EPIDEMIOLOGY OF INVASIVE PNEUMOCOCCAL DISEASE IN ADULTS

IMPLICATIONS FOR PREVENTION

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Streptococcus pneumoniae, a common gram-positive pathogen, often appears in diplococcal form.

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"The art of epidemiologic reasoning is to draw
sensible conclusions from imperfect data"
George W. Comstock, 1990

CONTENTS

DEFINITIONS OF ABBREVIATIONS

ABCs	Active Bacterial Core Surveillance
ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired Immunodeficiency Syndrome
ASD	Adult and adolescent spectrum of HIV disease project
BRFSS	Behavioral Risk Factor Surveillance System
CD4	CD4+ T lymphocyte count
CDC	Centers for Disease Control and Prevention
CFR	Case-fatality ratio
CI	Confidence interval
CSF	Cerebrospinal fluid
DRSP	Drug-resistant *Streptococcus pneumoniae*
EIP	Emerging Infections Program Network
ETS	Environmental tobacco smoke
MDRSP	Multi-drug resistant *Streptococcus pneumoniae*
MIC	Minimum inhibitory concentration
MMWR	Morbidity and Mortality Weekly Report
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IPD	Invasive pneumococcal disease
LTCF	Long-term care facility
NCCLS	National Committee for Clinical Laboratory Standards
NCID	National Center for Infectious Diseases
NHIS	National Health Interview Survey
OR	Odds ratio
PAR	Population attributable risk
PPV	Pneumococcal polysaccharide vaccine
RDD	Random-digit dialing
RR	Risk ratio, relative risk or rate ratio
RCT	Randomised controlled trial
VE	Vaccine efficacy

LIST OF ORIGINAL PUBLICATIONS

This thesis includes the following original papers which are referred to in the text by Roman numerals (I to III). In addition, unpublished data are presented.

I J. Pekka Nuorti M.D., Jay C. Butler M.D., Monica M. Farley M.D., Lee H. Harrison M.D., Allison McGeer M.D., Margarette S. Kolczak Ph.D., Robert F. Breiman M.D., and the Active Bacterial Core Surveillance Team. Cigarette smoking and invasive pneumococcal disease. N Engl J Med 2000;342:681–9.

II J. Pekka Nuorti, M.D., Jay C. Butler, M.D., Lisa Gelling, M.P.H., Jacob L. Kool, M.D., M.S., Arthur L. Reingold, M.D., Duc J. Vugia, M.D., M.P.H. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000;132:182–190.

III J. Pekka Nuorti, M.D., Jay C. Butler, M.D., James M. Crutcher, M.D., M.P.H., Ramon Guevara, M.P.H., David Welch, Ph.D., Patricia Holder, M.T., John A. Elliott, Ph.D. An Outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. N Engl J Med 1998;338:1861–8.

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 (1). The pathogenesis, treatment and prevention of infections caused by *S. pneumoniae* have been studied for more than 100 years (2), but important developments have occurred in the epidemiology of invasive pneumococcal disease during the past decade. The focus of this study is in the epidemiology and prevention of invasive pneumococcal disease (i.e. infection of normally sterile sites) in adults.

The reasons for recent developments include several demographic and epidemiologic factors. *First*, because the available data on conditions predisposing adults to pneumococcal infection have come from studies which were not adjusted for multiple risk factors (3, 4), it has been unclear which specific underlying conditions increase the risk of pneumococcal disease and what are the attributable risks associated with these conditions in different adult populations. It has also been unclear why otherwise healthy, nonelderly adults get invasive pneumococcal infections. *Second*, the increasing number of persons who are immunocompromised because of HIV/AIDS and susceptible to pneumococcal infection has had a major impact on the disease burden and clinical characteristics of pneumococcal disease in many areas (5, 6). *Third*, the prevalence of beta-lactam resistance among invasive isolates of *S. pneumoniae* is increasing in the United States and many European countries, as is the prevalence of strains resistant to multiple classes of drugs (7, 8). The emergence of antimicrobial resistance has made treatment of pneumococcal infections more difficult (9, 10). *Fourth*, the aging of the population in North American and European countries contributes to an increasing number of persons susceptible to pneumococcal infection including those residing in institutions such as nursing homes. *S. pneumoniae* is the most common cause of pneumonia and bacterial meningitis in the elderly (11, 12), and the growing institutionalized population has resulted in an increased potential for spread of drug-resistant strains as well as for pneumococcal outbreaks. An increase in pneumonia death rates in the elderly was recently reported (13).

The above developments highlight the need for updated epidemiologic data and new strategies for prevention of pneumococcal disease in adults. The purpose of this study was to investigate the impact of the recent developments in the epidemiology of invasive pneumococcal disease in adults. We also assessed the public health policy implications of these epidemiologic trends for prevention of pneumococcal disease in the U.S. and other industrialized countries, in particular through the use of pneumococcal polysaccharide vaccine. A clear understanding of which persons are at increased risk of infection and the attributable disease burden are needed for effective and efficient use of pneumcoccal vaccines and implementing other preventive measures in adults. These data are also needed for assessing the potential impact of prevention programs. The three studies (I to III) included in this thesis were completed after the publication of the recommendations of the Advisory Committee on Immunization Practices (ACIP) concerning prevention of pneumococcal disease (1), and provide new information that update the epidemiologic data included in the statement. Because these studies were conducted in the U.S. and because the epidemiologic features of pneumococcal disease (e.g., reported incidence rates and prevalence of drug resistance) and distribution of risk factors in the population may differ in other countries, the overall focus is on the epidemiologic situation in the U.S.

REVIEW OF LITERATURE

1. Descriptive epidemiology of invasive pneumococcal disease

1.1. Incidence

Severe pneumococcal infections result from dissemination of bacteria to the bloodstream and the central nervous system. "Invasive pneumococcal infection" is defined as an illness in which *S. pneumoniae* is isolated from blood, cerebrospinal fluid (CSF) or other normally sterile body site. More than 90% of documented invasive pneumococcal infections are bacteremias and approximately 5–10% of the patients with invasive pneumococcal disease have meningitis (14). A small proportion of patients (1–2%) have septic arthritis, purulent pericarditis or peritonitis. Most adults with pneumococcal bacteremia also have pneumonia; 60–87% of pneumococcal bacteremias are associated with pneumonia (4, 15, 16).

