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Prevention of Pneumococcal Disease

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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LIAISON REPRESENTATIVES

American Academy of Family Physicians
Richard Zimmerman, M.D.
Pittsburgh, PA

American Academy of Pediatrics
Georges Peter, M.D.
Providence, RI
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Baltimore, MD

American Association of Health Plans
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South Field, MI

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Houston, TX

Pharmaceutical Research and Manufacturers of America
David J. Williams
Swiftwater, PA

The following CDC staff members prepared this report:

Pekka J. Nuorti, M.D.
Jay C. Butler, M.D.
Robert F. Breiman, M.D.
Division of Bacterial and Mycotic Diseases
National Center for Infectious Diseases

Prevention of Pneumococcal Disease:

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

*This report updates the last recommendations by the Advisory Committee on Immunization Practices (ACIP) concerning pneumococcal polysaccharide vaccine (*MMWR *1989;38:64–8, 73–6). ACIP recommends that the vaccine be used more extensively and administered to all persons in the following groups: a) persons aged ≥65 years, b) immunocompetent persons aged ≥2 years who are at increased risk for illness and death associated with pneumococcal disease because of chronic illness, c) persons aged ≥2 years with functional or anatomic asplenia, d) persons aged ≥2 years living in environments in which the risk for disease is high, and e) immunocompromised persons aged ≥2 years who are at high risk for infection. This report contains updated information regarding a) antimicrobial resistance among pneumococci, b) vaccine effectiveness and cost-effectiveness, c) indications for vaccination, d) guidelines for revaccination, e) strategies for improving delivery of vaccine, and f) development of pneumococcal conjugate vaccine.*

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a bacterial pathogen that affects children and adults worldwide. It is a leading cause of illness in young children and causes illness and death among the elderly and persons who have certain underlying medical conditions. The organism colonizes the upper respiratory tract and can cause the following types of illnesses: a) disseminated invasive infections, including bacteremia and meningitis; b) pneumonia and other lower respiratory tract infections; and c) upper respiratory tract infections, including otitis media and sinusitis. Each year in the United States, pneumococcal disease accounts for an estimated 3,000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and 7 million cases of otitis media (*1–4*). The focus of this report is the prevention of invasive pneumococcal disease (i.e., bacteremia, meningitis, or infection of other normally sterile sites) through the use of pneumococcal polysaccharide vaccine. This vaccine protects against invasive bacteremic disease, although existing data suggest that it is less effective in protecting against other types of pneumococcal infections.

BACKGROUND

Incidence of Invasive Disease

Severe pneumococcal infections result from dissemination of bacteria to the bloodstream and the central nervous system. Data from community-based studies indicate that overall annual incidence of pneumococcal bacteremia in the United States is an

estimated 15–30 cases per 100,000 population; the rate is higher for persons aged ≥65 years (50–83 cases per 100,000 population) and for children aged ≤2 years (160 cases per 100,000 population) (*5–9*). In adults, 60%–87% of pneumococcal bacteremia is associated with pneumonia (*10–12*); in young children, the primary sites of infection are frequently not identified.

In the United States, the risk for acquiring bacteremia is lower among white persons than among persons in other racial/ethnic groups (i.e., blacks, Alaskan Natives, and American Indians). Black adults have a threefold to fivefold higher overall incidence of bacteremia (49–58 cases per 100,000 population) than whites (*5–8*). Rates of invasive pneumococcal disease are exceptionally high among Alaskan Natives and American Indians. The age-adjusted annual incidence of invasive pneumococcal infection among Alaskan Natives and Alaskan Native children aged <2 years was determined by a prospective surveillance study to be 74 cases and 624 cases per 100,000 population, respectively; rates for meningitis and bacteremic pneumonia are eightfold to tenfold higher for Alaskan Natives of all ages than for other U.S. population groups (*13*). The highest incidence rates for any U.S. population have been reported among specific American Indian groups (e.g., Apache) (*14*). The overall annual incidence for such groups is 156 cases per 100,000 population; the incidence for children aged 1–2 years in these groups is 2,396 cases per 100,000 population.

In the United States, the estimated overall annual incidence of pneumococcal meningitis is one to two cases per 100,000 population (*15*). The incidence of pneumococcal meningitis is highest among children aged 6–24 months and persons aged ≥65 years; rates for blacks are twice as high as those for whites and Hispanics. Because the incidence of *Haemophilus influenzae* type b (Hib) meningitis in children rapidly decreased following the introduction of Hib conjugate vaccines, *S. pneumoniae* has become the most common cause of bacterial meningitis in the United States (CDC, unpublished data).

Other Pneumococcal Infections

Lower Respiratory Tract Infections

S. pneumoniae is the most common cause of community-acquired bacterial pneumonia, occurring most frequently among the elderly and young children. The precise incidence of pneumococcal pneumonia is difficult to ascertain because routine diagnostic tests are insufficiently specific and sensitive. Nonetheless, at least 500,000 cases of pneumococcal pneumonia are estimated to occur annually in the United States; *S. pneumoniae* accounts for approximately 25%–35% of cases of community-acquired bacterial pneumonia in persons who require hospitalization (*16–19*). Concomitant bacteremia occurs in approximately 10%–25% of adult patients who have pneumococcal pneumonia (*17,20*).

Acute Otitis Media and Other Upper Respiratory Tract Infections

S. pneumoniae is a substantial cause of acute otitis media (AOM) and other upper respiratory tract infections (e.g., sinusitis). Although these types of infections usually do not progress to invasive disease, they cause considerable morbidity and medical cost. In the United States, AOM results in more than 24 million visits to pediatricians

per year (*21*); approximately 30%–50% of AOM infections are caused by *S. pneumoniae* (*22*). AOM infection most often occurs in children aged <4 years. In the United States, 62% of children experience an episode of AOM during their first year of life, and nearly half have had three or more episodes before their third birthday (*23*).

