,000/mm^3$, regardless of the number of doses of PCV7, should continue to be considered at risk for bacteremia until studies detail the incidence of IPD in immunized children with leukocytosis.

Current data on otopathogens recovered from the middle ear of immunized children who have acute otitis media and reside in communities with a significant prevalence of antibiotic-resistant pneumococci have not been reported. Given the modest efficacy of PCV7 against acute otitis media caused by vaccine serotypes, the changing pattern of pneumococcal colonization in children after immunization, and the lack of information about antimicrobial susceptibilities among the expanded populations of nonvaccine serotypes, no change in the management of acute otitis media is indicated at present. Ongoing collection of data demonstrating the serotypes and antimicrobial susceptibilities of respiratory pathogens in communities with high penetration of conjugate vaccine use will guide the development of subsequent strategies.

CONCLUSIONS

Clinical trials and postmarketing studies have demonstrated a dramatic decline in the entire clinical spectrum of IPD caused by *S pneumoniae*. However, ongoing studies are still needed to determine 1) whether serotype replacement effects efficacy for invasive or mucosal disease; 2) whether the effect of universal immunization in children younger than 2 years decreases the volume of antibiotic prescriptions; 3) whether the proportion of pneumococcal isolates in the community with multidrug-resistant phenotype decreases as hypothesized; 4) the effect of administering PCV7 to children younger than 5 years on disease rates in adults, particularly the elderly; and 5) whether additional evaluation of the optimal regimen and appropriate use of PPV23 will result in changes in formulation and schedules for PCV7 and its successors that further increase effectiveness, especially against mucosal surface disease.

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