Data from community-based studies indicate that overall annual incidence of invasive pneumococcal disease in the United States is an estimated 16–30 cases per 100,000 population; the rate is higher for persons aged ≥65 years (42–83 cases per 100,000 population) and for children aged ≤2 years (160 cases per 100,000 population) (3, 17-20) (Table 1, Figure 1). Few studies have reported incidence rates for nonelderly adults (i.e, those aged 18-64 years) (18, 20, 21). In this age group, the reported rates are generally low, approximately 10 cases per 100,000 population (Table 1). The Centers for Disease Control and Prevention's (CDC) multistate Active Bacterial Core surveillance (ABCs) provides comparable national data on the incidence of invasive pneumococcal disease by using standardized, population-based surveillance methods in 7 regions representing a geographically diverse population of more than 16 million (22, 23). In 1997, the overall incidence in these regions was 24 cases per 100,000 population. However, the rates varied widely by geographical area (from 19 in Minnesota to 35 cases per 100,000 population in California (24)).

In the U.S., the risk for acquiring bacteremia is lower among white persons than among persons in certain other racial/ethnic groups (i.e., blacks, Alaskan Natives, and American Indians). Black adults living in the U.S. have a threefold to fivefold higher overall incidence of bacteremia (49–58 cases per 100,000 population) than whites (3, 17–19, 21).

Follwing succesful control of *Haemophilus influenzae* type b (Hib) meningitis in children by vaccination, *S.pneumoniae* has become the most common cause of bacterial meningitis in the U.S. The estimated overall annual incidence of pneumococcal meningitis is one to two cases per 100,000 population (12). The incidence of pneumococcal meningitis is highest among children

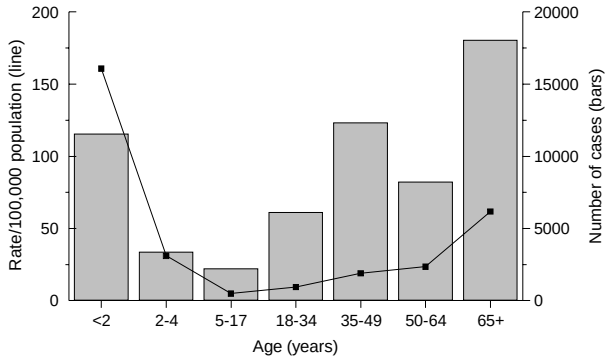

Figure 1. Age-specific incidence and estimated annual number of invasive pneumococcal infections, United States, 1997. Projected from CDC Active Bacterial Core Surveillance (23).

Table 1. Incidence of invasive pneumococcal disease and case-fatality ratios in recent studies conducted in the U.S.

Study site (reference)	Study period	Annual incidence/ 100,000 pop			Case-fatality ratio (%)		
		all ages	adults 18-64 years (subgroup)	≥65 years	all ages	adults 18-64 years (subgroup)	≥65 years
Oklahoma City, OK (Istre)	1984	16	—	55	—	—	—
Charleston, SC (Breiman)	1986–87	19 *	—	53	18	23 (19-64 yrs)	43
Monroe County, NY (Bennet)	1985–89	19 *	9 (20-64 yrs)	57	15	—	29
Oklahoma City,OK (Haglund)	1989–90	17	—	42	15	—	—
Franklin County, OH (Plouffe)	1991–93	19 *(≥18 yrs)	10	83	19	11	26 (≥65 yrs) 22 (65-84 yrs) 38 (85+)
Metropolitan Atlanta, GA (Hofmann)	1994	30	—	74	—	—	—
Dallas County, TX (Pastor)	1995	22	7 (20-29 yrs) 19 (30-64 yrs)	80	16	14 (30-64 yrs)	30
ABCs multistate, 7 areas† (CDC)	1997	24	16 9 (18-34 yrs) 19 (35-49 yrs) 24 (50-64 yrs)	62	9	9 6 (18-34 yrs) 9 (35-49 yrs) 12 (50-64 yrs)	18

* Includes pneumococcal bacteremias only.
† The CDC Active bacterial core surveillance (ABCs) network conducts population-based surveillance for invasive pneumococcal disease with standardized methods in the following areas: California (San Francisco County), Connecticut, Georgia (20 county metropolitan Atlanta area), Mayland (6 county Baltimore area), Minnesota (7 county Twin Cities area), Oregon (3 county Portland area),Tennessee (5 urban counties). In 1997, the surveillance areas represented a geographically diverse population of more than16 million (23).

aged 6–24 months and persons aged ≥65 years; rates for blacks are twice as high as those for whites and Hispanics.

1.2. Disease burden

Each year in the U.S., pneumococcal disease accounts for an estimated 2,600 cases of meningitis, 63,000 cases of bacteremia and 100,000–135,000 hospitalizations for pneumonia (12, 23, 25). Although the rates of invasive pneumococcal disease are lower in nonelderly adults than in young children and the elderly, the largest absolute number of infections occur in nonelderly adults, who make up the largest part of the population (Figure 1). In the Active Bacterial Core population-based surveillance in 1997 43% of all identified cases of invasive pneumococcal disease occurred in persons aged 18–64 years; 29% of cases occurred in persons aged ≥65 years (23). Approximately one third of the cases among nonelderly adults occured in immunocompromised persons. Projected to the whole U.S. population, these figures represent approximately 26,700 cases annually in persons aged 18–64 years and 18,000 cases in persons aged ≥65 years (Figure 1). Adults aged 18–64 years accounted for 52% of 5837 cases of community-acquired invasive pneumococcal pneumonia requiring hospitalization during 1995–97 (25).

Although isolation of *S. pneumoniae* from blood is virtually 100% specific for diagnosing pneumococcal infections, the sensitivity of blood cultures in detecting pneumococcal infections is low. Because only approximately 10% to 25% of adult patients with pneumococcal pneumonia have concomitant bacteremia (1), surveillance studies of invasive pneumococcal infections underestimate the total disease burden due to *S. pneumoniae.* However, the precise incidence of pneumococcal pneumonia without bacteremia is difficult to ascertain because routine diagnostic tests are insufficiently specific and sensitive. Nevertheless, *S pneumoniae* is the most common cause of community-acquired bacterial pneumonia requiring hospitalization in adults accounting for approximately 30–50% of all pneumonia cases (2).