Mortality

Pneumococcal infection causes an estimated 40,000 deaths annually in the United States (*1,2,24*), accounting for more deaths than any other vaccine-preventable bacterial disease (*25*). Approximately half of these deaths potentially could be prevented through the use of vaccine. Case-fatality rates are highest for meningitis and bacteremia, and the highest mortality occurs among the elderly and patients who have underlying medical conditions. Among children, death from pneumococcal infection is relatively uncommon, except among those who a) have meningitis, b) are immunocompromised, or c) have undergone splenectomy and have severe bacteremia. Despite appropriate antimicrobial therapy and intensive medical care, the overall case-fatality rate for pneumococcal bacteremia is 15%–20% among adults. Among elderly patients, this rate is approximately 30%–40% (*5–7,15,26–28*). An overall case-fatality rate of 36% was recently documented for adult inner-city residents who were hospitalized for pneumococcal bacteremia (*12*).

Risk Factors

Children aged <2 years and adults aged ≥65 years are at increased risk for pneumococcal infection. Persons who have certain underlying medical conditions also are at increased risk for developing pneumococcal infection or experiencing severe disease and complications. Adults at increased risk include those who are generally immunocompetent but who have chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease [COPD] or emphysema), or chronic liver diseases (e.g., cirrhosis). Diabetes mellitus often is associated with cardiovascular or renal dysfunction, which increases the risk for severe pneumococcal illness. The incidence of pneumococcal infection is increased for persons who have liver disease as a result of alcohol abuse (*10,20,29,30*). Asthma has not been associated with an increased risk for pneumococcal disease, unless it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids.

Persons with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy) are at highest risk for pneumococcal infection, because this condition leads to reduced clearance of encapsulated bacteria from the bloodstream. Children who have sickle cell disease or have had a splenectomy are at increased risk for fulminant pneumococcal sepsis associated with high mortality. Before the widespread use of penicillin chemoprophylaxis for these patients, children with sickle cell disease were 600-fold more likely than children without this disease to develop pneumococcal meningitis (*24*).

The risk for pneumococcal infection is high for persons who have decreased responsiveness to polysaccharide antigens or increased rate of decline in serum antibody concentrations as a result of a) immunosuppressive conditions (e.g., congenital immunodeficiency, human immunodeficiency virus [HIV] infection, leukemia,

lymphoma, multiple myeloma, Hodgkins disease, or generalized malignancy); b) organ or bone marrow transplantation; c) therapy with alkylating agents, antimetabolites, or systemic corticosteroids (*31*); or d) chronic renal failure or nephrotic syndrome (*20,30*). *S. pneumoniae* is the most commonly identified bacterial pathogen that causes pneumonia in HIV-infected persons (*32*). In children, invasive pneumococcal disease is often the first clinical manifestation of HIV infection. The annual attack rate of pneumococcal bacteremia is as high as 1% (940 cases per 100,000 population) among persons with acquired immunodeficiency syndrome (AIDS) (*33*). As many as 91% of adults who have invasive pneumococcal infection have at least one of the previously mentioned underlying medical conditions, including age ≥65 years (*6,9,24,27*). Recurrent pneumococcal meningitis may occur in patients who have chronic cerebrospinal fluid (CSF) leakage resulting from congenital lesions, skull fractures, or neurosurgical procedures.

A case-control study conducted in Finland identified day care center attendance among children aged <2 years as a major risk factor for invasive pneumococcal disease (*34*). Although the risk for invasive pneumococcal infection associated with day care center attendance was significantly higher (i.e., 36-fold) among children aged <2 years compared with those who did not attend day care, the risk among children aged ≥2 years (the age group in which pneumococcal polysaccharide vaccine could potentially prevent disease) was not significantly different from that for those who did not attend day care. Studies conducted in the United States also have indicated that children aged <2 years who attend day care are at higher risk for infection than are those who do not (*35*). In addition, clusters of invasive pneumococcal disease have been reported among children who attend day care (*36,37*).

Antimicrobial Resistance

Strains of drug-resistant *S. pneumoniae* (DRSP) have become increasingly common in the United States and in other parts of the world (*38,39*). In some areas, as many as 35% of pneumococcal isolates have been reported to have intermediate- (minimum inhibitory concentration [MIC]=0.1–1.0 μg/mL) or high-level (MIC ≥2 μg/mL) resistance to penicillin (*CDC, unpublished data*;*8,40,41*). Many penicillin-resistant pneumococci are also resistant to other antimicrobial drugs (e.g., erythromycin, trimethoprim-sulfamethoxazole, and extended-spectrum cephalosporins). High-level penicillin resistance and multidrug resistance often complicate the management of pneumococcal infection and make choosing empiric antimicrobial therapy for suspected cases of meningitis, pneumonia, and otitis media increasingly difficult (*42*). Treating patients infected with nonsusceptible organisms may require the use of expensive alternative antimicrobial agents and may result in prolonged hospitalization and increased medical costs. The impact of antimicrobial resistance on mortality is not clearly defined. Emerging antimicrobial resistance further emphasizes the need for preventing pneumococcal infections by vaccination.

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

The currently available pneumococcal vaccines, manufactured by both Merck and Company, Inc. (Pneumovax® 23) and Lederle Laboratories (Pnu-Immune® 23), include

23 purified capsular polysaccharide antigens of *S. pneumoniae* (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). These vaccines were licensed in the United States in 1983 and replaced an earlier 14-valent formulation that was licensed in 1977. One dose (0.5 mL) of the 23-valent vaccine contains 25 μg of each capsular polysaccharide antigen dissolved in isotonic saline solution with phenol (0.25%) or thimerosal (0.01%) added as preservative and no adjuvant. The 23 capsular types in the vaccine represent at least 85%–90% of the serotypes that cause invasive pneumococcal infections among children and adults in the United States (*43–45*). The six serotypes (6B, 9V, 14, 19A, 19F, and 23F) that most frequently cause invasive drug-resistant pneumococcal infection in the United States are represented in the 23-valent vaccine (*8,39*).

Immunogenicity

Pneumococcal capsular polysaccharide antigens induce type-specific antibodies that enhance opsonization, phagocytosis, and killing of pneumococci by leukocytes and other phagocytic cells. After vaccination, an antigen-specific antibody response, indicated by a twofold or greater rise in serotype-specific antibody, develops within 2–3 weeks in ≥80% of healthy young adults (*46*); however, immune responses may not be consistent among all 23 serotypes in the vaccine. The levels of antibodies that correlate with protection against pneumococcal disease have not been clearly defined.

