Rethinking Recommendations for Use of Pneumococcal Vaccines in Adults

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Streptococcus pneumoniae remains a major cause of disease worldwide; the emergence of antibiotic-resistant strains emphasizes the importance of disease prevention by use of vaccines. Recent studies have provided information that is useful for the evaluation of current vaccine recommendations. Recommendations target most people who are at high risk for invasive pneumococcal disease. However, higher risk has also been identified for African Americans and smokers, but these groups are not specifically targeted by current recommendations. The vaccine is effective against invasive disease in immunocompetent people, although studies in immunocompromised subjects have found few subgroups in which the vaccine appears to be effective. Questions with regard to optimal timing and indications for revaccination remain a challenge, because the duration of protection and effectiveness of revaccination remain unknown. New pneumococcal vaccines appear promising but will need to be tested against the performance of the polysaccharide vaccine. Improving delivery of the currently available pneumococcal polysaccharide vaccine to adults who will benefit should be a high priority.

Pneumococcus remains a major cause of morbidity and mortality worldwide in spite of the availability of vaccines. Although young children have the highest rates of pneumococcal disease, elderly persons and adults with certain chronic illnesses are also at high risk for invasive pneumococcal disease, and in industrialized countries, they are much more likely to die of pneumococcal disease than are children [1]. In spite of appropriate therapy, case-fatality rates for bacteremic pneumococcal pneumonia have a range of 7%–35% [2]. Pneumococci that are resistant to penicillin and to multiple agents are becoming increasingly common among patients in all age groups [3], which makes pneumococcal infections more difficult to treat. The emergence of antibiotic-resistant pneumococci has placed renewed emphasis on the importance of disease prevention.

Pneumococcal vaccines were used as early as 1911 [4]. The first pneumococcal polysaccharide vaccines to be licensed in the United States, 2 different 6-valent formulations, were available shortly after World War II, but interest was very low in these vaccines and both were withdrawn from the market [5]. A 14-valent formulation was licensed in 1977, and in 1983, this vaccine was replaced by the 2 currently available 23-valent pneumococcal polysaccharide vaccines (Pneumovax 23, Merck; and Pnu-Immune 23, Wyeth-Ayerst Laboratories).

Although pneumococcal polysaccharide vaccines are no longer new, new information has become available in the past few years regarding people who are at risk for pneumococcal infections and the performance of the polysaccharide vaccines in a variety of populations. Periodic review of new information is critical to ensure that vaccines are used in the best possible manner. We summarize the recent literature related to pneumococcal vaccines for adults and factors that should be considered for recommendations to prevent invasive pneumococcal disease and pneumococcal pneumonia in adults.

CURRENT RECOMMENDATIONS FOR USE OF PNEUMOCOCCAL VACCINES IN ADULTS

Pneumococcal polysaccharide vaccines are recommended for use in adults in many countries. In the United States, use of pneumococcal polysaccharide vaccines is recommended by several governmental and professional groups, including the Centers for Disease Control and Prevention’s (CDC’s) Advisory
Committee on Immunization Practices (ACIP), the US Preventive Services Task Force, the American College of Physicians, the Infectious Diseases Society of America, the American College of Preventive Medicine, and the American Academy of Family Physicians [1, 6–11]. Although there are some minor differences in the recommendations, all these groups recommend vaccination for all adults aged ≥65 years and for selected people aged <65 years.

According to the 1997 ACIP statement [1], people aged 2–64 years who have chronic illnesses that place them at moderate to high risk for pneumococcal disease or complications of pneumococcal disease should receive pneumococcal polysaccharide vaccine. These people include those with chronic cardiovascular disease (e.g., congestive heart failure or cardiomyopathies), chronic pulmonary disease (e.g., chronic obstructive pulmonary disease or emphysema, but not asthma), diabetes mellitus, alcoholism, chronic liver disease (e.g., cirrhosis), CSF leaks, or functional or anatomic asplenia. In addition, people who live in settings that may place them at higher risk for invasive pneumococcal disease or its complications (e.g., certain Alaska Native or American Indian populations or residents of long-term care facilities) should receive vaccine. The ACIP also recommends pneumococcal polysaccharide vaccine for immunocompromised people, which it defines as those with HIV infection or AIDS, hematologic or other generalized malignancy, chronic renal failure, and nephrotic syndrome, as well as those taking immunosuppressive therapy, including corticosteroids, and those who have undergone organ or bone marrow transplantation.

The ACIP does not recommend routine revaccination. A second dose of vaccine is recommended 5 years after the first dose for persons with asplenia or for immunocompromised persons. In addition, persons ≥65 years who were vaccinated before age 65 years may be revaccinated a single time if at least 5 years have passed since their previous dose. The ACIP does not recommend multiple revaccinations because of insufficient data on the duration of protection and the safety of pneumococcal polysaccharide vaccines when administered ≥3 times. However, the committee states that the vaccine should be given to people with an indication who are unsure if they have previously received the vaccine.

In their statement on the use of pneumococcal polysaccharide vaccine [1], the ACIP gave a value to the strength of their recommendations for various groups. The ACIP gave stronger recommendations for use of vaccine for elderly persons, persons with chronic conditions, and persons with asplenia, stating that there was moderate to strong epidemiologic evidence supporting the use of the vaccine in these groups at the time the recommendations were made. The ACIP’s recommendations were less strong for vaccination of immunocompromised people, for persons involved in high-risk social situations, and for all revaccination recommendations, stating that there was limited or no evidence of vaccine effectiveness in these groups, but that the high risk of disease, potential benefits, and safety of the vaccine supported its use.