1.3. Mortality

Pneumonia and influenza are the sixth leading cause of death in the United States (26). In 1997, invasive pneumococcal infection caused more than 6000 deaths (2.3 deaths per 100,000

population) in the U.S. (23), accounting for more deaths than any other vaccine-preventable bacterial disease (27). Over half of these deaths occurred in persons older than 65 years of age and in adults aged 18–64 who had underlying illnesses considered to be pneumococcal vaccine indications (23). In 1996, an estimated 7000–12,500 deaths occurred from pneumococcal pneumonia requiring hospitalization (25).

Case-fatality ratios are highest for meningitis and bacteremia, and among the elderly and patients who have underlying medical conditions. Before the availability of antibiotics and serum therapy more than 80% of patients with pneumococcal bacteremia died (28). Mortality and complications decreased dramatically with increasing use of penicillin as therapy for pneumococcal infections. However, the overall case-fatality ratio for pneumococcal bacteremia is still 15–20% among all adults (i.e., persons aged ≥18 years) despite appropriate antimicrobial therapy and intensive medical care (Table 1). Among elderly patients, this ratio is approximately 20% in those aged ≥65 years and approaches 40% in persons aged ≥85 years (3, 17, 18, 20, 25, 29, 30). An overall case-fatality ratio of 36% was recently documented for adult inner-city residents who were hospitalized for pneumococcal bacteremia (16). The case-fatality ratio of invasive pneumococcal disease among non-elderly adults aged 18–64 years is approximately 10% (23, 25; Table 1). A recent surveillance analysis of epidemiologic factors affecting mortality from community-acquired pneumococcal pneumonia requiring hospitalization, confirmed older age and underlying disease as the most important factors influencing death from pneumococcal pneumonia (25).

2. Factors influencing the risk of invasive pneumococcal infection

Several factors have been recognized as increasing the risk of invasive pneumococcal infection (Table 2). However, the available data on conditions predisposing nonelderly adults to pneumococcal infection have come from clinical case-series and community-based surveillance studies and were not adjusted for multiple risk factors. In recent population-based studies, about one third of cases of invasive pneumococcal disease in adults occurred in persons without recognized risk factors (20, 31). In multistate surveillance conducted by the CDC from 1995 to 1998, 41% of over 3000 patients aged 18–64 years with invasive pneumococcal disease did not have a condition recognized as an indication for pneumococcal vaccine (CDC, unpublished data; 1). Characteristics associated with pneumococcal disease among adults, particularly behavioral and socioeconomic factors, have not been previously evaluated in controlled, population-based studies.

2.1. Host factors

2.1.1. Immunocompetent persons

The rates of invasive pneumococcal infection are highest in children aged <2 years and in adults aged ≥65 years. In adults, the incidence of invasive disease begin increasing after age 50 years and then increase sharply after age 65 years (32). In persons aged ≥85 years, the annual incidence is generally over 100 cases per 100,000 population. In one study, age was independently associated with the risk of pneumococcal infections even when controlling for other risk factors (33). Rates of disease are generally higher in men than in women (3, 20, 21).

Several community-based studies have found that black persons have a threefold to fivefold higher rate of invasive pneumococcal disease than white persons (3, 12, 18). However, the difference in incidence is greatest in children and non-elderly adults. In elderly persons, the rates of invasive pneumococcal disease are only slightly higher in blacks than whites (32). In a recent study conducted in Baltimore, black race was independently associated with increased incidence of pneumococcal infection among persons younger than 30 years but not in older persons (31).

Many chronic medical conditions have been associated with increased risk of pneumococcal disease because these conditions have been observed in disproportionately high numbers of patients with pneumococcal disease (3, 4, 21), (Table 2). Persons who have certain underlying medical conditions may therefore be at increased risk for developing pneumococcal infection or experiencing severe disease and complications. Although the strength of evidence documenting the increased risk associated with each specific condi-

Table 2. Factors associated with increased risk of pneumococcal disease in adults

Host factors

Immunocompetent persons

- -Increasing age
- -Race (black, American Indian, Alaskan Native)
- -Male sex
- -Chronic medical conditions
  - chronic cardiovascular disease
  - chronic pulmonary disease
  - diabetes mellitus
  - functional or anatomic asplenia
  - alcoholism
  - chronic liver disease
  - cerebrospinal fluid leaks

Immunocompromised persons

- -HIV infection
- -chronic renal failure
- -nephrotic syndrome
- -cancer, particularly hematological malignacies
- -organ or bone marrow transplant
- -hypogammaglobulinaemia
- -immunosuppressive chemotherapy, including corticosteroids

Other factors

Socioeconomic

- -Low median household income (low socioeconomic status)
- -Poverty
- -Crowding (residence in shelters for homeless)

Environmental

- -Preceding viral respiratory illness (influenza and other)
- -High air pollution levels
- -Winter season
- -Residence in an institution (military training camps, prisons, nursing homes)

Behavioral

- -Smoking
- -Heavy alcohol use

tion varies, these chronic medical conditions are considered as indications for pneumococcal vaccination in non-elderly adults (1).

Adults at increased risk for invasive pneumococcal disease include those who are generally immunocompetent but who have chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (in particular, chronic obstructive pulmonary disease [COPD] or emphysema), or chronic liver diseases (e.g., cirrhosis). The incidence of invasive pneumococcal disease is particularly high in persons with chronic lung conditions (503 cases/100,000 person-years), probably because of defective mucociliary clearance mechanisms (21). Diabetes mellitus often is associated with cardiovascular or renal dysfunction, which may increase the risk for severe pneumococcal illness (14). The incidence of pneumococcal infection is increased for persons who have liver disease as a result of alcohol abuse (4, 21). 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. A small, clinic-based, retrospective case-control study of white, chronically ill, elderly male veterans found that congestive heart failure, COPD, dementia and institutionalization were associated with increased risk of invasive pneumococcal disease (34). Persons with functional or anatomic asplenia (e.g., sickle cell disease or splenectomy) have extremely high rates of pneumococcal infection, because this condition leads to reduced clearance of encapsulated bacteria from the bloodstream (35) and increased risk of fulminant pneumococcal sepsis.

2.1.2. Immunocompromised persons

The risk of pneumococcal infection is high in persons who have decreased responsiveness to polysaccharide antigens or accelerated 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) solid organ or bone marrow transplantation; c) therapy with alkylating agents, antimetabolites, or systemic corticosteroids (36); or d) chronic renal failure or nephrotic syndrome (14).

