Pneumococcal Conjugate Vaccine for Young Children

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EXECUTIVE SUMMARY

Pneumococcal disease is a common cause of morbidity and mortality in the pediatric population. Pneumococcal infections, which account for most serious bacterial disease in infancy and early childhood, are a major cause of acute otitis media, sinusitis, pneumonia, bacterial meningitis, and bacteremia. *Streptococcus pneumoniae* is the causative agent in a large percentage of these infections, although other microorganisms also play a role. The recent emergence of drug-resistant strains has provided a strong incentive for preventing pneumococcal infections by vaccination. However, the capsular polysaccharide pneumococcal vaccines used to immunize adults are neither immunogenic nor protective in young children due to poor antibody responses. Therefore, research has focused on development of additional immunogenic pneumococcal vaccines to provide long-term immunity in children <2 years of age.

The most promising approach has been the development of a protein-polysaccharide conjugate vaccine for the seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) that most commonly cause infections in childhood. An effective conjugate vaccine that protects against these serotypes has the potential to prevent 85 percent of bacteremia episodes, 83 percent of meningitis episodes, and 65 percent of otitis media cases in the U.S. among children younger than 6 years.

The Food and Drug Administration (FDA) recently approved the first protein-polysaccharide conjugate vaccine to prevent invasive pneumococcal diseases in infants and toddlers <2 years of age. This conjugated vaccine against pneumococcus uses the same technology as the successful vaccine against *Haemophilus influenzae* type b. It consists of an immunogenic but inert protein coupled covalently to the polysaccharide coat of the selected strains of pneumococci. The conjugated antigen induces a more powerful, T-cell-based immune response in infants, which is developed by the time they are 2 months of age.

Some important questions regarding this vaccine for children <2 years of age:

- Is the vaccine safe?
- Is it immunogenic?
- Is it efficacious in preventing invasive pneumococcal disease and controlling otitis media?

Findings: Results of three randomized double-blind trials designed to evaluate the safety and immunogenicity of this vaccine in healthy children <2 years of age were reported within the last three years. The studies found that the vaccine is safe and highly immunogenic for all seven serotypes. The most recent study, involving over 37,000 young children, also evaluated the vaccine's efficacy, and reported that the vaccine is highly effective in preventing invasive disease and has had an impact on otitis media.

Conclusions: The heptavalent pneumococcal conjugate vaccine is safe and highly effective in preventing pneumococcal meningitis and bacteremic pneumonia in young children <2 years of age; it is less effective in preventing otitis media. Based on the results of three well-designed studies demonstrating the vaccine's safety, immunogenicity, and efficacy, the vaccine is safe and effective for active immunization of children <2 years of age against invasive disease caused by seven *Streptococcus pneumoniae* serotypes included in the vaccine. At this time, there is no clear medical consensus regarding its safety and efficacy for control of otitis media in children <2 years of age. This application has not been evaluated by the FDA. The pneumococcal conjugate vaccine should be considered experimental, and has not been shown to be safe or efficacious for *Streptococcus pneumoniae* disease other than that caused by the serotypes included in the vaccine and for invasive infection, such as bacteremia or meningitis, caused by other microorganisms.

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MEDICAL BACKGROUND

Streptococcus pneumoniae (pneumococcus), a common bacterial pathogen, affects children and adults worldwide (Käyhty and Eskola 1996, CDC 1997). It is a leading cause of illness in young children: a major cause of the common childhood ear infection, acute otitis media, as well as more invasive infections such as bacteremia, meningitis, and pneumonia. Acute otitis media infections, which most often occur in children <4 years of age, result in more than 24 million visits to pediatricians each year in the U.S. *S. pneumoniae* is the causative agent in approximately 30 percent to 50 percent of these infections (CDC 1997). About 16,000 cases of pneumococcal bacteremia and 1,400 cases of pneumococcal meningitis occur annually in the U.S. among children <5 years old. In as many as 50 percent of pneumococcal meningitis cases, brain damage and hearing loss occur. About 10 percent of patients who contract pneumococcal meningitis die (FDA 2000a). There is a marked decline in the incidence of invasive pneumococcal disease after age 5 (*Medical Letter* 2000).