Antibody responses also occur in the elderly and in patients who have alcoholic cirrhosis, COPD, and insulin-dependent diabetes mellitus (*20,24,46*); however, antibody concentrations and responses to individual antigens may be lower among such persons than among healthy young adults. Persons aged ≥2 years with anatomic or functional asplenia (e.g., from splenectomy or sickle cell disease) generally respond to pneumococcal vaccination with antibody levels comparable with those observed in healthy persons of the same age (*47*).

In immunocompromised patients, antibody responses to pneumococcal vaccination are often diminished or absent. In patients with leukemia, lymphoma, or multiple myeloma, antibody response to pneumococcal vaccination is substantially lower than response among patients who are immunocompetent. Patients who have chronic renal failure requiring dialysis, renal transplantation, or nephrotic syndrome have a diminished immune response to vaccination, resulting in lower antibody concentrations than those observed in healthy adults (*24*). In patients with Hodgkins disease, the antibody response to pneumococcal vaccination is greater if the vaccine is administered before splenectomy, radiation, or chemotherapy; however, during chemotherapy, preexisting pneumococcal antibodies may decrease, and responses to pneumococcal vaccine may be diminished (*48*). Patients who have AIDS may have a diminished antibody response to pneumococcal vaccine (*49,50*). The reduction in titers of antibody corresponds to the degree of immunosuppression; some asymptomatic HIV-infected persons or those with only generalized lymphadenopathy respond to the 23-valent polysaccharide vaccine (*51*). HIV-infected patients with CD4+ T-lymphocyte counts <500 cells/μL often have lower responses to pneumococcal vaccination than either HIV-infected persons with higher CD4+ T-lymphocyte counts or persons who are not HIV-infected (*52*).

Bacterial capsular polysaccharides induce antibodies primarily by T-cell–independent mechanisms. Therefore, antibody response to most pneumococcal capsular types is generally poor or inconsistent in children aged <2 years whose immune systems are immature. Age-specific immune responses also vary by serotype, and the response to some common pediatric pneumococcal serotypes (e.g., 6A and 14) also is decreased in children aged 2–5 years (*53–55*).

Duration of Antibody Levels

Levels of antibodies to most pneumococcal vaccine antigens remain elevated for at least 5 years in healthy adults. In some persons, antibody concentrations decrease to prevaccination levels by 10 years (*56,57*). A more rapid decline (i.e., within 3–5 years after vaccination) in antibody concentrations may occur in certain children who have undergone splenectomy following trauma and in those who have sickle cell disease (*58,59*). Similar rates of decline can occur in children with nephrotic syndrome (*60*). Antibody concentrations also have declined after 5–10 years in elderly persons, persons who have undergone splenectomy, patients with renal disease requiring dialysis, and persons who have received transplants (*24,56,57,61–63*). Low or rapidly declining antibody concentrations after vaccination also have been noted among patients with Hodgkins disease (*64*) and multiple myeloma (*65*). However, these quantitative measurements of antibodies do not account for the quality of the antibody being produced and the level of functional immune response. Tests measuring opsonophagocytic activity and the quality of antibodies produced (i.e., avidity for pneumococcal antigens) may ultimately be more relevant for evaluating response to pneumococcal vaccination (*66*).

Precautions and Contraindications

The safety of pneumococcal polysaccharide vaccine during the first trimester of pregnancy has not been evaluated, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. For additional information about precautions and contraindications, the vaccine manufacturer's package insert should be reviewed.

Side Effects and Adverse Reactions

Pneumococcal polysaccharide vaccine generally is considered safe based on clinical experience since 1977, when the pneumococcal polysaccharide vaccine was licensed in the United States. Approximately half of persons who receive pneumococcal vaccine develop mild, local side effects (e.g., pain at the injection site, erythema, and swelling). These reactions usually persist for <48 hours. Moderate systemic reactions (e.g., fever and myalgias) and more severe local reactions (e.g., local induration) are rare. Intradermal administration may cause severe local reactions and is inappropriate. Severe systemic adverse effects (e.g., anaphylactic reactions) rarely have been reported after administration of pneumococcal vaccine (*20,24*). In a recent meta-analysis of nine randomized controlled trials of pneumococcal vaccine efficacy, local reactions were observed among approximately one third or fewer of 7,531 patients receiving the vaccine, and there were no reports of severe febrile or anaphylactic

reactions (*67*). No neurologic disorders (e.g., Guillain-Barré syndrome) have been associated with administration of pneumococcal vaccine. Although preliminary data have suggested that the pneumococcal vaccine may cause transient increases in HIV replication (*68*), the importance of this occurrence is unknown. Pneumococcal vaccination has not been causally associated with death among vaccine recipients. Health-care providers should report suspected adverse events after administration of pneumococcal polysaccharide vaccine to the Vaccine Adverse Event Reporting System (VAERS) by calling (800) 822-7967, a 24-hour, toll-free telephone number.

Vaccine Efficacy, Effectiveness, and Cost-Effectiveness

Several clinical trials have been conducted evaluating the efficacy of vaccine against pneumonia and pneumococcal bacteremia. In addition, multiple case-control and serotype prevalence studies have provided evidence for pneumococcal vaccine effectiveness against invasive disease (Table 1 [*44,69–80*]).

Efficacy Against Nonbacteremic Pneumococcal Disease

Prelicensure randomized controlled trials (RCTs) of pneumococcal vaccine efficacy were conducted in the 1970s among young, healthy gold miners in South Africa who had high rates of pneumococcal pneumonia and bacteremia; a multivalent polysaccharide vaccine significantly reduced the occurrence of radiographically diagnosed pneumonia in this group (*71,72*). In non-epidemic situations in the United States, most pneumococcal disease in adults occurs in the elderly or in persons with chronic medical conditions. Vaccine efficacy for nonbacteremic pneumonia was not demonstrated for these populations in two postlicensure RCTs conducted in the United States (*74,76*). However, these studies may have lacked sufficient statistical power to detect a difference in the incidence of laboratory-confirmed, nonbacteremic pneumococcal pneumonia between the vaccinated and nonvaccinated study groups (*81*). A meta-analysis evaluating pneumococcal vaccine efficacy by combining the results of nine randomized, controlled trials also did not demonstrate a protective effect for nonbacteremic pneumonia among persons in high-risk groups (*67*). The ability to evaluate vaccine efficacy in these studies is limited because of the lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. The pneumococcal polysaccharide vaccine is not effective for the prevention of common upper respiratory diseases (e.g., sinusitis or AOM) in children (*82*).