2.3. Socioeconomic factors

The relation of socioeconomic status and risk of pneumococcal infections is complex and poorly understood. In ecological comparisons, the observed rates of pneumococcal disease have been higher in low-income census tracts than in those with high incomes (3, 21, 37). However, the association with low median household income (an indicator of low socioeconomic status) may be confounded by over-representation of blacks among persons with low incomes. In metropoli-

tan Atlanta, the rates of invasive pneumococcal disease were up to 10-fold higher in blacks than in whites among people living in the lowest household income census tracts. However, the difference between races was smaller in areas with higher household incomes, and no difference was found between races among people living in highest income areas (37).

2.4. Environmental factors

Pneumococcal pneumonia is a recognized complication of influenza epidemics. Preceding or co-existing upper respiratory illness may increase the risk of subsequently developing invasive pneumoccocal disease (38). The rates of invasive pneumococcal disease and the recovery of viruses from clinical specimes submitted from patients with respiratory tract infections in the same community were compared in an ecological analysis (39). Among adults, the monthly number of pneumococcal bacteremias was correlated with the number of influenza or respiratory syncytial virus isolations. This report also suggested another ecological association of pneumococcal disease with air pollution levels. In an outbreak of pneumococcal pneumonia in a long-term care facility, preceding parainfluenza virus 1 infection was associated with pneumonia (40).

Among children, parental smoking has been linked with pneumococcal disease (41). Among adults, exposure to environmental tobacco smoke (ETS) has also been implicated as a risk factor for meningococcal disease (42), but the relation between ETS exposure and invasive pneumococcal disease has not been evaluated previously. In children, invasive pneumococcal disease has been associated with day care center attendance (43, 44) and lack of breastfeeding (45), but it has been unknown whether living with young children who attend day-care centers increases the risk of pneumococcal infection in adults.

2.5. Behavioral factors

Cigarette smoking and exposure to environmental tobacco smoke increase the risk of many respiratory infections including bacterial pneumonia, meningococcal disease and legionnaires disease (46–48). Smokers accounted for approximately half of otherwise healthy adult patients with invasive pneumococcal disease in two recent community-based surveillance studies (20, 21). Smoking is also the most common cause of COPD. Current smoking was previously identified as an independent risk factor for pneumococcal disease among elderly veterans in a small, hospital-based case-control study (34). Heavy alcohol use has been identified as one of the most common underlying conditions among patients with pneumococcal infections in population-based surveillance studies (4, 21). Between 26% and 32% of adult patients were reported as heavy alcohol users, and the incidence of invasive pneumococcal disease among heavy alcohol users has been reported to be 62 cases/100,000 person-years (21), similar to that among elderly persons.

3. HIV and pneumococcal disease

Streptococcus pneumoniae is the leading cause of community-acquired bacterial pneumonia and bacteremia among HIV-infected persons (46, 49). Persons infected with HIV currently account for at least 40% of all adult cases of invasive pneumococcal disease in many U.S. medical centers (50, 51). Pneumococcal disease can occur early in the course of HIV infection, before onset of other opportunistic infections specifically associated with AIDS (5, 52, 53), and recurrent infection is common (49, 53). The precise deficits in the immune system that predispose HIV-infected persons to pneumococcal infections are not well characterized, but progressive loss of the ability to produce specific functional antibodies is probably a contributing factor (49).

In studies conducted in the 1980's, the annual attack rate of pneumococcal bacteremia in persons who had AIDS was reported to be as high as 1% (940 cases per 100,000 population) (5, 6), but no detailed data have been available concerning rates among different demographic groups of AIDS patients. Recent reports have shown substantial decreases in the incidence of AIDS-related opportunistic illnesses due to increased use of highly active antiretroviral therapy (54). However, no population-based data have been previously available regarding the secular trends in the incidence of pneumococcal disease among AIDS patients.

4. Drug-resistant *Streptococcus pneumoniae*

Strains of drug-resistant *S. pneumoniae* (DRSP) have become increasingly common in the United States and in other parts of the world (7, 8, 55). Nationally, the overall prevalence of DRSP increased from 14% of the isolates tested in 1993-94 to 25% in 1997 (8, 22). However, the prevalence of DRSP varies widely, ranging from approximately 10% to 35% between geographic regions. In some areas, as many as 35% of pneumococcal isolates have been reported to be nonsusceptible to penicillin (19, 56, 57). The term "nonsusceptible" refers to both intermediate (I, minimum inhibitory concentration [MIC]=0.1–1.0 μg/mL) and resistant (R, MIC >2 μg/mL) isolates. Many penicillin-nonsusceptible pneumococci are also nonsusceptible to other antimicrobial drugs (e.g., erythromycin, trimethoprim-sulfamethoxazole, and extended-spectrum cephalosporins) and some pneumococci are multidrug-resistant. High-level penicillin resistance, macrolide resistance and multidrug-resistance often complicate the management of pneumococcal infection and make choosing empiric antimicrobial therapy for suspected cases of meningitis and pneumonia increasingly difficult (9, 10).

Treatment failures and fatal outcomes have been reported in patients with meningitis caused by *S. pneumoniae* nonsusceptible to beta-lactam antibiotics (58, 59), and who had received a beta-lactam drug as therapy. However, the relation of antimicrobial resistance with the clinical course and outcome of other pneumococcal infections is not clearly defined. One study of adults who had pneumococcal pneumonia and bacteremia found that mortality was not increased in patients infected with penicillin nonsusceptible strains, even when treated with penicillin or ampicillin (60). However, many of the patients in this study were infected with *S. pneumoniae* strains that had intermediate susceptibility to penicillin. In a recent study, mortality was not elevated in most infections caused by beta-lactam-resistant *S. pneumoniae* (25). However, when deaths during the first 4 hospital days were excluded from the analysis, increased mortality was associated with high level resistance to penicillin and cefotaxime. In another study, nonsusceptibility to cefotaxime was not associated with increased mortality in patients with pneumococcal meningitis (61). In addition, 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 (20).

Drug-resistant *S. pneumoniae* infections were initially reported in children. High rates of nonsusceptible infections continue to occur in this group (7, 19, 56, 57), but data from CDC population-based surveillance indicate that pneumococcal drug resistance has become a common problem also in elderly persons (62). In the U.S., the prevalence of drug-resistant strains in persons aged ≥65 years has increased dramatically, and in some areas, nearly 40% of sterile-site isolates from persons aged ≥65 years, were intermediate or resistant to penicillin. During 1995 and 1996, more than 30% of all penicillin-resistant infections occurred in persons aged ≥65 years.