Children ≤2 years of age are at increased risk for pneumococcal infection, and, in fact, the peak occurrence is in this age group. Epidemiologic studies in Finland and the U.S. suggest that daycare attendance is associated with a significantly higher risk of infection (CDC 1997, Adelson 1999). In addition, immunocompromised children and African American, Native American, Alaskan Native, and socially disadvantaged children are at the highest risk (*Medical Letter* 2000).

Traditionally, pneumococcal infections have been treated with penicillin and other antibiotics. However, in recent years, the emergence of drug-resistant strains of *S. pneumoniae* to penicillin and other antimicrobial drugs, such as erythromycin, trimethoprim-sulfamethoxazole, and extended-spectrum cephalosporins, has created an urgent need for preventing pneumococcal infections by vaccination (Käyhty and Eskola 1996, CDC 1997, Rennels et al. 1998). The currently available pneumococcal vaccines, consisting of 23 purified capsular polysaccharide antigens of *S. pneumoniae*, including the six serotypes that most frequently cause invasive drug-resistant pneumococcal infection in the U.S., induce antibodies primarily by T-cell-independent mechanisms, i.e., by stimulating mature B cells without the help of T cells. These capsular polysaccharide vaccines, however, are neither immunogenic nor protective in young children, whose immune systems are immature. The B cells of newborns do not tend to respond to polysaccharide antigens, which are T-cell-independent antigens. This responsiveness develops slowly during the first years of life. In addition, polysaccharide antigens do not induce immunologic memory and the maturation of the immune response. Therefore, development of additional pneumococcal vaccines to provide long-term immunity in children <2 years old has been a high priority (Käyhty and Eskola 1996, CDC 1997).

The most promising approach has been development of a protein-polysaccharide conjugate vaccine for selected serotypes to improve immunogenicity and protective efficacy of vaccination in young children. Research has demonstrated that covalent coupling of the polysaccharide antigen to a carrier protein improves the immune response to many capsular polysaccharides. This linkage converts the polysaccharide into a T-cell-dependent antigen to which infants can respond, resulting in development of immunologic memory and maturation of the immune response. The response involves stimulation of T-helper cells, which then stimulate adjacent B cells for antibody production and maturation into memory cells. The development of immunologic memory implies that protection does not entirely depend on existing antibody concentrations; instead, the vaccinated individual can respond with a rapid, high, and effective antibody response to invasion by the infectious agent. This conjugate vaccine technology has been used successfully to prepare vaccines against *Haemophilus influenzae* type b (Hib), leading to a dramatic decrease in the incidence of Hib infection among immunized populations of children (Käyhty and Eskola 1996, Barbour 1996, CDC 1997, Rennels 1998).

The focus of conjugate vaccine development has been on the serotypes that most commonly cause childhood infections. Thus, vaccine formulations have included at least seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) of pneumococcal polysaccharides conjugated to one or several protein carriers. An effective conjugate vaccine against these serotypes has the potential to prevent 85 percent of bacteremia, 83 percent of meningitis, and 65 percent of otitis media cases in the U.S. among children <6 years of age. Further, preliminary evidence suggests that conjugate vaccines, such as the Hib vaccines, may reduce the nasopharyngeal carriage of pneumococcal serotypes included in the vaccine (CDC 1997, Rennels 1998). Carriers, who harbor the infectious agent in the absence of clinical illness, may spread infection to others. A reduction in the carriage rates of *S. pneumoniae* has the potential to increase the impact of the vaccine by reducing transmission and, consequently, the incidence of disease. Thus, the vaccine may not only induce protective immunity in the person vaccinated, but also, by reducing spread of the organisms, have the indirect effect of providing herd immunity for the population (Chen and Orenstein 1996).

DESCRIPTION

The newly developed heptavalent pneumococcal conjugate vaccine is composed of the seven aforementioned pneumococcal serotypes, each independently conjugated to CRM_{197} via reductive amination. CRM_{197} is a nontoxic variant of diphtheria toxin that serves as a protein carrier. The vaccine is manufactured as a liquid preparation, and each 0.5 ml dose is formulated to contain 2 μg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F; 4 μg of serotype 6B (16 μg total saccharide); approximately 20 μg of CRM_{197} carrier protein; and 0.125 mg of aluminum as aluminum phosphate adjuvant (FDA 2000c).