Recommendations for pneumococcal polysaccharide vaccine issued in the 1996 report by the US Preventive Services Task Force [6] are similar to the ACIP statement with regard to both the groups for whom the vaccine is recommended and in the strength of the recommendations made. In contrast to the ACIP recommendations, the task force recommends vaccination of all institutionalized people aged ≥50 years. The task force, like the ACIP, does not recommend routine revaccination but rather states that revaccination may be appropriate for immunocompetent people at the highest risk for morbidity and mortality (e.g., people aged ≥75 years or with severe chronic disease) or for immunocompromised people.

Groups at Risk for Pneumococcal Disease

Young children and elderly persons. The risk of invasive pneumococcal disease is highest in young children, is low in older children and young adults who are immunocompetent, and increases with age (figure 1). According to provisional surveillance data from CDC’s Active Bacterial Core surveillance [ABCs, 12], part of the Emerging Infections Program Network, annual incidence of invasive pneumococcal disease in 1999 was ∼7 cases per 100,000 population in adults aged 18–34 years, 19 per 100,000 population in people aged 35–49 years, 24 per 100,000 population in people aged 50–64 years, and 61 per 100,000 population in people aged ≥65 years [12]. The measured incidence of invasive disease has varied markedly over time and between populations; a review of published studies performed among people aged ≥65 years found rates between
The likelihood of dying of an invasive pneumococcal disease also increases with age. Among adults with invasive pneumococcal disease, 7% of people aged 18–34 years die of their illness, compared with 21% of those aged ≥65 years; people aged ≥65 years account for one-third of cases but over half of deaths from invasive pneumococcal disease [12]. Because the risk of disease and death increases with age, recommendations for vaccination should attempt to provide optimal protection for older adults.

**Certain ethnic groups.** There are marked differences in risk for some racial/ethnic groups. The rate of invasive pneumococcal disease in African-American persons aged 35–49 years exceeds that for white persons aged ≥65 years (figure 1), and African Americans at all ages have at least twice the risk of invasive pneumococcal disease as white persons in the United States [12, 14–17]. The higher disease incidence means that African-American adults are more likely to die of pneumococcal disease than whites, although case-fatality ratios for the 2 groups do not differ [17]. Rates of invasive pneumococcal infection are also higher among Alaska Natives [18] and certain other American Indian groups [19]. The reasons for these differences in risk of invasive disease are not well defined. Differences in the prevalence of chronic diseases, such as HIV infection, AIDS, or diabetes, may contribute to the differences in risk between racial and ethnic groups [18, 20]. However, studies that controlled for underlying diseases have still found higher risk of infection for African American persons than for persons of white race [20, 21].

Low socioeconomic status has also been suggested as an explanation for some of the racial/ethnic disparity, and recent studies have identified both poverty and African-American ethnicity as independent risk factors for invasive pneumococcal disease [14, 21, 22]. Although ACIP recommends that Alaska Natives and American Indians of all ages should receive pneumococcal polysaccharide vaccine because of high risk for invasive infection, current recommendations do not include African-American adults aged <65 years without underlying illnesses. The ACIP’s new recommendations for use of pneumococcal conjugate vaccine in young children may be the first set of recommendations to suggest that clinicians should offer a vaccine to African Americans on the basis of the higher risk of disease in that race group [23].

**Immunocompromised people and people with chronic illnesses.** Immunocompromised people and people with certain chronic illness are at increased risk for invasive pneumococcal disease or for severe sequelae from their infections. People with chronic diseases that are ACIP indications for vaccine are twice as likely as others to die if they develop invasive pneumococcal disease [17]. The emergence of HIV and the subsequent development of highly active antiretroviral therapy (HAART) have had notable effects on the epidemiology of invasive pneumococcal disease in young adults. In a study from San Francisco that reviewed cases of invasive pneumococcal disease that occurred during 1994–1997, the rate of invasive pneumococcal disease in people with AIDS was 46 times higher than was the rate among people without known HIV infection [24]. In this population, a significant decrease in disease rates was noted among people with HIV or AIDS during this time period, possibly due to the increasing use of HAART. In some communities in the United States, HIV or AIDS is the most common underlying illness to be found in people who are 18–64 years old and who have invasive pneumococcal disease [17, 20, 24].

**Smokers.** Smoking is not currently an indication for pneumococcal polysaccharide vaccine, but smoking has recently been identified as another major risk factor for invasive pneumococcal disease in adults. In population-based surveillance in Texas, smokers who were 18–64 years old had 2.6 times the risk for invasive pneumococcal disease as nonsmokers who were the same age, and 31% of disease in the patients in this age group was attributable to smoking [14]. In a recent risk-factor study of immunocompetent adults aged 18–64 years, 51% of disease in this population was attributed to smoking, and smoking conferred a greater risk of invasive pneumococcal disease than that of any other characteristic studied [21]. When researchers adjusted for other factors, people with invasive pneumococcal infection were 4.1 times more likely to be cigarette smokers than was the control group. The association increased with the number of cigarettes smoked and the number of years that the patient had smoked, indicating a dose-response relationship. Among current nonsmokers, case patients were more likely than were controls to be former smokers who had quit <10 years earlier or to be exposed to passive (secondhand) cigarette smoke.

**Residents of long-term care facilities.** Pneumococcal disease is a major problem in long-term care facilities, and current vaccine recommendations suggest that institutionalized adults should receive polysaccharide vaccine. Not only are long-term care facility residents at high risk for sporadic pneumococcal disease as a result of their advanced age or the presence of chronic illnesses, but long-term care facilities also provide an optimal setting for pneumococcal outbreaks. Several outbreaks of infection have recently been reported, including one in which the outbreak strain was multidrug resistant [25–28]. Low vaccine coverage may facilitate institutional outbreaks of pneumococcal disease; at the time of these reported outbreaks, <10% of residents in the facilities had received pneumococcal polysaccharide vaccine. Outbreaks of pneumococcal disease are rare outside of institutional settings.