5. Epidemic pneumococcal disease

Most cases of pneumococcal infection occur sporadically, and during the antibiotic era, outbreaks caused by a single pneumococcal serotype have been rare. Outbreaks of pneumococcal disease occur mainly in closed populations and institutions such as hospitals (63), military camps (38), shelters (64, 65), jails (66), day care centers (67, 68), and nursing homes (69, 70). In these settings, susceptible persons are exposed to crowding and other persons who may be colonized with *S. pneumoniae* or viral respiratory pathogens. Stress factors, such as sleep and calory deprivation and insufficient ventilation may further increase risk of transmission and disease in these conditions (38, 66).

Drug-resistant infections have also been associated with certain institutional settings, particularly day care centers (71–73), hospitals (74, 75), and a pediatric chronic care facility (76). Epidemics of drug-resistant pneumococcal disease have not been previously reported among adults in the United States. However, pneumococcal serotype 23F, one of the most common multidrug-resistant serotypes in the United States (77), has been associated with outbreaks in day-care centers (57, 72) and a pediatric chronic care facility (76).

6. Pneumococcal polysaccharide vaccine

The first commercially available 14-valent pneumococcal polysaccharide vaccine was licensed in 1977. In 1983, a reformulated 23-valent vaccine replaced the 14-valent vaccine. This vaccine includes 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) (1). 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 (78–80). 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, 19).

6.1. 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 levels, develops within 2–3 weeks in ≥80% of healthy young adults (81); however, immune responses may not be consistent for all 23 serotypes in the vaccine. Certain vaccine components are more immunogenic and appear to be more protective, whereas others (e.g., 6B and 23F) are poorly immunogenic (2). Antibody responses also occur in the elderly and in patients who have alcoholic cirrhosis, COPD, and insulin-dependent diabetes mellitus (2, 81); however, antibody levels and responses to individual antigens may be lower among such persons than among healthy young adults.

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 levels than those observed in healthy adults (1, 2).

Patients who have AIDS have a diminished antibody response to pneumococcal vaccine (35, 49). The reduction in antibody levels corresponds to the degree of immunosuppression; some asymptomatic HIV-infected persons or those with only generalized lymphadenopathy respond to the 23-valent polysaccharide vaccine (82). HIV-infected patients with CD4 T-lymphocyte counts <500 cells/mm^3 often have lower responses to pneumococcal vaccination than either HIV-infected persons with higher CD4 counts or persons who are not HIV-infected (83).

6.2. 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 (84, 85). Antibody concentrations decline more rapidly (after 3–5 years or 5–10 years) in some groups, such as elderly persons (86), and persons with certain underlying illnesses (e.g., persons who have undergone splenectomy, patients with renal disease requiring dialysis, and persons who have received transplants (2, 87–89). Low or rapidly declining antibody levels after vaccination also have been noted among patients with Hodgkins disease (90) and multiple myeloma (91).

However, the levels of antibodies that correlate with clinical protection against pneumococcal infection have not been clearly defined. The quantitative measurements of antibody concentrations do not account for the quality of the antibody being produced and the level of functional immune response. Tests assessing functional immune responses to vaccination, such as opsonophagocytic activity and the quality of antibodies produced (i.e., antibody avidity for pneumococcal antigens) may be more relevant for evaluating response to pneumococcal vaccination and for predicting clinical protection (92–94).

6.3. Vaccine efficacy and vaccination effectiveness in adults

Several clinical trials have been conducted evaluating the efficacy of pneumococcal polysaccharide vaccine against pneumonia and pneumococcal bacteremia. In addition, multiple case-control and serotype prevalence studies have assessed pneumococcal vaccine effectiveness against invasive disease. Findings from studies of pneumococcal vaccine efficacy and effectiveness are summarized in Table 3. It is important to recognize how these studies differ with respect to design, population studied, and outcome evaluated because these differences may explain some of the contradictory findings.

6.3.1. Efficacy against nonbacteremic pneumococcal disease

Most clinical trials demonstrating efficacy against pneumococcal pneumonia were conducted among young healthy persons who were in special situations placing them at risk for epidemic 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 (95).

In non-epidemic situations in industrialized countries, however, the rates of pneumococcal disease in adults are highest in the elderly and 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 (96, 97). In one clinical trial among U.S. veterans at increased risk of pneumococcal disease which did not demonstrate efficacy (97), the primary outcome was pneumococcal pneumonia or bronchitis diagnosed by recovery of pneumococcus from the sputum. The definition and clinical significance of pneumococcal bronchitis are uncertain, and the statistical power of this study to detect protection against bacteremic infection was limited (98). Of 2,354 randomized patients and 71 episodes of pneumococcal infection, only two cases of pneumococcal bacteremia were documented.

A meta-analysis evaluating pneumococcal polysaccharide vaccine efficacy by combining the results of nine randomized, controlled trials conducted between 1976 and 1987, did not demonstrate a protective effect for non-bacteremic pneumonia among persons in high-risk groups (99). However, these clinical trials may have lacked sufficient statistical power to detect a difference in the incidence of laboratory-confirmed, nonbacteremic pneumococcal pneumonia be-

Table 3. Studies of pneumococcal polysaccharide vaccine efficacy and effectiveness [modified from (1)]

Study, publication year	Population studied	Design	Type of pneumococcal infection studied	% Efficacy or effectiveness (95% CI)†
MacLeod, 1945	Young U.S. military recruits	Clinical trial: 4-valent vaccine	Pneumonia	100 (79–100)
Kaufman, 1947	Long-term care facility residents (80% >60 years old) in New York City	Clinical trial 3-valent vaccine	Pneumonia	92 (72–98)
		3-valent vaccine	Bacteremia	93 (45–100)
Austrian, 1976	Young adult South African gold miners	Clinical trial: 13-valent vaccine	Pneumonia	79 (65–88)
		13-valent vaccine	Bacteremia	82 (66–92)
Smit, 1977	Young adult South African gold miners	Clinical trial: 6-valent vaccine	Pneumonia	76 (52–89)
		12-valent vaccine	Pneumonia	92 (49–100)
Riley, 1977	Persons >10 years old in Papua New Guinea	Clinical trial: 14-valent vaccine	Bacteremic pneumonia	86 (<0–99)
Shapiro, 1984	Patients admitted to Yale-New Haven Hospital	Case-control	Invasive infection	67 (13–87)