For infants, the immunization series consists of three doses of 0.5 ml each, at approximately two-month intervals, followed by a fourth dose of 0.5 ml at 12 to 15 months of age. The customary age for the first dose is 2 months, but it can be given as young as 6 weeks. The routine schedule, then, is 2, 4, and 6 months for the primary series, and 12 to 15 months for the booster dose. For previously unvaccinated older infants and children, a separate schedule applies (FDA 2000c).

GOVERNMENT AGENCIES/ PROFESSIONAL ORGANIZATIONS

Food and Drug Administration (FDA): On Feb. 17, 2000, the FDA approved the first vaccine to prevent invasive pneumococcal diseases in infants and toddlers caused by *Streptococcus pneumoniae.* The vaccine, pneumococcal seven-valent conjugate vaccine (Diphtheria CRM_{197} Protein), will be marketed for use in infants 2, 4, 6, and 12 to 15 months of age to prevent invasive pneumococcal disease (AHP 2000, FDA 2000a, FDA 2000b).

National Institute of Allergy and Infectious Diseases (NIAID): According to the Jordan Report 2000, the introduction of pneumococcal conjugate vaccines "will help to: (1) offset drug resistance and reduce antibiotic usage; (2) protect against the spread of uncontrolled invasive strains of pneumococci; (3) reduce the incidence of pneumococcal otitis media and tympanostomy; (4) reduce carriage and household community transmission of pneumococci; and (5) promote a significant degree of herd immunity" (Klein 2000a).

Centers for Disease Control and Prevention (CDC): According to information from the vaccine's manufacturer and the *Medical Letter*®, the Advisory Committee on Immunization Practices (ACIP), on Feb. 16, 2000, voted to recommend the use of pneumococcal seven-valent conjugate vaccine for all infants <2 years old and high-risk children aged 2 to 5 years. High-risk children include African Americans; Native Americans; Alaskan Natives; children with sickle cell anemia, human immunodeficiency virus (HIV), or chronic diseases; and immunocompromised children (AHP 2000; *Medical Letter* 2000).

EVALUATION OF EVIDENCE

Search Strategy: Evidence for this technology assessment was obtained from a search in the Medline and Healthstar databases, spanning from 1997 to April 4, 2000, and limited to English-language articles on human subjects age 1 month to 5 years. Search terms included *pneumococcal vaccine* as subject words combined with *children*, *infants*, or *toddlers* as title words. No other articles were found in a search of the Current Contents/Clinical Medicine database using the same keywords. An earlier search of the Medline database, spanning 1995 through October 1998 and limited to children <2 years old used the key words *pneumococcal infections* in combination with *bacterial vaccines* or *vaccines, conjugate.* Finally, a search of the Centers for Disease Control and Prevention (CDC) Web site provided relevant information.

Literature Review: The Table summarizes three recent clinical studies of the newly developed heptavalent pneumococcal conjugate vaccine, PNCRM7, in healthy young children <2 years of age. All were randomized double-blind trials. The first two reports, by Rennels et al (1998) and Shinefield et al (1999), detailed safety and immunogenicity of this vaccine, while the most recent report by Black et al (2000) evaluated vaccine efficacy, in addition to safety and immunogenicity, in healthy infants and toddlers. All three studies administered vaccine at 2, 4, and 6 months in the primary series and a booster dose at 12 to 15 months. The first report, by Rennels et al (1998), was conducted at four centers in the Eastern and Southern U.S. and compared PNCRM7 with an investigational meningococcal group C conjugate vaccine (menC) in 212 healthy infants; half of the subjects received PNCRM7 and half received the control vaccine, menC. In the Shinefield et al (1999) study, conducted at six centers within the Northern California Kaiser Permanente (NCKP) Health Plan, 302 healthy infants were randomized 2:1 to receive either PNCRM7 vaccine or the control menC vaccine. The largest study, reported by Black et al (2000), involved 37,868 healthy infants at 23 medical centers within NCKP who were randomized 1:1 to receive either the pneumococcal conjugate vaccine or the control meningococcal conjugate vaccine. In all of the studies, the infants and toddlers also received routine childhood vaccines at the recommended ages, including diphtheria-tetanus toxoid-pertussis vaccine (DTP), Hib vaccine, oral polio vaccine (OPV) or inactivated polio vaccine (IPV), measles-mumps-rubella (MMR) vaccine, and hepatitis B vaccine (HBV).