The current ACIP recommendations account for most adults.
at high risk for invasive pneumococcal disease. According to CDC estimates, approximately one-third of all invasive pneumococcal cases occur in people aged ≥65 years and 38% occur in adults aged 18–64 years (figure 2; ABCs, unpublished data). Among adults aged 18–64 years, approximately two-thirds of cases occur in people who have a chronic medical condition that is an ACIP indication for pneumococcal polysaccharide vaccine [14, 20, 29]. Overall, ∼9000 cases (20%) of invasive pneumococcal disease in adults occur in people who do not currently have an indication for pneumococcal polysaccharide vaccine. Expanding the recommendations to include either all smokers, all African American persons, or all people aged ≥50 years may reduce the number of cases that occur in people without a vaccine indication to ∼4000–5000 cases (table 1).

VACCINATION WITH PNEUMOCOCCAL POLYSACCHARIDE VACCINE

The currently available pneumococcal polysaccharide vaccines are designed to provide serotype-specific protection and include 25 mg of purified capsular polysaccharide antigens from each of 23 different serotypes. More than 90 pneumococcal serotypes and ≥40 serogroups, distinguishable by the structure of the polysaccharide capsule, have been identified as causing disease. A recent review of data from around the world found regional differences in distribution of serogroups, but 11 serogroups accounted for at least 75% of the isolates that caused invasive disease in adults in each geographic region [31]. In the United States, serotypes included in the 23-valent vaccine account for at least 85%–90% of strains that cause invasive disease in adults [1]. Vaccine antigens targeted against some serotypes may provide cross-protection against other serotypes in the same group [32]. Although recent studies that used molecular subtyping techniques have demonstrated that pneumococci have the ability to change their capsule type [33, 34], all capsular switching described to date has been between serotypes contained in the pneumococcal polysaccharide vaccine.

Immunogenicity. Pneumococcal capsular polysaccharide vaccines provide protection by inducing serotype-specific antibodies that enhance opsonization, complement-dependent phagocytosis, and killing of pneumococci by leukocytes and other phagocytic cells. Concentrations of antibodies to pneumococcal polysaccharides increase within 1 week after vaccination and, for most vaccine antigens, remain greater than prevaccination levels for ≥5 years in healthy adults [35, 36]. In some people at increased risk of pneumococcal disease, such as elderly persons and those with certain underlying illnesses, immune responses to pneumococcal polysaccharides may be limited and antibody concentrations may decrease more rapidly after vaccination, compared with healthy adults [37–46]. However, the clinical relevance of antibody concentrations measured after vaccination is difficult to determine because the quantity of antibodies that correlate with protection against pneumococcal disease has not been clearly defined. Measurements of antibody concentration do not take into consideration the functional activity of the antibody produced. Laboratory methods that assess the functional immune responses to vaccination, such as opsonophagocytic activity and antibody avidity for pneumococcal antigens, may prove to be a better way to predict protection and be more clinically relevant than are quantitative antibody measurements [47, 48]. Although substantial antibody responses may occur even among people aged ≥85 years, effectiveness may be reduced in very elderly persons because of functional differences in antibodies produced by people in this age group compared with younger vaccinees [49]. Immune responses are often not consistent among all 23 serotypes in the vaccine, and the magnitude of responses among vaccinees varies widely [50]. Genetic factors may play an important role in the response to polysaccharide antigens and could account for some of this variability [51].

Safety. On the basis of a quarter century of clinical experience, pneumococcal polysaccharide vaccines are considered safe [1]. Severe adverse effects (e.g., anaphylactic reactions) are rarely reported, and neurologic disorders (e.g., Guillain-Barré syndrome) have not been associated with administration of pneumococcal vaccine [52]. In a meta-analysis of 9 randomized controlled trials of pneumococcal vaccine efficacy, mild local reactions (e.g., pain at the injection site, erythema, and swelling) were observed among approximately one-third or fewer of patients who received the vaccine, and there were no reports of severe febrile or anaphylactic reactions [53]. In a prospective study of people aged 50–74 years, large localized reaction (red-
ness or swelling extending ≥4 inches [10.2 cm] around the injection site) were reported by 3% of vaccinees after the first dose of pneumococcal vaccine [54]. However, even these large localized reactions did not interfere with the activities of daily life and were self-limited. The mean interval from vaccination to complete resolution of symptoms was 3.6 days. Swelling, pain, and redness at the injection site have been associated with the higher prevaccination concentrations of antcapsular antibodies, indicating a localized Arthus-type reaction (type III hypersensitivity reaction) caused by formation of antibody-antigen complexes at the injection site [44, 54]. Intradermal administration may cause severe local reactions and is inappropriate [1].

Pneumococcal vaccine may cause transient increases in HIV replication [55, 56], but these studies were performed before the use of HAART became commonplace, so the clinical significance of this occurrence is unknown. This phenomenon has also been observed in HIV-infected people after they have been immunized with other vaccines [57] and during episodes of acute bacterial pneumonia [58]. One study, a randomized trial of 23-valent pneumococcal polysaccharide vaccine among HIV-infected adults in Uganda [59], found that the rates of all-cause pneumonia among people who were receiving pneumococcal vaccine were higher than they were among those who were given placebo. However, overall mortality during the follow-up period was the same (28%) in vaccine and placebo recipients. It is unclear whether these findings can be generalized outside of sub-Saharan Africa. Studies evaluating safety and efficacy of pneumococcal vaccines in HIV-infected people in the United States who are being treated with HAART are in progress. Pneumococcal vaccines do not appear to alter the course of chronic, noninfectious diseases. Among 40 people with systemic lupus erythematous randomized to receive pneumococcal polysaccharide vaccine or placebo, no changes in lupus activity were observed during follow-up [60]. The safety of pneumococcal polysaccharide vaccine during early pregnancy has not been evaluated in prospective studies, but no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy.