Simberkoff, 1986	Veterans at risk for pneumococcal infection due to chronic medical conditions	Clinical trial: 14-valent vaccine	Pneumonia/bronchitis	<0	(<0–45)
Bolan, 1986	Patients with pneumococcal bacteremia or meningitis at institutions participating in national surveillance	Indirect cohort	Bacteremia and/or meningitis	64	(47–76)
Forrester, 1987	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	Patients admitted to one of five participating hospitals in eastern Pennsylvania	Case-control	Invasive infection	70	(37–86)
Shapiro, 1991	Patients admitted to one of 11 participating hospitals in Connecticut	Case-control	Invasive infection		
			All patients	56	(42–67)
			Immunocompromised§	21	(<0–60)
			Immunocompetent¶	61	(47–72)
			Age 65–74 yrs	80**	(51–92)
	Patients with invasive pneumococcal infection at participating hospitals in Connecticut	Indirect cohort	Invasive infection		
			All patients	48	(3–72)
			Immunocompromised§	<0	(<0–64)
			Immunocompetent¶	62	(24–81)
Butler, 1993	Patients with pneumococcal bacteremia or meningitis at institutions participating in national surveillance	Indirect cohort	Bacteremia and/or meningitis		
			All patients	57	(45–66)
			Immunocompromised††	49	(22–67)
			Immunocompetent§§	49	(23–65)
			Age ≥65 yrs¶¶	75	(57–85)
Farr, 1995	Patients aged ≥2 years with pneumococcal bacteremia and chronic illness or those aged ≥65	Matched Case-control	Bacteremia	81	(34–94)
Koivula, 1997	Persons aged ≥60 years in Finland	Clinical trial	Pneumonia		
			All patients	15	(-43–50)
			High risk patients	59	(6–82)
Örtqvist, 1998	Non-immunocompromised patients aged 50-85 years who were discharged from hospital after treatment for pneumonia in Sweden	Clinical trial	Pneumonia	-28	(-150–34)
Honkanen, 1998	Persons aged ≥65 years in North Finland	Clinical trial	Pneumonia	-20	(-90–20)
			Bacteremia	60	(-40–90)

* for prevention of infection due to pneumococcal serotypes included in vaccine
† if not provided in the published report, 95% CI were calculated using Epi-Info version 5.01a (CDC/World Health Organization, Atlanta)
§ includes persons with anatomic or functional asplenia, dysgammaglobulinemia, hematologic malignancy, metastatic cancer, or systemic lupus erythematosus
¶ includes persons with chronic pulmonary disease, alcoholism, diabetes melitus, chronic renal failure, or congestive heart failure, and persons ≥55 years old without underlying illness
** efficacy during first 3 years after vaccination
†† includes persons with sickle cell disease, anatomic asplenia, dysgammaglobulinemia, hematologic malignancy, chronic renal failure, nephrotic syndrome, history of organ transplant, systemic lupus erythematosus
§§ includes persons with chronic obstructive pulmonary disease, asthma, alcoholism, diabetes mellitus, coronary vascular disease, congestive heart failure, or cirrhosis, and persons ≥65 years old without underlying illness
¶¶ includes person ≥65 years old with coronary vascular disease, congestive heart failure, chronic obstructive pulmonary disease, asthma, diabetes mellitus, or no underlying illness

tween the vaccinated and nonvaccinated study groups (98). In addition, the ability of these studies to evaluate vaccine efficacy was limited because of the lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. Nevertheless, the meta-analysis concluded that pneumococcal polysaccharide vaccine is efficacious in reducing the frequency of bacteremic pneumococcal pneumonia among adults in low-risk groups.

Three prospective clinical trials of pneumococcal polysaccharide vaccine efficacy in elderly persons have been published recently (100–102), (Table 3). Because of the high disease burden due to pneumococcal pneumonia, each of these studies evaluated this condition as the outcome. All three used serologic tests such as detection of pneumolysin immunocomplexes or a two-fold or greater rise in antibody to pneumolysin for diagnosis. However, the predictive value of these innovative diagnostic tests is currently unknown and they have not been widely accepted as reliable methods for diagnosing community-acquired pneumococcal pneumonia (103). Misclassification of pneumonia due to etiologic agents other than *S. pneumoniae* as pneumococcal would result in an underestimation of vaccine efficacy (i.e. the vaccine would not be expected to protect against non-pneumococcal pneumonia).

A Swedish study assessing vaccine efficacy in persons aged 50–85 years who had been discharged from hospital after treatment for pneumonia did not demonstrate a reduction in pneumococcal pneumonias (101). In addition to uncertainty of the specificity of the case definition used for pneumococcal pneumonia (60% of cases were diagnosed by serologic methods), this study had other limitations (104). The study population appears unrepresentative of the population for whom the vaccine is recommended in the age-group studied. The selected study population had an unusually high rate of pneumonia and bacteremic disease (600/100,000 in the placebo group) and represented only <1% of all middle aged and elderly persons (103).

One randomized trial conducted in Finland suggested that the vaccine may be efficacious in a subgroup of elderly persons who had underlying medical conditions, but the overall results of the trial did not show efficacy against pneumococcal pneumonia (100). Another large Finnish study of elderly persons also did not demonstrate protection against pneumonia, although the authors suggest that their findings may be consistent with the previously reported protective efficacy figures against pneumococcal bacteremia (102). Because all three recent trials may have had methodological limitations, including an unspecific case-definition for pneumococcal pneumonia which may have biased the findings of these studies towards the null, and lack of statistical power to assess effectiveness against pneumococcal bacteremia (102), it has been argued that the results of these three trials should be considered inconclusive, rather than negative, in evaluating vaccine efficacy against nonbacteremic pneumococcal pneumonia (103).

6.3.2. Effectiveness against invasive disease

Although randomized controlled trials are the most scientifically rigorous method of assessing vaccine efficacy, the large sample size required for adequate statistical power makes such studies expensive and impractical, and the conduct of such studies may have substantial ethical and logistic problems (105). Observational studies, such as case-control and cohort studies provide a practical means for achieving adequate statistical power, and large cohort studies provide information on effectiveness among specific risk groups. These designs evaluate the effectiveness of vaccination under real world conditions but may be more susceptible to selection bias, misclassification and confounding than randomized clinical trials.