Effectiveness Against Invasive Disease

Effectiveness in case-control studies generally has ranged from 56% to 81% (*75,78–80*). Only one case-control study did not document effectiveness against bacteremic disease (77)—possibly because of study limitations, including small sample size and incomplete ascertainment of vaccination status of patients. In addition, case-patients and persons who served as controls may not have been comparable regarding the severity of their underlying medical conditions, potentially creating a biased underestimate of vaccine effectiveness (*81*).

A serotype prevalence study based on CDC's pneumococcal surveillance system demonstrated a 57% (95% confidence interval [CI]=45%–66%) overall protective effectiveness against invasive infections caused by serotypes included in the vaccine

TABLE 1. Studies of pneumococcal vaccine efficacy and effectiveness

Study, publication year (reference)	Population studied	Study design	Type of pneumococcal infection studied	% Efficacy or effectiveness* (95% confidence interval)†
MacLeod, 1945 (*69*)	Young U.S. military recruits	Clinical trial: 4-valent vaccine	Pneumonia	100 (79–100)
Kaufman, 1947 (*70*)	Long-term–care facility residents (80% were aged >60 years) in New York City	Clinical trial: 3-valent vaccine	Pneumonia	92 (72– 98)
		3-valent vaccine	Bacteremia	93 (45–100)
Austrian, 1976 (*71*)	Young adult gold miners in South Africa	Clinical trial: 13-valent vaccine	Pneumonia	79 (65– 88)
		13-valent vaccine	Bacteremia	82 (66– 92)
Smit, 1977 (*72*)	Young adult gold miners in South Africa	Clinical trial: 6-valent vaccine	Pneumonia	76 (52– 89)
		12-valent vaccine	Pneumonia	92 (49–100)
Riley, 1977 (*73*)	Persons aged >10 years in Southern Highlands Province, Papua, New Guinea	Clinical trial: 14-valent vaccine	Bacteremic pneumonia	86 (<0– 99)
Austrian, unpublished§ (*74*)	Outpatients aged >45 years in San Francisco	Clinical trial: 12-valent vaccine	Pneumonia	15 (<0– 52)
		12-valent vaccine	Bacteremia	100 (<0–100)
Shapiro, 1984 (*75*)	Patients admitted to Yale-New Haven Hospital	Case-control	Invasive infection¶	67 (13– 87)
Simberkoff, 1986 (*76*)	Veterans at risk for pneumococcal infection because of chronic, underlying medical conditions	Clinical trial: 14-valent vaccine	Pneumonia/bronchitis	<0 (<0– 45)
Forrester, 1987 (*77*)	Patients admitted to Denver Veterans Administration Medical Center	Case-control	Bacteremia	<0 (<0– 35)
	Patients with pneumococcal bacteremia at Denver Veterans Administration Medical Center	Indirect cohort	Bacteremia	<0 (<0– 55)
Sims, 1988 (*78*)	Patients admitted to one of five participating hospitals in eastern Pennsylvania	Case-control	Invasive infection¶	70 (37– 86)

Shapiro, 1991 (*79*)	Patients admitted to one of 11 participating hospitals in Connecticut	Case-control	Invasive infection[¶]		
			All patients	56	(42–67)
			Immunocompromised patients**	21	(<0–60)
			Immunocompetent patients[††]	61	(47–72)
			Persons aged 65–74 years	80[§§]	(51–92)
	Patients with invasive pneumococcal infection[¶] at participating hospitals in Connecticut	Indirect cohort	Invasive infection[¶]		
			All patients	48	(3–72)
			Immunocompromised patients**	<0	(<0–64)
			Immunocompetent patients[††]	62	(24–81)
Butler, 1993 (*44*)	Patients with pneumococcal bacteremia meningitis at institutions participating in national pneumococcal surveillance	Indirect cohort	Bacteremia and/or meningitis		
			All patients	57	(45–66)
			Immunocompromised patients[¶¶]	49	(22–67)
			Immunocompetent patients***	49	(23–65)
			Persons aged ≥65 years[†††]	75	(57–85)
Farr, 1995 (*80*)	Patients aged ≥2 years with pneumococcal bacteremia and chronic illness or those aged ≥65 years	Case-control	Bacteremia	81	(34–94)

[*] For prevention of infection caused by pneumococcal serotypes included in the vaccine.
[†] If not provided in the published report, 95% confidence intervals were calculated by using Epi-Info version 5.01a (CDC/World Health Organization, Atlanta, GA).
[§] Unpublished study summarized in reference 74.
[¶] *S. pneumoniae* recovered from a normally sterile body site.
[**] Included persons with anatomic or functional asplenia, dysgammaglobulinemia, hematologic malignancy, metastatic cancer, or systemic lupus erythematosus.
[††] Included persons with chronic pulmonary disease, alcoholism, diabetes mellitus, chronic renal failure, or congestive heart failure and persons aged ≥55 years without underlying illness.
[§§] Efficacy during first 3 years after vaccination.
[¶¶] Included persons with sickle cell disease, anatomic asplenia, dysgammaglobulinemia, hematologic malignancy, chronic renal failure, nephrotic syndrome, history of organ transplant, and systemic lupus erythematosus.
[***] Included persons aged ≥6 years with chronic obstructive pulmonary disease, asthma, alcoholism, diabetes mellitus, coronary vascular disease, congestive heart failure, or cirrhosis and persons aged ≥65 years without underlying illness.
[†††] Included persons aged ≥65 years with no underlying illness or those with coronary vascular disease, congestive heart failure, chronic obstructive pulmonary disease, asthma, or diabetes mellitus.