Clinical impact. Prelicensure randomized, controlled trials of a single dose of pneumococcal polysaccharide vaccine were conducted in the 1970s among young, healthy South African gold miners, a group with high rates of pneumococcal pneumonia. Protective efficacy against pneumococcal pneumonia in these trials had a range of 76%–92% [61, 62]. In non-epidemic situations in industrialized countries, most pneumococcal disease in adults occurs in elderly persons or in people with chronic medical conditions. Pneumococcal polysaccharide vaccine efficacy has not consistently been proven in randomized, double-blind, controlled trials among elderly persons. Results of 1 randomized clinical trial suggested that the vaccine provided some protection against pneumococcal pneumonia among high-risk elderly people [63], whereas 2 other trials did not demonstrate efficacy against pneumonia or bronchitis in patients without bacteremia [64, 65].

The inability of these studies to document vaccine efficacy partly results from a lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. The diagnosis of pneumococcal pneumonia in the majority of patients in 2 of the trials [63, 65] was based on detection of rising antibodies to pneumolysin or pneumolysin immune complexes in patient serum. Subsequent work by Mushor et al. [66] indicates that the latter assay, which was the basis for most of the diagnoses of pneumococcal pneumonia, is not specific. A nonspecific case definition of pneumococcal pneumonia would bias the findings of a trial to the null. In addition, these studies lacked statistical power to assess efficacy against bacteremia or meningitis. In the trial conducted by Ortvist et al. [65] in Sweden, for example, the point estimate for vaccine efficacy against bacteremia was 79% (P = .22; Fisher’s exact test), but the power to detect a statistically significant difference in rates of invasive disease in vaccine and placebo recipients was only 5%. An additional trial among people aged ≥65 years in northern Finland who received influenza vaccination either alone or

Table 1. Number of cases of invasive pneumococcal disease (IPD) in the United States in persons with a vaccine indication, by various vaccination strategies.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Annual cases of IPD</th>
<th>No. of cases in persons with vaccine indication, by strategya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Based on current ACIP recommendationsb</td>
</tr>
<tr>
<td>18–49</td>
<td>15,500</td>
<td>10,100</td>
</tr>
<tr>
<td>50–64</td>
<td>9200</td>
<td>6000</td>
</tr>
<tr>
<td>≥65</td>
<td>21,100</td>
<td>21,100</td>
</tr>
<tr>
<td>Total</td>
<td>45,800</td>
<td>37,200</td>
</tr>
</tbody>
</table>

NOTE. ACIP Advisory Committee on Immunization Practices.

a Estimates were made using 1998 postcensus population estimates and 1999 data from Active Bacterial Core Surveillance.
b From [1]. The proportion of cases with an ACIP indication was assumed to be 100% for persons aged ≥65 years and 65% for persons aged 18–64 years [14, 20, 29].
c Estimate based on smokers having 4.1 times the risk of invasive pneumococcal disease as nonsmokers [21] and a prevalence of smoking of 22.9% [30].
in combination with 23-valent pneumococcal polysaccharide vaccine showed that use of both vaccines had no advantage over use of influenza vaccine alone for prevention of pneumococcal pneumonia [67]. However, the diagnosis of pneumococcal pneumonia was also based primarily on pneumolysin serological testing in this study. Moreover, only 2 of the 7 cases of pneumococcal bacteremia occurred in people who received pneumococcal vaccine; therefore, the point estimate for protection against invasive disease was 60% (95% CI, −40 to 90) [67]. Two open trials have suggested protection against pneumococcal pneumonia among elderly residents of long-term care facilities [68, 69].

Although randomized, double-blind, controlled trials provide the greatest scientific rigor for evaluating pneumococcal vaccines, epidemiological studies, such as case-control and serotype distribution (indirect cohort) studies, offer a number of advantages. They permit rapid gathering of data with better statistical power to adequately evaluate vaccine effectiveness [70]. Moreover, ethical concerns about withholding a vaccine from control subjects make postlicensure randomized trials among people at highest risk of disease impractical. Finally, randomized trials evaluate vaccine performance under optimal conditions, whereas epidemiological studies provide a more pragmatic perspective by assessing the impact of a vaccine under ordinary conditions of clinical practice [71].

Postlicensure epidemiological studies have documented the effectiveness of pneumococcal polysaccharide vaccines for prevention of invasive infection (bacteremia and meningitis) among elderly persons and younger adults with certain chronic medical conditions [72–75]. Only 1 case-control study failed to demonstrate effectiveness against bacteremic disease [76]—possibly because of study limitations, such as small sample size and incomplete ascertainment of vaccination status of patients. The overall rate of effectiveness against invasive pneumococcal disease among immunocompetent people aged ≥65 years is 75% [72]; however, efficacy may decrease with advancing age [74]. An indirect cohort analysis of CDC surveillance data indicates that polysaccharide vaccine is effective for the prevention of bacteremia and meningitis among people at increased risk for infection due to certain medical conditions, including diabetes mellitus, chronic heart and lung diseases, and anatomic asplenia (table 2) [72]. Although immunogenicity of polysaccharide vaccines is limited for persons with some immunocompromising conditions, it should be noted that the wide confidence intervals for many of the conditions for which effectiveness could not be confirmed may reflect small numbers of patient with non-vaccine serotype infections rather than reflecting a lack of benefit from the vaccine.