The overall pneumococcal polysaccharide vaccination effectiveness in case-control studies generally has ranged from 56% to 81% (106–109; Table 3). Only one case-control study did not document effectiveness against bacteremic disease (110). The limitations of this study included small sample size and incomplete ascertainment of vaccination status of patients potentially resulting to misclassification. 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 (98).

A serotype prevalence (indirect cohort) study based on CDC's pneumococcal surveillance

system demonstrated a 57% (95% CI, 45– 66%) overall protective effectiveness against invasive infections caused by serotypes included in the vaccine among persons aged ≥6 years (79). Vaccine effectiveness between 65% to 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, effectiveness in each of these groups could not be accurately measured because of the small numbers of unvaccinated patients with these illnesses.

6.4. Cost-effectiveness of pneumococcal vaccination

The currently available 23-valent polysaccharide vaccine substantially reduces the risk of invasive bacteremic disease among the immunocompetent adult groups currently targetted for vaccination, but it is less effective in protecting against other types of pneumococcal infections and has not been demonstrated to reduce the risk for non-bacteremic pneumococcal pneumonia in elderly persons. Results of a recent cost-effectiveness analysis which was based on the efficacy of polysaccharide vaccine for the prevention of bacteremia, suggest that vaccination of persons aged ≥65 years with pneumococcal polysaccharide vaccine is not only cost-effective, but may be cost-saving under certain assumptions (111). These assumptions included a disease incidence of 50/100,000 persons, mortality of 30%, as well as estimates for age-specific effectiveness of vaccination and duration of protection (108), frequency of severe adverse events and medical care costs. In the U.S. health care context, the vaccine compares favorably with other standard preventive practices in the elderly, of which few are cost-saving (e.g., annual vaccination against influenza).

In a recent retrospective cohort study among elderly persons with chronic lung disease, pneumococcal vaccination was associated with significantly fewer hospitalizations for pneumonia (a 43% reduction), a 29% reduction in deaths, and direct medical care cost savings (112). In contrast to the findings of a Finnish study (102), combined pneumococcal and influenza vaccination also showed an incremental benefit over influenza vaccination alone. When controlling for influenza vaccination status during influenza seasons in multivariate analysis, a statistically significant independent contribution of pneumococcal vaccination was observed. In addition, the effectiveness of pneumococcal vaccination was similar during both influenza seasons and interim periods whereas influenza vaccination was only effective during influenza seasons (113).

6.5. Duration of protection

Following pneumococcal vaccination, serotype-specific antibody levels decline after 5-10 years, decreasing more rapidly in some groups than others (84, 85, 87-89). Although the initial serum antibody levels in most elderly persons are similar to younger adults following pneumococcal vaccination, serotype-specific antibody levels may decline to near pre-vaccination levels after 3-5 years in the elderly (86). These data suggest that revaccination may be indicated to provide continued protection. However, because the data concerning serologic correlates of protection are not conclusive, the ability to define indications for revaccination based on serologic data alone is limited. Data from one epidemiologic study have suggested that vaccination may provide protection for at least 9 years after receipt of the initial dose (79). Decreasing estimates of effectiveness with increasing interval since vaccination, particularly among the very elderly (i.e., persons aged ≥85 years) have been reported (108).

Polysaccharide vaccines do not induce T-cell immunologic memory. Antibody levels rise after revaccination, but an anamnestic response does not occur. The overall increase in antibody levels among elderly persons has been shown to be lower after revaccination than following primary vaccination (114). Long-term follow-up data concerning antibody levels in persons who have been revaccinated are not yet available, and no data are available concerning the relative clinical effectiveness of a second dose of vaccine.

6.6. Recommendations of the Immunization Practices Advisory Committee (ACIP) for the use of pneumococcal polysaccharide vaccine

Because of the high risk of invasive pneumococcal disease, clinical effectiveness of vaccination for prevention of bacteremia and cost-effectiveness of vaccination in the elderly, the CDC's Immunization Practices Advisory Committee recommended in 1997 that all persons aged ≥65 years and persons aged ≥2 years who are at increased risk because of chronic medical conditions should receive the 23-valent pneumococcal polysaccharide vaccine (1) (Table 4). Vaccination is also recommended for immunocompromised persons who are at high risk for severe pneumococcal disease or its complications. Although the vaccine is not as effective for immunocompromised persons as it is for immunocompetent persons, the potential benefits and safety of the vaccine were considered to justify its use.

Because public health practice recommendations need to include clear statements about the strength of each recommendation, the quality of supporting evidence and expert judgement behind them (115), the following categories reflecting the

Table 4. Recommendations of the Immunizations Practices Advisory Committee (ACIP) for the use of pneumococcal vaccine, 1997 (1).

Groups for which vaccination is recommended	Strength of recommendation*	Revaccination†
Immunocompetent persons §		
Persons aged ≥65 years	A	Second dose of vaccine if received vaccine ≥5 years previously and were aged <65 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 CSF 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 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 perivious 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 not proven, but the high risk for disease, and the potential benefits and safety of 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.

strength of each recommendation and quality of supporting evidence for pneumococcal vaccination were used [modified from (116)]:

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.

Because of lack of available data, the strength of all revaccination recommendations is "C". Routine revaccination of immunocompetent persons previously vaccinated is not recommended. However, a single revaccination is recommended at least 5 years after initial immunization for immunocompromised persons who are at highest risk for pneumococcal infections and for those who are most likely to have a rapid decline in pneumococcal antibody levels. In addition, for individuals vaccinated before age 65 years, a second dose of vaccine should be administered at age 65 years or later if ≥5 years have passed since the primary vaccination. Elderly persons with unknown vaccination status should be administered one dose of vaccine (Figure 2). According to two recent studies, revaccination is not associated with increased incidence of serious adverse events (117, 118).

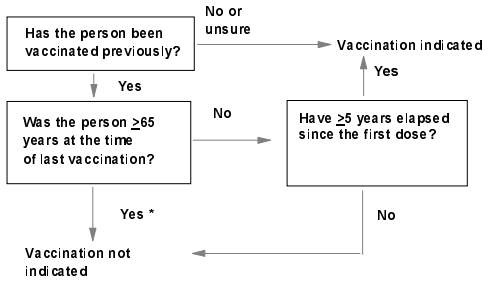

Figure 2. Algorithm for vaccinating persons aged ≥65 years. *Note: For any person who has received a dose of pneumococcal vaccine at age ≥65 years, revaccination is not indicated (1).