among persons aged ≥6 years (*44*). Vaccine effectiveness of 65%–84% also was demonstrated among specific patient groups (e.g., persons who have diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia). Effectiveness in immunocompetent persons aged ≥65 years was 75% (95% CI=57%–85%). Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients (e.g., those with sickle cell disease, chronic renal failure, immunoglobulin deficiency, Hodgkins disease, non-Hodgkins lymphoma, leukemia, or multiple myeloma). However, this study could not accurately measure effectiveness in each of these groups because of the minimal numbers of unvaccinated patients with these illnesses. In an earlier study, vaccinated children and young adults aged 2–25 years who had sickle cell disease or who had undergone splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated (*47*). A meta-analysis of nine randomized controlled trials of pneumococcal vaccine concluded that pneumococcal vaccine is efficacious in reducing the frequency of bacteremic pneumococcal pneumonia among adults in low-risk groups (*67*). However, the vaccine is not effective in preventing disease caused by non-vaccine serotype organisms (*79*).

Cost-Effectiveness

Preliminary results of a cost-effectiveness analysis indicate that pneumococcal polysaccharide vaccine is cost-effective and potentially cost-saving among persons aged ≥65 years for prevention of bacteremia (*83*). The vaccine compares favorably with other standard preventive practices.

VACCINE ADMINISTRATION

Pneumococcal vaccine is administered intramuscularly or subcutaneously as one 0.5-mL dose. Pneumococcal vaccine may be administered at the same time as influenza vaccine (by separate injection in the other arm) without an increase in side effects or decreased antibody response to either vaccine (*62,84*). Pneumococcal vaccine also may be administered concurrently with other vaccines. The administration of pneumococcal vaccine with combined diphtheria, tetanus, and pertussis (DTP); poliovirus; or other vaccines does not increase the severity of reactions or diminish antibody responses (*85*).

RECOMMENDATIONS FOR VACCINE USE

Immunocompetent Persons

The vaccine is both cost effective and protective against invasive pneumococcal infection when administered to immunocompetent persons aged ≥2 years. Therefore, all persons in the following categories should receive the 23-valent pneumococcal polysaccharide vaccine (Table 2). If earlier vaccination status is unknown, persons in these categories should be administered pneumococcal vaccine.

Persons Aged ≥65 Years

All persons in this category should receive the pneumococcal vaccine, including previously unvaccinated persons and persons who have not received vaccine within 5 years (and were <65 years of age at the time of vaccination). All persons who have unknown vaccination status should receive one dose of vaccine (Figure 1).

Persons Aged 2–64 Years Who Have Chronic Illness

Persons aged 2–64 years who are at increased risk for pneumococcal disease or its complications if they become infected should be vaccinated. Persons at increased risk for severe disease include those with chronic illness such as chronic cardiovascular disease (e.g., congestive heart failure [CHF] or cardiomyopathies), chronic pulmonary disease (e.g., COPD or emphysema, but not asthma), diabetes mellitus, alcoholism, chronic liver disease (cirrhosis), or CSF leaks.

Persons aged 50–64 years commonly have chronic illness, and 12% have pulmonary risk factors for invasive pneumococcal disease. Therefore, persons in this age group who have these risk factors should receive the vaccine (*86*). Persons aged 50 years should have their overall vaccination status reviewed to determine whether they have risk factors that indicate a need for pneumococcal vaccination (*87*). Vaccination status also should be assessed during the adolescent immunization visit at 11–12 years of age (*88*).

Persons Aged 2–64 Years Who Have Functional or Anatomic Asplenia

Persons aged 2–64 years who have functional or anatomic asplenia (e.g., sickle cell disease or splenectomy) also should be vaccinated. Persons with such a condition should be informed that vaccination does not guarantee protection against fulminant pneumococcal disease, for which the case-fatality rate is 50%–80%. Asplenic patients with unexplained fever or manifestations of sepsis should receive prompt medical attention, including evaluation and treatment for suspected bacteremia. Chemoprophylaxis also should be considered in these patients (see Other Methods of Prevention). When elective splenectomy is being planned, pneumococcal vaccine should be administered at least 2 weeks before surgery.

Persons Aged 2–64 Years Who Are Living in Special Environments or Social Settings

Persons aged 2–64 years who are living in environments or social settings in which the risk for invasive pneumococcal disease or its complications is increased (e.g., Alaskan Natives and certain American Indian populations) should be vaccinated. In addition, because of recently reported outbreaks of pneumococcal disease (*89*), vaccination status should be assessed for residents of nursing homes and other long-term–care facilities.

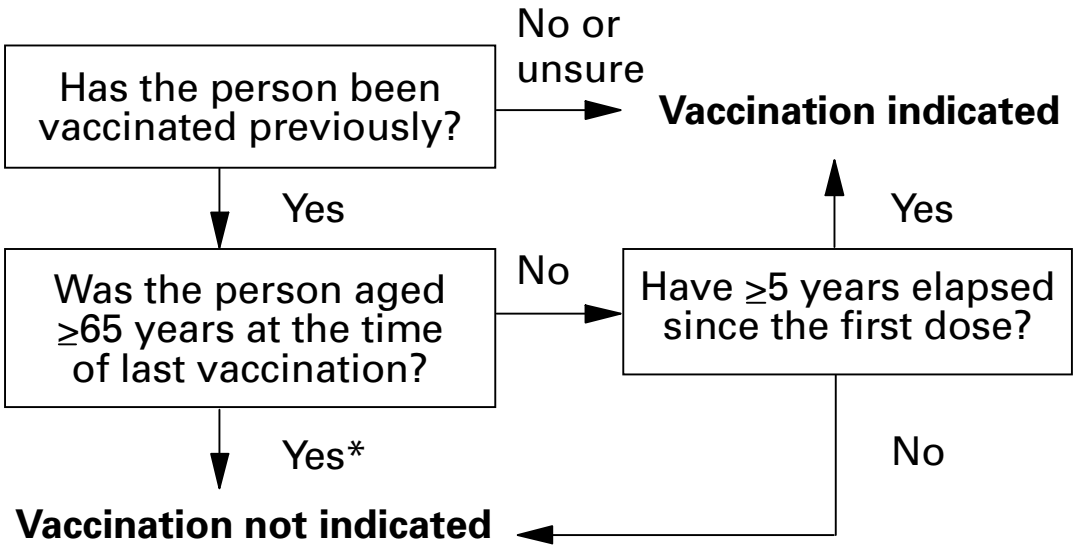
Available data do not support routine pneumococcal vaccination of healthy children attending day care facilities. Recurrent upper respiratory tract diseases, including otitis media and sinusitis, are not specific indications for pneumococcal vaccine.