A retrospective cohort study of all people aged ≥65 years who were enrolled in a managed care organization and who had chronic lung disease demonstrated significantly lower rates of all-cause pneumonia hospitalization and death among vaccinated persons, compared with unvaccinated people [77]. Rates of nonpneumonia hospitalization were similar in the 2 groups. In contrast to the findings of the trial in northern Finland [67], benefits of pneumococcal and influenza vaccinations were additive [77]. In a recent prospective study of residents in 5 nursing homes in Toronto, people developing any type of lower respiratory tract infections were less likely to have received pneumococcal vaccine than were those without these illnesses; however, the association was not statistically significant after controlling for other factors that influence the risk of lower respiratory infection, such as receipt of influenza vaccine [78].

The role of pneumococcal vaccine in people infected with HIV deserves special attention given the high rate of pneumococcal infection among people with HIV [24]. A nested case-control study from Baltimore in the early 1990s showed that people with pneumococcal disease and CD4+ cell counts of >200 cells/mm³ were less likely to have received pneumococcal vaccine than were control subjects without pneumococcal disease [79]. In a case-control study conducted in Atlanta and San Francisco, 23-valent pneumococcal vaccine was 49% effective (95% CI, 12%–70%) for prevention of invasive pneumococcal disease in HIV-infected people aged 18–55 years; however, in multivariable analysis, effectiveness was greater for white per-

### Table 2. Vaccine effectiveness among persons with chronic underlying medical conditions, based on indirect cohort analysis of Centers for Disease Control and Prevention surveillance data.

<table>
<thead>
<tr>
<th>Underlying conditions</th>
<th>Effectiveness, %a</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anatomic asplenia</td>
<td>77</td>
<td>14–95</td>
</tr>
<tr>
<td>COPD or asthmab</td>
<td>65</td>
<td>26–83</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>69</td>
<td>17–88</td>
</tr>
<tr>
<td>Coronary vascular disease</td>
<td>73</td>
<td>23–90</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>84</td>
<td>50–95</td>
</tr>
<tr>
<td>Effectiveness not confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholism or cirrhosis</td>
<td>&lt;0</td>
<td>−1093 to 61</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>27</td>
<td>−152 to 78</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>11</td>
<td>−505 to 89</td>
</tr>
<tr>
<td>Immunoglobulin deficiency</td>
<td>59</td>
<td>−239 to 95</td>
</tr>
<tr>
<td>Leukemia</td>
<td>&lt;0</td>
<td>−634 to 72</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>&lt;0</td>
<td>−550 to 78</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>64</td>
<td>−58 to 92</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>11</td>
<td>−545 to 88</td>
</tr>
</tbody>
</table>

**NOTE.** COPD, chronic obstructive pulmonary disease.

a Vaccine effectiveness in indirect cohort analyses is calculated by comparing the proportion of invasive disease cases caused by serotypes included in the vaccine among vaccinated and unvaccinated people. No data are available for patients with HIV infection or who take immunosuppressive therapy. Adapted from [72].

b Asthma is no longer an Advisory Committee on Immunization Practices indication for pneumococcal polysaccharide vaccine.
sons (76%; 95% CI, 35%–91%) than it was for African-American persons (24%; 95% CI, 50% to 61%) [80]. Failure to demonstrate effectiveness among African-American persons may be due to limited power because of low vaccination rates for African-Americans, immunization at a more advanced stage of AIDS progression for African-American persons, or unmeasured factors. A randomized trial of 23-valent polysaccharide vaccine among HIV-infected people in Uganda showed no evidence of efficacy [59]. It should be noted that none of these studies was conducted among people who were receiving highly active antiretroviral agents, and no published study to date has evaluated the clinical impact of pneumococcal polysaccharide vaccine for persons receiving optimal antiretroviral therapy.

Cost-effectiveness. On the basis of surveillance data collected in the late 1980s and early 1990s, and of vaccine effectiveness estimates from epidemiological studies, an analysis of cost-effectiveness of pneumococcal vaccination of all people aged ≥65 years for prevention of bacteremia and meningitis indicated that, from a social perspective, vaccination saved $8.27 per person vaccinated [81]. The cost savings associated with pneumococcal vaccination may be greater for elderly people who are at increased risk of serious pneumococcal disease due to certain chronic medical conditions. A review of pneumonia hospitalizations and deaths among elderly people with chronic lung disease in a managed care organization indicated that cost savings were between $115 and $512 over 2 years for each person vaccinated [77].

**REVACCINATION**

Anecdotal reports suggest that the recommendations for revaccination with pneumococcal polysaccharide vaccine are a source of confusion for clinicians. (The term “revaccination” is used for second or third doses of pneumococcal polysaccharide vaccine and other vaccines that do not induce immune memory. The term “booster dose” should be reserved for subsequent doses of vaccines that induce immune memory.) The ACIP recommends a one-time revaccination for people aged ≥65 years if the patient was first immunized before age 65 years and at least 5 years earlier [1]; this recommendation has been misinterpreted as suggesting revaccination every 5 years. Revaccination recommendations from the ACIP and US Preventive Services Task Force [6] differ, which may add to the confusion. Both groups agree that the evidence to support recommendations for revaccination is limited, and neither group strongly recommends revaccination for any population. Because the risk of developing invasive pneumococcal disease and of dying from it increase with age, the timing and frequency of revaccination to provide optimal protection are critical issues.

There are limited data regarding how long protection provided by pneumococcal polysaccharide vaccines lasts, however. Concentrations of antibodies to pneumococcal polysaccharides remain greater than prevaccination levels for ≥5 years in healthy adults [35, 36] but decrease more rapidly in elderly persons and in those with certain underlying illnesses [37–46]. One epidemiologic study of polysaccharide vaccine effectiveness suggested lower effectiveness 5 years after vaccination in elderly persons [74]; another found no clear difference in effectiveness in people vaccinated at least 9 years earlier compared with people vaccinated more recently [72].