Results of the three studies showed that the pneumococcal conjugate vaccine was well tolerated and can be administered safely to infants in the sequence described. All studies showed a substantial immunologic response to all seven serotypes after three doses, and an anamnestic response after the booster dose, demonstrating that the primary series of vaccinations effectively stimulated T-cell memory that can result in long-term immunity. In the Black et al (2000) trial, using intention-to-treat analysis, the vaccine prevented 94 percent of invasive disease caused by the strains of pneumococcus in the vaccine. In addition, there was an approximately 89-percent reduction in all cases of invasive disease, including those caused by nonvaccine serotypes. Both analyses were statistically significant. While the prevention of otitis media was not as complete as for invasive disease, there was a significant reduction in otitis media and related events, most marked for children with frequent otitis media and for tympanostomy tube placement. However, otitis media is an off-label use of the vaccine, because its efficacy in preventing ear infections has not been evaluated by the FDA (FDA 2000a).

Selection Criteria: The patients selected for the three vaccine studies were similar, healthy 2-month-old infants. The Black et al (2000) study specifically excluded subjects with sickle cell disease, known immunodeficiency, serious chronic or progressive disease, history of seizures, or history of either pneumococcal or meningococcal disease.

Pneumococcal seven-valent conjugate vaccine is indicated for active immunization of infants and toddlers against invasive disease caused by *Streptococcus pneumoniae* due to capsular serotypes included in the vaccine. Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication. The manufacturer notes that the vaccine should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration. Also, the vaccine should be administered with caution to patients with a possible history of latex sensitivity, because the packaging contains dry natural rubber (FDA 2000c).

ISSUES OF CONTROVERSY

Measures of Outcome: In the study by Black et al (2000) spanning a 3.5-year period, the primary endpoint was protective efficacy of the vaccine against invasive pneumococcal disease caused by the serotypes. Invasive pneumococcal disease was defined as a positive culture of *Streptococcus pneumoniae* from normally sterile body fluid obtained from a child presenting with acute illness compatible with pneumococcal disease. Cases must have been caused by a serotype in the vaccine, occurred >14 days after the third dose, and occurred in subjects vaccinated according to protocol. The protective efficacy was estimated by calculating the ratio of the number of cases of invasive disease in the pneumococcal conjugate group to the number of cases in the control meningococcal group and subtracting the ratio from 1. Secondary endpoints included efficacy against clinical episodes of otitis media, i.e., the number of episodes of otitis media.

Possible Mechanisms of Immune System Response: Compared with the Hib vaccine, the role of antibodies in conferring protection against pneumococcal disease after immunization with the pneumococcal conjugate vaccine is not completely understood. The polysaccharide capsule of *S. pneumoniae* enables it to evade the host immune system and resist phagocytosis. In the absence of functional antibodies to the capsular polysaccharide, the organism can invade the host and avoid phagocytosis and bactericidal activity mediated by the complement system and other serum components. However, the presence of pneumococcal serotype-specific antibodies, either alone or coupled to complement proteins, may act to opsonize pneumococcal bacteria and make them susceptible to phagocytosis and intracellular killing by macrophages and natural killer cells. In addition, the antibody-antigen complex plays a role in activation of the complement system (Madhi and Klugman 1999).

Durability of Response: Since trial follow-ups were <4 years, long-term protective efficacy of the pneumococcal conjugate vaccine is not yet known. According to the recently updated Jordan Report (Klein 2000a), there is some evidence that immunity induced by the vaccine may be short-lived, especially in infants, necessitating repeat vaccinations through the first several years of life. The duration of protection provided by the vaccine, the persistence of antibodies, and whether additional booster doses should be administered are issues that need to be addressed by future studies.