TABLE 2. Recommendations for the use of pneumococcal vaccine

Groups for which vaccination is recommended	Strength of recommendation*	Revaccination†
Immunocompetent persons§		
Persons aged ≥65 years	A	Second dose of vaccine if patient received vaccine ≥5 years previously and were aged <65 years at the time of vaccination.
Persons aged 2–64 years with chronic cardiovascular disease,¶ chronic pulmonary disease,** or diabetes mellitus	A	Not recommended.
Persons aged 2–64 years with alcoholism, chronic liver disease,†† or cerebrospinal fluid leaks	B	Not recommended.
Persons aged 2–64 years with functional or anatomic asplenia§§	A	If patient is aged >10 years: single revaccination ≥5 years after previous dose. If patient is aged ≤10 years: consider revaccination 3 years after previous dose.
Persons aged 2–64 years living in special environments or social settings¶¶	C	Not recommended.
Immunocompromised persons§		
Immunocompromised persons aged ≥2 years, including those with HIV infection, leukemia, lymphoma, Hodgkins disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephrotic syndrome; those receiving immunosuppressive chemotherapy (including corticosteroids); and those who have received an organ or bone marrow transplant.	C	Single revaccination if ≥5 years have elapsed since receipt of first dose. If patient is aged ≤10 years: consider revaccination 3 years after previous dose.

*The following categories reflect the strength of evidence supporting the recommendations for vaccination:
A=Strong epidemiologic evidence and substantial clinical benefit support the recommendation for vaccine use.
B=Moderate evidence supports the recommendation for vaccine use.
C=Effectiveness of vaccination is not proven, but the high risk for disease and the potential benefits and safety of the vaccine justify vaccination.
†Strength of evidence for all revaccination recommendations is "C."
§If earlier vaccination status is unknown, patients in this group should be administered pneumococcal vaccine.
¶Including congestive heart failure and cardiomyopathies.
**Including chronic obstructive pulmonary disease and emphysema.
††Including cirrhosis.
§§Including sickle cell disease and splenectomy.
¶¶Including Alaskan Natives and certain American Indian populations.

FIGURE 1. Algorithm for vaccinating persons aged ≥65 years



*Note: For any person who has received a dose of pneumococcal vaccine at age ≥65 years, revaccination is not indicated.

Immunocompromised Persons

Persons who have conditions associated with decreased immunologic function that increase the risk for severe pneumococcal disease or its complications should be vaccinated. Although the vaccine is not as effective for immunocompromised patients as it is for immunocompetent persons, the potential benefits and safety of the vaccine justify its use.

The vaccine is recommended for persons in the following groups: immunocompromised persons aged ≥2 years, including persons with HIV infection, leukemia, lymphoma, Hodgkins disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation); and persons receiving immunosuppressive chemotherapy, including long-term systemic corticosteroids. If earlier vaccination status is unknown, immunocompromised persons should be administered pneumococcal vaccine.

Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis is confirmed. Plasma HIV levels have been found to be transiently elevated after pneumococcal vaccination in some studies (*68*); other studies have not demonstrated such an elevation (*90*). However, no adverse effects of pneumococcal vaccination on patient survival have been detected (*68,90*). When cancer chemotherapy or other immunosuppressive therapy is being considered (e.g., for patients with Hodgkins disease or those who undergo organ or bone marrow transplantation), the interval between vaccination and initiation of immunosuppressive therapy should be at least 2 weeks. Vaccination during chemotherapy or radiation therapy should be avoided.

REVACCINATION

Duration of Immunity

Following pneumococcal vaccination, serotype-specific antibody levels decline after 5–10 years and decrease more rapidly in some groups than others (*56,57,61–63*), which suggests that revaccination may be indicated to provide continued protection. However, data concerning serologic correlates of protection are not conclusive, which limits the ability to precisely define indications for revaccination based on serologic data alone. Polysaccharide vaccines, including the currently available pneumococcal vaccine, do not induce T-cell–dependent responses associated with immunologic memory. Antibody levels increase after revaccination, but an anamnestic response does not occur (*91*). The overall increase in antibody levels among elderly persons has been determined to be lower after revaccination than following primary vaccination (*92*). Long-term follow-up data concerning antibody levels in persons who have been revaccinated are not yet available.

Data from one epidemiologic study have suggested that vaccination may provide protection for at least 9 years after receipt of the initial dose (*44*). Decreasing estimates of effectiveness with increasing interval since vaccination, particularly among the very elderly (i.e., persons aged ≥85 years), have been reported (*79*).

Adverse Reactions Following Revaccination

Early studies have indicated that local reactions (i.e., arthus-type reactions) among adults receiving the second dose of 14-valent vaccine within 2 years after the first dose are more severe than those occurring after initial vaccination (*20,93*). However, subsequent studies have suggested that revaccination after intervals of ≥4 years is not associated with an increased incidence of adverse side effects (*20,94,95*). Although severe local reactions may occur following a second dose of pneumococcal vaccine, the rate of adverse reactions is no greater than the rate after the first dose. An evaluation of 1,000 elderly Medicare enrollees who received a second dose of pneumococcal vaccine indicated that they were not significantly more likely to be hospitalized in the 30 days after vaccination than were the approximately 66,000 persons who received their first dose of vaccine (*96*). No data are available to allow estimates of adverse reaction rates among persons who received more than two doses of pneumococcal vaccine.