Revaccination with pneumococcal polysaccharide vaccine is associated with few systemic adverse events, although a recent large study found that local side effects are more common with revaccination than with initial vaccination [54]. This study compared the frequency of side effects in 901 patients who were aged 50–74 years and who had never been immunized with those in 513 patients who were the same age and who had been immunized at least 5 years earlier. Local reactions of ≥4 inches (10.2 cm) were more common in revaccinated people (11%) than in people receiving their first dose (3%); healthy subjects had a 5-fold risk of a large local reaction after revaccination compared with initial vaccination. The likelihood of a large local reaction correlated with prevaccination antibody concentrations. Investigators found no difference in the frequency of systemic symptoms and no serious side effects in either group.

Several studies have compared the immune response of revaccinees to first-time vaccine recipients [42, 54, 82–85]. In all studies but one [42], a study that mostly included Alaska Natives with chronic illnesses, peak antibody concentrations were lower after revaccination than they were after initial vaccination. Aging of the study subjects has been suggested as an explanation for the suboptimal immune response after revaccination, but the interval between immunizations was only 1–6 years [82–85]. A similar finding of hyporesponsiveness on revaccination has been well documented in children and young adults who had received a second dose of meningococcal serogroup C polysaccharide vaccine [86–89]; the reason for this finding is unknown. There are no studies that have measured the effectiveness of second or third doses of pneumococcal polysaccharide vaccine. Because the quantity of antibodies that correlate with protection against pneumococcal disease has not been clearly defined, it is unknown if the lower antibody levels seen on revaccination correlate with inferior protection.

**DELIVERING PNEUMOCOCCAL VACCINE**

Most patients who could benefit from pneumococcal polysaccharide vaccine have not yet received it. According to the 1997 Behavior Risk Factor Surveillance System, a phone survey of noninstitutionalized adults, only 46% of adults aged ≥65 years...
reported ever having received pneumococcal vaccine [90]. Coverage levels were significantly higher in 1997 than they were in 1995, when only 37% of respondents aged ≥65 years reported receiving vaccine [91]. Vaccine coverage levels differ by race and ethnic group, age, and health status; coverage is significantly lower among African-American persons (30% among African-Americans aged ≥65 years) and Hispanic persons (34%) than it is among non-Hispanic white persons (47%) [91]. Only 17% of people 18–64 years old with high-risk conditions reported previous receipt of pneumococcal vaccine in another national survey conducted in 1997 [92]. Use of vaccines in institutionalized adults also is suboptimal. Estimates from the 1997 National Nursing Home Survey indicate that only 28% of people in long-term care facilities had received pneumococcal vaccines [92]. The Healthy People 2010 objectives for pneumococcal immunization call for 90% of all people aged ≥65 years and 65% of high-risk adults 18–64 years old to receive pneumococcal vaccine [93].

The reasons why pneumococcal vaccine has not been delivered more effectively to its targeted populations are numerous and varied. They relate to adult immunization issues generally and to pneumococcal vaccine specifically. Adults often do not visit physicians regularly, and when they do, many insurance plans do not cover provision of preventive services, including vaccines. Even in instances in which insurance plans include vaccine administration, payment to the physician usually is modest, providing little incentive to aggressively pursue immunization.

Although many physicians wish to provide appropriate vaccine services to their patients, information about vaccine developments and recommendations may reach them only sporadically. Although pediatricians regularly receive updates regarding the childhood immunization schedule from public health agencies, professional societies, and vaccine manufacturers, these sources of continuing education are less likely to deliver vaccine information to physicians who care for adults. This type of information may be even less likely to reach medical subspecialists, such as rheumatologists, cardiologists, or nephrologists, who provide care for a substantial proportion of adults and who frequently are the sole source of medical care for their patients, many of whom have indications for immunization.

Some features of the successful childhood immunization program in the United States are not applicable to adult immunization activities. The National Immunization Program provides funding and technical assistance to state and local health departments in providing immunization services to infants and children. Furthermore, in many states, school entry laws require nearly all children to be vaccinated with certain vaccines. Neither of these mechanisms is available to assist in the vaccination of adults; however, some states recently have instituted requirements that pneumococcal vaccine be offered to all patients admitted to long-term care facilities. Electronic immunization registries for tracking childhood immunizations are underway in some states; whether registries would be useful or feasible for improving adult immunization is unknown.

Several factors specific to pneumococcal vaccine have impeded its more widespread use. Whereas an examination of national morbidity data clearly defines invasive pneumococcal disease as a substantial public health problem, clinicians may perceive the issue with less concern. Rates of invasive disease in the general population are sufficiently low such that even busy practitioners may go many years without encountering a case of pneumococcal bacteremia in their practice. Therefore, practitioners may not feel compelled to protect their patients against a risk that is perceived as remote. Although protection against pneumonia is considered important, the efficacy of the vaccine in preventing pneumonia continues to be treated with skepticism in the literature [65, 94]. Concern regarding side effects with revaccination may inhibit some clinicians from vaccinating patients, especially those patients with several doctors or whose vaccination records are missing or incomplete.

Nevertheless, even many patients who feel negatively about vaccines would agree to receive pneumococcal vaccine if their health care provider offered it [95]. In addition, many options are available to improve vaccine delivery. Several studies have found that the use of standing orders—orders that authorize nurses or pharmacists to administer vaccines according to a preapproved protocol and without direct physician involvement at the time of the interaction—may be the best means of improving vaccine delivery to adults in hospitals, clinics, and long-term care facilities [96–98]. A recent review of interventions to improve rates of vaccination concluded that there was strong evidence that standing orders are effective in improving vaccination coverage in adults [99]. Standing orders for vaccine delivery are recommended by the Task Force on Community Preventive Services [100], the ACIP [92], and by the Canadian Community Health Practice Guidelines Working Group [101]. Other recommended methods of improving vaccine coverage among adults include the use of client and provider reminders, patient education, interventions that reduce client out-of-pocket costs, and assessment and feedback of provider vaccination rates; for populations that are difficult to reach, home visits or expanded access to health care settings may be needed [100]. Financial incentives, such as increasing reimbursement for vaccination, providing reimbursement for preventive health visits, or ensuring that insurers cover adult immunizations, could improve vaccine coverage.