Cost: Lieu et al (2000) evaluated the projected health and economic impact of pneumococcal conjugate vaccination of healthy infants and children. The investigators performed a cost-effectiveness analysis based on data from the NCKP trial and other published and unpublished sources, using a hypothetical U.S. birth cohort of 3.8 million. They constructed a decision tree to compare two situations: vaccination of all healthy infants and no vaccination. Under no vaccination, infection with *S. pneumoniae* could cause meningitis, bacteremia, pneumococcal pneumonia, simple or complex otitis media, or otitis media with tympanostomy tube placement; both meningitis and bacteremia were classified as invasive pneumococcal disease. Meningitis could result in death, disability, deafness, or no sequelae, while bacteremia, defined as all other bacteremic infections, including bacteremic pneumonia, could result in death or no sequelae. Under vaccination, the incidence of each infection was reduced proportional to the demonstrated efficacy of the vaccine. Routine vaccination of healthy infants required 4 doses, at 2, 4, 6, and 12 to 15 months, and catch-up vaccination of children aged 2 to 4.9 years required only one dose.

The model accounted for the fact that the vaccine includes seven serotypes, but other pneumococcal serotypes also may cause the disease; pneumonia and otitis media may be caused by other organisms, and children with these conditions typically do not receive bacterial cultures to confirm the causative agent. The model used a microsimulation (semi-Markov) approach to calculate disease incidence on a monthly basis. The authors derived probabilities of events in the decision model from published studies, unpublished data from local and national sources, and expert panel consensus, and based estimates of vaccine efficacy on the findings of the NCKP trial. They derived mean medical costs of pneumococcal diseases by analyzing the costs of disease episodes using NCKP's Cost Management Information System, which uses a step-down method of allocating all fixed and variable costs to units of service, e.g., a 10-minute visit to a pediatrician. The cost analysis included all hospital, emergency department, outpatient, and prescription medication use. The main outcome measures were cost per life-year saved and cost per episode of meningitis, bacteremia, pneumonia, and otitis media prevented. The authors calculated cost-effectiveness ratios as dollars invested in the vaccination program minus dollars saved due to disease episodes averted divided by health benefits, i.e., cost per life-year saved and cost per episode of disease prevented. They performed sensitivity analyses by varying key assumptions over plausible ranges to evaluate how the model's results changed. Finally, the analysis made conservative assumptions that likely biased against a vaccination program.

The study determined that vaccination of all healthy infants would prevent >12,000 cases of meningitis and bacteremia, 53,000 cases of pneumonia, 1 million episodes of otitis media, and 116 deaths due to pneumococcal infection. Projected cost offsets due to the vaccination program, before accounting for vaccine costs, would be $342 million in medical expenses, and $415 million in work-loss and other costs from averted pneumococcal disease. Vaccination of healthy infants would result in net societal (medical and nonmedical costs, in-

Table 1. Studies of Pneumococcal Vaccine in Young Children

AUTHORS, STUDY DESIGN, OBJECTIVE	**Rennels et al (1998)*** Four centers (Atlanta, Baltimore, Nashville, Pittsburgh) in Eastern and Southern U.S. Randomized double-blind study to determine safety and immunogenicity of newly developed heptavalent (7-valent) pneumococcal conjugate poly-saccharide vaccine, PNCRM7, in infants
STUDY POPULATION	212 healthy 2-month-old infants randomized to receive 4 consecutive doses of either PNCRM7 (treatment group, n=106) or investigational meningococcal group C conjugate vaccine (menC) (control group, n=106)
METHODS	PNCRM7 composed of 7 common pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) each independently conjugated to CRM_{197}, a nontoxic mutant diphtheria toxin serving as a protein carrier. PNCRM7 or control vaccine administered (IM) at 2, 4, and 6 months, and booster dose given at 12–15 months; at three primary series visits, infants received routine vaccines (OPV and DTP/HbOC) in opposite thigh; at booster visit, toddlers randomized to receive MMR or HbOC in opposite thigh. Parents conducted active safety surveillance for 3 days after each dose. ELISA measured antibody concentrations to 7 pneumococcal serotypes in blood samples collected prior to vaccination, after doses 2 and 3, prebooster, and postbooster.
RESULTS	95 (89.6%) of PNCRM7 and 99 (93.3%) of menC recipients completed primary series study; 122 (57.5%) of original cohort received booster (58 [54.7%] in PNCRM7 group and 64 [60.4%] in menC group). Vaccine well tolerated and can be administered safely to infants in 4-dose sequence; local reactions at injection site generally mild and occurred at significantly lower rate than w/ DTP/HbOC vaccine in primary series; no increase in incidence or severity of local reactions at PNCRM7 site w/ repeated doses of vaccine; no local reactions severe enough to require medical attention; mild to moderate postvaccination fever in 25%–38% of PNCRM7 vs 16%–30% control vaccine recipients (fevers may be attributable to concurrent DTP/HbOC administration). 7 vaccine serotypes immunogenic after 3 doses; GMC of antibody significantly higher for each serotype in PNCRM7 group than in menC vaccine group; 4-fold to 27-fold rise in GMC from prevaccination to postdose 3 in PNCRM7 group; substantial decline in antibody levels 1 month after dose 3, but rapid rise after booster dose to levels greater than that after primary 3-dose series (brisk anamnestic response).
COMMENTS/ CONCLUSIONS	Primary immunization followed by booster dose of PNCRM7 has acceptable safety and produces significant rises in antibody to all 7 serotypes. Brisk anamnestic response to all 7 serotypes following booster dose demonstrates that primary series of vaccinations with PNCRM7 effectively stimulated T-cell memory that can result in long-term immunity.