Indications for Revaccination

Routine revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not recommended. However, revaccination once is recommended for persons aged ≥2 years who are at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody levels, provided that 5 years have elapsed since receipt of the first dose of pneumococcal vaccine. Revaccination 3 years after the previous dose may be considered for children at highest risk for severe pneumococcal infection who would be aged ≤10 years at the time of revaccination. These children include those with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy) and those with conditions

associated with rapid antibody decline after initial vaccination (e.g., nephrotic syndrome, renal failure, or renal transplantation). Revaccination is contraindicated for persons who had a severe reaction (e.g., anaphylactic reaction or localized arthus-type reaction) to the initial dose they received.

Persons at highest risk and those most likely to have rapid declines in antibody levels include persons with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy), HIV infection, leukemia, lymphoma, Hodgkins disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation), and those receiving immunosuppressive chemotherapy (including long-term systemic corticosteroids). If vaccination status is unknown, patients in these categories should be administered pneumococcal vaccine.

Persons aged ≥65 years should be administered a second dose of vaccine if they received the vaccine ≥5 years previously and were aged <65 years at the time of primary vaccination. Elderly persons with unknown vaccination status should be administered one dose of vaccine (Figure 1).

The need for subsequent doses of pneumococcal vaccine is unclear and will be assessed when additional data become available. Because data are insufficient concerning the safety of pneumococcal vaccine when administered three or more times, revaccination following a second dose is not routinely recommended.

Persons with Uncertain Vaccination Status

To help avoid the administration of unnecessary doses, every patient should be given a record of the vaccination. However, providers should not withhold vaccination in the absence of an immunization record or complete medical record. The patient's verbal history should be used to determine prior vaccination status. When indicated, vaccine should be administered to patients who are uncertain about their vaccination history.

OTHER METHODS OF PREVENTION

Chemoprophylaxis

Oral penicillin V (125 mg, twice daily), when administered to infants and young children with sickle cell disease, has reduced the incidence of pneumococcal bacteremia by 84% compared with those receiving placebo (*97*). Therefore, daily penicillin prophylaxis for children with sickle cell hemoglobinopathy is recommended beginning before 4 months of age. Consensus on the age at which prophylaxis should be discontinued has not been achieved. However, children with sickle cell anemia who had received prophylactic penicillin for prolonged intervals (but who had not had a prior severe pneumococcal infection or a splenectomy) have stopped prophylactic penicillin therapy at 5 years of age without increased incidence of pneumococcal bacteremia or meningitis (*98*).

Oral penicillin G or V is recommended for prevention of pneumococcal disease in children with functional or anatomic asplenia (*85*). Antimicrobial prophylaxis against pneumococcal infection may be particularly useful for asplenic children not likely to

respond to the polysaccharide vaccine (e.g., those aged <2 years or those receiving intensive chemotherapy or cytoreduction therapy). However, the impact of the emergence of drug-resistant *S. pneumoniae* on the effectiveness of antimicrobial prophylaxis is not known.

Passive Immunization

Intramuscular or intravenous immunoglobulin administration may be useful for preventing pneumococcal infection in children with congenital or acquired immunodeficiency diseases, including those with HIV infection, who have recurrent, serious bacterial infections (i.e., two or more serious bacterial infections [e.g., bacteremia, meningitis, or pneumonia] in a 1-year period) (*85,99*). Data are inadequate to evaluate the utility of intravenous immunoglobulin administration in the prevention of pneumococcal disease among HIV-infected adults.

STRATEGIES FOR IMPLEMENTING RECOMMENDATIONS FOR THE USE OF VACCINE

The use of pneumococcal polysaccharide vaccine consistently has been recommended by ACIP (*20,100*), the American Academy of Pediatrics (*85*), the American College of Physicians (*87*), and the American Academy of Family Physicians. In addition, Medicare has provided a payment for pneumococcal vaccine since 1981 and a specific billing code (i.e., G009) for its administration since 1994. Roster billing for pneumococcal vaccination was authorized in August 1996. Hospitals may receive a separate payment for pneumococcal vaccination of Medicare beneficiaries independent of reimbursement based on prospective payment systems for services provided for other conditions. Despite these factors, the vaccine remains underutilized.

Pneumococcal vaccine is recommended for approximately 31 million persons aged ≥65 years and approximately 23 million persons aged <65 years who are at high risk for pneumococcal disease (U.S. Immunization Survey, 1985). The year 2000 objectives of the Public Health Service call for vaccinating at least 60% of persons at risk for influenza and pneumococcal disease (and 80% of the institutionalized elderly) by the year 2000 (*101*). Most persons considered at risk for pneumococcal infection also should receive annual influenza vaccinations. However, as of 1993, only 28% of persons aged ≥65 years had ever received the pneumococcal vaccine. This percentage is considerably lower than the reported annual influenza vaccination rates (52%) for the same population (*102*).

Barriers to achieving high pneumococcal vaccination levels among adults include a) missed opportunities to vaccinate adults during contacts with health-care providers in offices, outpatient clinics, and hospitals; b) lack of vaccine delivery systems in the public and private sectors that can reach adults in different settings (e.g., health-care, workplace, and college or university settings); c) patient and provider fears concerning adverse events following vaccination; and d) lack of awareness among both patients and providers of the seriousness of pneumococcal disease and benefits of pneumococcal vaccination (*2,103*). Because pneumococcal vaccine effectively reduces the

incidence of bacteremia, the use of vaccine must be increased in accordance with recommendations.

Age-Based Strategies

Persons aged 50–64 years commonly have chronic illness, and 12% have pulmonary conditions that place them at increased risk for pneumococcal disease (*86*). However, <20% of those with risk factors are estimated to have received pneumococcal vaccine. A specific age-based standard should improve vaccination rates among persons with high-risk conditions. Therefore, age 50 years has been established as a time to review the overall immunization status of patients; risk factors that indicate the need to administer pneumococcal vaccine should be evaluated at this visit (*86,87*). Vaccination status also should be assessed during the adolescent immunization visit at age 11–12 years (*88*). This visit provides an opportunity to review the need for pneumococcal vaccine; adolescents with high-risk conditions should be vaccinated.