Changing pneumococcal vaccine recommendations to include all adults aged ≥50 years has been suggested as a means of simplifying the vaccine indications, harmonizing the indications with the expanded recommendations for influenza vacc-
cine, and improving coverage among high-risk people aged <65 years. Research data are limited on whether such a strategy would raise coverage rates, although experience with other vaccines suggests that age-based recommendations might be effective. One study from Finland suggested that an age-based strategy was effective, but the age-based intervention that was used also included either mailed reminders or a mass media campaign [102].

Currently, at least 61 million adults in the United States have an indication for pneumococcal polysaccharide vaccine (table 3). If recommendations for pneumococcal polysaccharide vaccine were expanded to include all adults who are African American, who smoke, or who are aged >50 years, the number of adults with a vaccine indication would increase by 17–37 million, depending on the strategy. Currently, only 2 manufacturers produce pneumococcal polysaccharide vaccine in the United States. In addition to concerns regarding the timing and effectiveness of revaccination, vaccine supply will need to be considered if health care providers were to begin immunizing new groups without causing relative shortages in vaccine availability for others at high risk. Adequacy of the vaccine supply has recently been a concern with influenza vaccine [103]. In 1994, orders for pneumococcal vaccine were delayed during a shortage that lasted a few months (R. Strikas, personal communication); the shortage was resolved after manufacturers increased capacity to keep up with increases in demand that had occurred from 1993 through 1994.

NEW PNEUMOCOCCAL VACCINES

Pneumococcal conjugate vaccines. A recent advancement in prevention of pneumococcal disease is the development of pneumococcal conjugate vaccines. A 7-valent pneumococcal conjugate vaccine was licensed in the United States for prevention of invasive pneumococcal disease in infants and young children in early 2000 [23] and is now licensed in several other countries. By conjugating polysaccharide antigens to a carrier protein, the immunologic responses elicited become T cell dependent. Memory B cells are produced and primed for booster responses—rapid and dramatic increases in antibody concentrations to subsequent immunizations with pneumococcal polysaccharide [104]. Pneumococcal conjugate vaccines appear to be safe and to induce primary and booster antibody responses in infants and young children [104, 105]. A randomized trial of 7-valent pneumococcal conjugate vaccine among 37,000 infants enrolled in a large northern California health maintenance plan documented efficacy >90% for prevention of invasive pneumococcal disease caused by the 7 serotypes included in the vaccine [106]. Several other large randomized trials assessing the efficacy of conjugate vaccines to prevent invasive infection and acute otitis media in infants are ongoing.

The role of conjugate vaccines among adults with underlying medical conditions and elderly persons remains to be determined. Preliminary data from studies of healthy people aged ≥50 years and of patients vaccinated after treatment for Hodgkin’s disease indicate that antibody responses to pneumococcal conjugate vaccines have not been substantially better than responses to the polysaccharide vaccine [107, 108]. In one study, localized reactions (pain, stiffness, and induration at the injection site) were more common among people who received the conjugate vaccine, although these symptoms were generally mild [107]. In one family, administration of pneumococcal conjugate vaccine produced IgG responses in several people who lacked the capacity to respond to polysaccharide vaccine [109]. One approach to the use of conjugate vaccines in adults is to sequentially administer conjugate vaccine and 23-valent polysaccharide vaccine; giving conjugate vaccine first could prime the immune system, and the polysaccharide vaccine could then induce a booster response to the serotypes present in both vaccines as well as induce primary T cell–independent responses to the serotypes in the 23-valent vaccine only [104, 110, 111].

A potential shortcoming of conjugate vaccines is that the number of serotypes that can be included may be limited [112], and people who are vaccinated would remain susceptible to most of the serotypes not included in the vaccine. Most con-

Table 3. Number of adults in the United States with vaccine indications, according to various strategies.

<table>
<thead>
<tr>
<th>Age group, year(s)</th>
<th>US population, millions</th>
<th>According to current ACIP recommendations</th>
<th>Current ACIP plus all smokers</th>
<th>Current ACIP plus all African Americans</th>
<th>Current ACIP plus all persons aged ≥50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–49</td>
<td>127.6</td>
<td>15.3</td>
<td>45.9</td>
<td>30.2</td>
<td>15.3</td>
</tr>
<tr>
<td>50–64</td>
<td>38.4</td>
<td>11.1</td>
<td>17.3</td>
<td>13.8</td>
<td>38.4</td>
</tr>
<tr>
<td>65+</td>
<td>34.4</td>
<td>34.4</td>
<td>34.4</td>
<td>34.4</td>
<td>34.4</td>
</tr>
<tr>
<td>Total</td>
<td>200.4</td>
<td>60.8</td>
<td>97.6</td>
<td>78.4</td>
<td>88.1</td>
</tr>
</tbody>
</table>

NOTE. ACIP: Advisory Committee on Immunization Practices.

* Estimates were made using 1998 postcensus population estimates and results from the 1997 National Health Interview Survey. Estimates of the number of vaccine-eligible people do not include people with immunocompromising conditions.