* The Rennels, Shinefield and Black studies were funded by Wyeth-Lederle Vaccines and Pediatrics (West Henrietta, NY), developer of the vaccine; several authors are employees of company.

Key: CRM_{197}, cross-reactive material 197; DtaP, diphtheria-tetanus toxoid-acellular pertussis vaccine (ACEL-IMUNE); DTP or DTwP, diphtheria-tetanus toxoid-whole cell pertussis vaccine; DTP/HbOC, combined diphtheria-tetanus-whole cell pertussis Hib vaccine (TETRAMUNE); ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration (of antibody); HBV, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b (conjugate vaccine); HbOC, Hib vaccine consisting of capsular oligosaccharides conjugated to CRM_{197}; IM, intramuscularly; IPV, inactivated polio vaccine; menC, meningococcal group C conjugate vaccine; MMR, measles-mumps-rubella vaccine; NCKP (Northern California Kaiser Permanente; OPV, oral polio vaccine (ORIMUNE); PNCRM7, heptavalent pneumococcal saccharide vaccine conjugated to CRM_{197}.

Table 1. Studies of Pneumococcal Vaccine in Young Children (continued)

AUTHORS, STUDY DESIGN, OBJECTIVE	**Shinefield et al (1999)***
	Six centers within NCKP Health Plan (Kaiser Permanente Pediatric Vaccine Study Center of Northern California, Oakland) Randomized double-blind study to determine: (1) safety and immunogenicity of heptavalent pneumococcal CRM_{197} conjugate vaccine, PNCRM7, in infants; and (2) effect of concurrent hepatitis B immunization during primary series and effect of concurrent DtaP and HbOC immunization at time of booster dose on safety and immunogenicity of PNCRM7 and other concurrently administered vaccines
STUDY POPULATION	302 healthy 2-month-old infants randomized 2:1 to receive either PNCRM7 vaccine (treatment group) or menC (control group)
METHODS	PNCRM7 contained polysaccharides of pneumococcal serotypes 4, 6B, 9V, 14, 19F, and 23F and oligosaccharide of serotype 18C conjugated to protein carrier CRM_{197} (nontoxic variant of diphtheria toxin); menC contained a *Neisseria meningitidis* Group C oligosaccharide coupled to CRM_{197}. PNCRM7 or control vaccine administered at 2, 4, and 6 months; all subjects received DTwP/HbOC and OPV concurrently at each visit, and within each vaccine group, half of subjects received concurrent injection of HBV in same right thigh as DTwP/HbOC while other half received HBV $\geq$2 wks before or after investigational conjugate vaccines; at 12–15 months, subjects in each study vaccine group further randomized 3:3:2 to receive either fourth dose of PNCRM7 concurrently with DtaP and HbOC, PNCRM7 alone, or DtaP and HbOC alone; on one-month follow-up visit, subjects given vaccines they had not received at first visit (no vaccination, DtaP and HbOC alone, or fourth dose of PNCRM7). Parents monitored untoward effects for 14 days after each vaccination. Antibodies titers, using standard ELISA methods, determined on blood samples drawn before and 1 month after primary series and booster dose.
RESULTS	272 (90%) completed three-dose primary series, and 211 (69.9%) rerecruited for booster dose. Substantial immunologic response elicited to all 7 pneumococcal serotypes but marked difference in response to individual serotypes in primary and toddler responses as well as degree of antibody decay following dose 3; >90% had post-third dose titer of $\geq$0.15 µg/ml for all serotypes, and percentage of infants with post-third dose titer $\geq$1.0 µg/ml ranged from 51% for type 9V to 89% for type 14; following PNCRM7 booster dose, GMCs of all 7 serotypes increased significantly over both post-dose 3 and pre-dose 4 antibody levels. In primary series, no significant differences in GMCs of pneumococcal antibodies between infants given PNCRM7 alone or concurrently with HBV; at booster dose, GMCs for all serotypes higher when PNCRM7 given alone than when concurrently administered with DtaP and HbOC; for all antigens, no differences between study groups in defined antibody titers that are considered protective. Safety: Local reaction rate and systemic reaction rate to PNCRM7 similar to those seen with other licensed infant vaccines; no untoward reactions seen in study cohort; injection site reactogenicity greater for DTP/HbOC/HBV than for PNCRM7 vaccine after each primary series dose, with statistically less severe erythema, induration, and tenderness; some emergency room visits and other hospitalizations were not vaccine-related.
COMMENTS/ CONCLUSIONS	PNCRM7 vaccine is safe and immunogenic; anamnestic response following booster dose with marked serotype variation; when vaccine administered concurrently with DtaP and HbOC at booster dose, some antigens showed lower antibody titers compared with antibody response when PNCRM7 given separately; these differences probably not clinically significant since GMCs of booster responses generally were all high and all subjects achieved similar percentages above prede-fined antibody titers.