Organizational Strategies

Organizational strategies (e.g., standing orders [rather than requiring a physician's order] for pneumococcal vaccination of high-risk patients who are eligible to receive vaccine) are the most effective methods for increasing pneumococcal vaccination rates among persons at high risk (*104*). In a New York hospital, instituting standing orders for pneumococcal vaccination of the elderly and at-risk patients increased the pneumococcal vaccination rate from zero to 78% (*105*). Similar increases were achieved for influenza vaccination in community hospitals in Minnesota (*106*). The Health Care Financing Administration recently has approved a regulation that permits the use of standing orders to administer pneumococcal vaccine to Medicare patients (*103*). Pneumococcal vaccination also should be routinely provided for residents of nursing homes and other long-term–care facilities.

High vaccination coverage rates can be achieved when pneumococcal vaccination programs are targeted to hospitalized patients at high risk (*104*). A hospital-based immunization strategy is effective and capable of reaching those patients most likely to develop pneumococcal disease (*106–109*). Two thirds of persons with serious pneumococcal disease had been hospitalized within the previous 4 years before their pneumococcal illness, yet few had received pneumococcal vaccine (*109*). Among these patients, 87% had one or more high-risk conditions. Administration of pneumococcal vaccine should be included in routine clinical practice, and the vaccine, when indicated, should be administered before discharge to hospitalized patients to prevent subsequent admissions for pneumococcal disease. Eligible patients in high-risk groups can be identified by physicians, infection-control practitioners, nurse specialists, and clinical pharmacists.

Community-Based Vaccination Programs

Vaccination coverage rates increase when public health departments promote and offer the vaccine. A community-based immunization program implemented in public health jurisdictions by the California State Department of Health Services resulted in a 33% higher rate of pneumococcal vaccination than jurisdictions without

such immunization programs (*110*). This program included interventions such as a) promoting and providing pneumococcal vaccine at health-department–sponsored outreach clinics, health-center clinics, and nursing and convalescent homes and b) promoting pneumococcal vaccine through leaflets, posters, and other material and referring persons to specific clinics for vaccination. Because rates of pneumococcal disease are high among blacks, particularly those of lower socioeconomic status, community outreach programs that are focused on underserved, often inner-city populations could be effective in preventing life-threatening pneumococcal disease among persons in these groups.

A community-based pneumococcal vaccine campaign was conducted as part of the Hawaii Pneumococcal Disease Initiative, which employed public and private sector partnerships to substantially increase vaccine delivery and improve vaccination levels among persons aged ≥65 years (*111*). This public vaccination program was considered cost-effective for vaccinating substantial numbers of adults and stimulated vaccination activity among private health-care providers.

Provider-Based Strategies

Provider-based strategies that have proved effective in increasing adult vaccination rates include practice-based tracking systems and physician reminder systems. In practice-based tracking systems, providers identify the total number of their patients who are at risk and maintain rosters showing the proportion of patients who receive vaccination. Physicians using such a tracking system have administered 30% more influenza vaccine than those not using the system (*112*).

Physician reminder systems consisting of charts, computers, or preventive-health checklists remind physicians to review the need for pneumococcal vaccine for each patient and to administer the vaccine to those at risk for pneumococcal disease. Staff in physicians' offices, clinics, health maintenance organizations, and employee health clinics can be instructed to identify and label the medical records of patients who should receive the vaccine. The use of preventive-health checklists has increased pneumococcal vaccination rates fourfold (*113*) and from 5% to 42% (*114*). In one hospital, implementation of a computer reminder system that prompted physicians to review pneumococcal vaccination status before discharge increased pneumococcal vaccination rates from <4% to 45% (*115*).

Health-care providers in facilities providing episodic or acute care (e.g., emergency rooms and walk-in clinics) should be familiar with pneumococcal vaccine recommendations. They should offer vaccine to persons in high-risk groups or provide written information concerning why, where, and how to obtain the vaccine.

Simultaneous Administration of Pneumococcal and Influenza Vaccines

Because the indications for pneumococcal and influenza vaccines are similar, the time of administration of influenza vaccine—including mass vaccination at outpatient clinics—should be used as an opportunity to identify and vaccinate patients with pneumococcal vaccine. However, influenza vaccine is administered each year, whereas pneumococcal vaccine typically is administered only once for persons in most groups (see Revaccination).

CONJUGATE VACCINE DEVELOPMENT

Additional immunogenic pneumococcal vaccines that provide long-term immunity are needed—especially for children aged <2 years, because incidence of disease is high and antibody responses to the polysaccharide vaccine antigens are poor in this age group. The most promising approach is the development of a protein-polysaccharide conjugate vaccine for selected serotypes, which improves the immunogenicity and potentially the protective efficacy of pneumococcal vaccination—especially in young children. Immune response to many capsular polysaccharides can be improved by covalent coupling of the polysaccharide antigen to a carrier protein (*116,117*). Current conjugate vaccine development has focused on the serotypes most commonly causing infections in childhood. Candidate vaccine formulations in development and evaluation phases include at least seven serotypes of pneumococcal polysaccharides conjugated to one or several protein carriers. An effective conjugate vaccine protecting against the seven most common serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F and serologically cross-reactive serotypes [e.g., 6A]) could potentially prevent 86% of bacteremia, 83% of meningitis, and 65% of otitis media cases among children aged <6 years in the United States (*45*). In persons aged ≥6 years, these serotypes have accounted for 50% of the cerebrospinal fluid and blood isolates (*44*). Preliminary results obtained in phase I and phase II studies suggest that these vaccines generally are safe and induce primary and booster antibody responses in children aged 2–5 years and infants aged 2 months (*118–121*). Multicenter trials to evaluate conjugate vaccine efficacy against acute pneumococcal otitis media and invasive disease in children are ongoing.

The polysaccharide vaccine has not reduced nasopharyngeal carriage of *S. pneumoniae* among children (*122*). However, preliminary data suggest that conjugate vaccines may reduce nasopharyngeal carriage of the pneumococcal serotypes included in the vaccine (*123*). Reduction in carriage rates of *S. pneumoniae* would potentially increase the overall impact of the vaccine by reducing transmission and, consequently, disease incidence. Prospective randomized trials are required to demonstrate the protective efficacy of conjugate vaccines against invasive pneumococcal infections. These vaccines also should be evaluated for utility in preventing pneumococcal disease in immunocompromised adults who respond poorly to the current 23-valent polysaccharide vaccine.

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