* From [1].
jugate pneumococcal vaccines under evaluation contain capsular polysaccharides of 7 to 11 serotypes. Among preschool-aged children in the United States, the 7 most common serotypes (4, 14, 6B, 19F, 18C, 23F, and 9V) account for 80% of blood and CSF isolates in the United States, but only 50% of isolates among older children and adults [17, 23, 113]. Therefore, vaccine formulations that are based on the most prevalent serotypes among children may not provide optimal serotype coverage for prevention of pneumococcal infections in adults. However, immunogenicity and effectiveness are limited for polysaccharide vaccine for several pneumococcal serotypes that commonly cause serious infection in adults. If conjugate vaccines are more immunogenic against these serotypes in adults, overall effectiveness could theoretically be greater with conjugate vaccines, despite more limited serotype coverage [114].

**Possible future pneumococcal vaccines.** A promising approach for prevention of pneumococcal infections is to develop vaccines directed against noncapsular antigens common to all pneumococcal serotypes. Candidate antigens include a number of pneumococcal proteins: neuraminidase, autolysin, pneumolysin, pneumococcal surface proteins A and C (PspA and PspC), pneumococcal surface adhesin A (PsaA or 37-kDa protein), and putative proteinase maturation protein A (PpmA) [115–119]. These proteins could not only provide protection against all pneumococcal serotypes, but they could also induce a T cell–dependent response with immunologic memory. To date, only pneumolysin, PspA, and PsaA have been extensively examined for suitability as vaccine candidates, and only PspA has been tested in humans [120]. In this trial, vaccination with PspA led to an increase in circulating antibodies, and analysis of postvaccination serum samples showed increased binding to a variety of PspA and capsular types. Intranasal immunization of mice with PspA induced mucosal and systemic antibody responses, prevented pneumococcal colonization, and provided protection against systemic infection after intravenous, intratracheal, and intraperitoneal challenge [121]. A vaccine consisting of a live recombinant *Salmonella typhimurium* vaccine strain expressing pneumococcal PspA colonized gut-associated lymphoid tissues, spleens, and livers of orally immunized mice, induced serum and mucosal anti-PspA antibodies, and provided protection against challenge by a mouse-virulent *Streptococcus pneumoniae* [122].

An innovative approach to immunization involves introduction of a DNA plasmid carrying a protein-coding gene into the vaccine recipient’s own cells, which leads to expression of an antigen that elicits an immune response (so-called “DNA vaccines”). Such immunizing agents could be manufactured more easily and may be more stable during storage and distribution than vaccines composed of inactivated or attenuated microorganism, subcellular fractions, or recombinant proteins. Results of preliminary work on a pneumococcal DNA vaccine in laboratory animals are promising. Immunization of mice with a plasmid expressing PspA has been shown to induce a significant immune response and provided some protection against a challenge with intravenously administered serotype 3 *S. pneumoniae* [123]. However, a great deal of research remains to be done to clearly demonstrate safety, immunogenicity, and efficacy of DNA vaccines in humans.

**CONCLUSIONS**

Given the substantial morbidity and mortality caused by pneumococcal disease, periodic evaluations of the appropriateness of guidelines for use of pneumococcal vaccines are important. Several recent studies have provided information that is useful for the evaluation of current vaccine recommendations. The current recommendations for use of pneumococcal polysaccharide vaccines address most adults at high risk for invasive pneumococcal disease. African-American persons and smokers have recently been noted to have higher disease rates than do white persons and nonsmokers, and the increased risk in these groups is not specifically addressed by current recommendations. Discussions of changing vaccine recommendations should include whether the expected benefit from adding new groups to the recommendations outweighs the potential problems of cost and limited vaccine supply. Vaccine coverage is suboptimal, especially in minority groups and in high-risk people aged <65 years. Simplifying vaccine recommendations might improve coverage, as would promoting adoption of standing orders in nursing homes, hospitals, and clinics.

Questions of when and how often to revaccinate also are important barriers to making rational decisions about who should receive pneumococcal vaccine before the age of 65 years. Little new evidence exists to clarify these questions. We have learned that revaccination results in more local side effects, but the frequency of side effects—even with revaccination—is relatively low, and side effects are self-limited. Immune responses appear to be less robust after revaccination than they are after an initial dose of polysaccharide vaccine. We do not know why this occurs, or in the absence of defined immunologic correlates of protection, if a lower immune response means that protection provided by the vaccine is reduced after revaccination. Because risk of disease and death from pneumococcal infection increase with age, the timing of initial and subsequent vaccine doses may be critical. If significant hyporesponsiveness occurs after revaccination, people who receive vaccine before the age of 65 years may respond less well when given the vaccine again later in life, when the risk of serious infection is greatest. In other words, if we only have 1 opportunity to provide an effective vaccine, when should that vaccine be given? What if we have ≥2 opportunities? Unfortunately, we do not know how many opportunities we have, and this uncertainty inhibits our
ability to make evidence-based recommendations for revaccination.

A growing body of evidence indicates that an initial dose of pneumococcal polysaccharide vaccine provides protection against invasive disease in immunocompetent adults. Conversely, some analyses have found limitations in the performance of the vaccine. Recent studies of people who are immunocompromised have found few subsets of patients in which the vaccine appears to be effective. Recommendations for use of pneumococcal polysaccharide vaccine in HIV-infected people should be reevaluated with regard to vaccine safety, the timing of immunization in relation to achieving optimal antiretroviral therapy, and identification of HIV-infected people most likely to benefit from the vaccine.

Pneumococcal protein-polysaccharide conjugate vaccines are now ready for testing in adults, and common protein vaccines may be ready soon. Many people continue to develop serious pneumococcal disease in spite of vaccination; whether vaccines that might be available in the next decade can improve on the performance of the polysaccharide vaccine is unknown. New vaccines will need to be compared with the polysaccharide vaccine in terms of immune response, effectiveness, safety, duration of protection, and economic impact. The short-term challenge for prevention of pneumococcal disease in adults, however, is to improve delivery of pneumococcal polysaccharide vaccine to all people who can benefit from it.

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