Table 1. Studies of Pneumococcal Vaccine in Young Children (continued)

AUTHORS, STUDY DESIGN, OBJECTIVE	**Black et al (2000)*** 23 medical centers within NCKP (Kaiser Permanente Pediatric Vaccine Study Center of Northern California, Oakland) Randomized double-blind trial withintention-to-treat analysis to determine: (1) efficacy, safety, and immunogenicity of heptavalent CRM_{197} pneumococcal conjugate vaccine against invasive disease caused by vaccine serotypes; and (2) its effectiveness against clinical episodes of otitis media
STUDY POPULATION	37,868 healthy infants randomized 1:1 to receive either pneumococcal conjugate (n=18,927) or meningococcus type C CRM_{197} conjugate vaccine (n=18,941) Exclusions: Sickle cell disease, known immunodeficiency, serious chronic or progressive disease, history of seizures or history of either pneumococcal or meningococcal disease
METHODS	Pneumococcal conjugate vaccine contained 2 µg each of saccharides of serotypes 4, 9V, 18C, 19F, and 23F and 4 µg of 6B coupled to protein carrier CRM_{197} (nontoxic mutant of diphtheria toxin); control meningococcal conjugate vaccine contained 10 µg of group C oligosaccharide conjugated to the same carrier protein. Pneumococcal conjugate vaccine or control vaccine administered at 2, 4, 6, and 12–15 months; routine childhood vaccines (DTwP or DtaP, OPV or IPV, Hib, HBV, MMR, varicella) administered at recommended ages. Primary endpoint was protective efficacy† of pneumococcal conjugate vaccine against invasive pneumococcal disease‡ caused by vaccine serotypes. Secondary endpoints were efficacy of vaccine against clinical episodes of otitis media.§ Serum antibody responses to 7 pneumococcal vaccine serotypes determined by ELISA using serum samples obtained before first vaccination and 1 month after dose 3 and in subset before and after dose 4.
RESULTS	17,174 (90.7%) received ≥2 doses of pneumococcal conjugate vaccine, 15,565 (82.2%) received ≥3 doses, and 10,940 (57.8%) received 4 doses. Interim efficacy analysis: 17/17 cases of invasive disease caused by vaccine serotype in fully vaccinated children (statistically significant) and 5/5 of partially vaccinated cases (not statistically significant) occurred in control group for vaccine efficacy of 100%. Final efficacy analysis: 40 fully vaccinated cases of invasive disease caused by vaccine serotypes, all but one in controls, for vaccine efficacy of 97.4%; 52 cases, all but three in controls, in intent-to-treat analysis for efficacy of 93.9%; nine cases of invasive disease caused by nonvaccine serotypes (6 in control group and 3 in vaccine group), for efficacy of 89.1%, regardless of serotype (all analyses statistically significant). Efficacy for otitis media against visits, episodes, frequent otitis, and ventilatory tube placement were 8.9%, 7.0%, 9.3%, and 20.1% (all statistically significant); for spontaneously draining ears, serotype-specific effectiveness was 66.7% (not statistically significant). Safety: No severe adverse events related to vaccination with either vaccine that resulted in hospitalization, emergency visits, or clinic visits; local (redness, swelling, tenderness) and systemic reactions (fever) generally relatively mild with either vaccine, and more severe reactions uncommon and self-limited. Substantial immunologic response to pneumococcal polysaccharide elicited to all seven serotypes; booster response seen for all serotypes.
COMMENTS/ CONCLUSIONS	Heptavalent pneumococcal conjugate vaccine appears to be highly effective in preventing invasive disease in young children and to have a significant impact on otitis media.

† Protective efficacy estimated by calculating ratio of number of cases of invasive disease in pneumococcal conjugate group to number of cases in meningococcal group and subtracting ratio from 1.

‡ Invasive pneumococcal disease was defined as positive culture of *Streptococcus pneumoniae* from normally sterile body fluid obtained from child presenting with acute illness compatible with pneumococcal disease. Cases must have been caused by serotype included in vaccine, must have occurred >14 days after dose 3 of study vaccine, and must have occurred in subjects vaccinated according to protocol.

§ Primary otitis media outcome was number of episodes of otitis media in fully vaccinated per protocol follow-up times in the two vaccine groups.

cluding work-loss cost of the parent) savings if the vaccine cost <$46 per dose, and net savings for the health care payer if the vaccine cost <$18 per dose. At the manufacturer's list price of $58 per dose, the cost to society of infant vaccination would be $80,000 per life-year saved, or $160 per otitis media, $3,200 per pneumonia, $15,000 per bacteremia, or $280,000 per meningitis episode prevented. The results were sensitive to variation in the incidence of invasive disease. The study found that, while routine pneumococcal conjugate vaccination of healthy infants is potentially cost-effective, its projected savings for society are more than double those for payers. Vaccination is projected to reduce pneumococcal disease costs by approximately $760 million from a societal perspective for each cohort of infants born in the U.S. each year, but >50 percent of the projected savings are from reduced work loss by parents or averted productivity loss due to disability or death caused by pneumococcal disease.

Lieu et al (2000) concluded that routine pneumococcal conjugate vaccination of healthy infants in the U.S. has the potential to be cost-effective relative to other preventive health interventions. To achieve cost savings, cost of the vaccine would need to be lower than the manufacturer's list price. In addition to cost considerations, decisions about implementing a vaccination program should be based on qualitative judgments regarding the value of preventing mortality and morbidity due to pneumococcal disease.

FUTURE OF PROCEDURE

Following introduction of the Hib conjugate vaccine, a large herd immunity effect was observed due to reduction in nasopharyngeal carriage of the organism in vaccinees. Whether the pneumococcal conjugate vaccine will induce a similar herd immunity effect awaits both the results of an ongoing trial among Southwest Native Americans and the imminent widespread distribution of the vaccine as a result of its licensure (Black 2000).

There are several efficacy trials under way or planned, including one in Finland that began in 1995 to evaluate the protective efficacy of the heptavalent pneumococcal conjugate vaccine against otitis media, and the previously mentioned trial that began in 1998 among Navajo and Apache infants to evaluate the vaccine's effect on invasive disease and herd immunity. Other trials in South Africa, Gambia, Israel, The Philippines, and Chile will assess 9- and 11-valent pneumococcal conjugate vaccines. The 9-valent vaccines add serotypes 1 and 5, and the 11-valent vaccines add serotypes 3 and 7F; however, it is expected that little clinical value will accrue for children in the U.S. from these additions to a 7-valent conjugate vaccine. Some issues these new trials will address include: (1) determining laboratory correlates of protection; (2) examining interference with other childhood vaccines, and (3) evaluating the overall impact on ecology, i.e., herd immunity (Klein 2000a).

Future studies will need to assess the long-term protective efficacy of pneumococcal conjugate vaccine, i.e., the persistence of antibodies and how long the vaccine provides protection.

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