7. Pneumococcal conjugate vaccines

Immune responses to many capsular polysaccharides can be improved by covalent coupling of the polysaccharide antigen to a carrier protein to produce a conjugate vaccine (78, 119, 120). The immunologic responses elicited by conjugate vaccines are T-cell dependent and induce higher antibody concentrations in infants. In addition, memory B cells are produced and booster responses occur with subsequent doses of the vaccine. Pneumococcal protein-polysaccharide conjugate vaccines have been developed for 7 to 11 selected serotypes (119, 121). Current conjugate vaccine development has focused on the serotypes most commonly causing infections in childhood and for use in children aged <2 years because antibody responses to the polysaccharide vaccine antigens are poor in this age group. The 7-valent conjugate vaccine serotypes (4, 14, 6B, 19F, 18C, 23F, and 9V and serologically cross-reactive serotypes (e.g., 6A) account for 86% of blood and 83% of CSF isolates causing disease among children aged <6 years in the United States (80). However, considerable geographic and temporal differences exist in distribution of serotypes (122), and in persons aged ≥6 years, these seven serotypes have accounted for only 50% of the blood and CSF isolates in the U.S. (79).

The new pneumococcal conjugate vaccines generally are safe and induce antibody responses in children aged 2-5 years and infants aged 2 months and induce booster responses (120). In healthy adults aged >50 years and among HIV-infected adults aged 18–65 years, however, the antibody levels after conjugate vaccination were not substantially greater than those following vaccination with the 23-valent polysaccharide vaccine, possibly because of lower antigen content in the conjugate, high preimmunization antibody levels or the fact that only one dose of vaccine was given (2, 119).

Multicenter trials to evaluate the immunogenicity, efficacy and safety of a 7-valent pneumococcal conjugate vaccine for prevention against invasive disease and acute pneumococcal otitis media in children have recently been completed in the U.S. (123) and Finland (124), and

the vaccine has shown substantial potential for prevention of pneumococcal disease in children. The Kaiser Permanente Vaccine Study Center found that the vaccine was immunogenic in infants beginning at age 2 months, safe, and prevented 94% of invasive disease caused by vaccine serotypes (123). It also reduced the number of clinic visits, episodes, recurrent disease and tube placements due to otitis media. In the Finnish trial, the 7-valent conjugate vaccine was 57% and 34% efficacious in preventing episodes of acute otitis media caused by vaccine serotypes and any culture-confirmed pneumococcal otitis media, respectively. However, the protection against acute otitis media of any etiology was only 6% (124).

An ACIP recommendation on the use of pneumococcal conjugate vaccines is under preparation and will update the 1997 recommendation (1) regarding the use of pneumococcal vaccines in children aged 24 to 59 months. The ACIP will recommend that the 7-valent conjugate vaccine be used for all children aged 2–23 months and for children aged 24–59 months who are at increased risk of pneumococcal disease because of underlying illness such as sickle cell disease, HIV infection, or other immunocompromising and chronic medical conditions (CDC, unpublished data). For children aged 24–59 months for whom the 23-valent polysaccharide vaccine is already recommended, the ACIP will recommend vaccination with the conjugate vaccine followed by the polysaccharide vaccine $\geq$2 months later. Persons aged $\geq$5 years should continue receiving the polysaccharide vaccine according to the 1997 ACIP recommendations (1).

OBJECTIVES OF THE STUDY

The purpose of this study was to characterize and evaluate recent developments in the epidemiology of invasive pneumococcal disease in three different adult populations in the United States. We determined the implications of the current epidemiologic trends for public health strategies to prevent invasive pneumococcal infections in adults. The findings were used to update the epidemiologic data included in the current prevention recommendations (1), and to assess the potential impact of different preventive strategies identified.

The specific objectives were:

1. To assess the contribution of active and passive smoking and other factors to the risk of invasive pneumococcal disease among immunocompetent, nonelderly adults, and to determine the attributable risks associated with these factors in a population-based case-control study (I).
2. To evaluate the epidemiologic and clinical effects of the HIV epidemic on invasive pneumococcal disease by conducting population-based surveillance in San Francisco County, an area with high prevalence of HIV and AIDS (II).
3. To study factors associated with colonization and disease due to multidrug-resistant *Streptococcus pneumoniae* in a retrospective cohort study, and to assess modes of transmission, and evaluate control measures in the context of an investigation of an outbreak among elderly nursing home residents (III).

SUBJECTS AND METHODS

1. Population-based case-control study to identify risk factors for invasive pneumococcal disease in adults (I)

1.1 Case definition and ascertainment

A case of invasive pneumococcal disease was defined as an illness in which *Streptococcus pneumoniae* was isolated from a normally sterile site such as blood or cerebrospinal fluid. Cases were identified prospectively among residents of metropolitan Atlanta, metropolitan Baltimore, Maryland, and the Peel region of Toronto, Canada (aggregate 1995 population, 8.3 million) through ongoing laboratory-based surveillance. Study patients were residents of the surveillance area who were aged 18 to 64 years, who had a telephone and who developed an illness meeting the case definition of invasive pneumococcal disease between January 1995 and May 1996. Only community-acquired cases were included. Patients were excluded if they had a recognized condition or treatment that led to immunocompromise or immunosupression (36), or they were residents of an institution.

1.2. Selection of patients and control subjects

Each month, we selected a sample of all incident cases reported in each surveillance area. Of 513 patients included in the samples, 42% were ineligible for the following reasons: immunocompromising condition (25%), no telephone (16%), or residence in an institution (1%). Of 297 eligible case-patients, 228 (77%) agreed to participate in the study, 8 % refused, 2 % had died and 13% were unreachable.

Control subjects were identified from the general population in each surveillance area by random-digit telephone dialing (125). They were frequency-matched to patients according to the month of positive culture, area and age-group (18 to 29, 30 to 49, and 50 to 64 years). The respondents in 26% of the residences declined to participate and there was no eligible respondent in 52% of the residences. A total of 301 control subjects were interviewed.

1.3. Data collection

Trained investigators obtained informed consent from the study subjects and conducted interviews using a standard questionnaire. Participants were asked about chronic illnesses, environmental and occupational exposures, and socioeconomic factors. Questions concerning cigarette smoking and alcohol consumption were adapted from the CDC Behavioral Risk Factor Surveillance System (126). The study was approved by the CDC and by the review board of each participating institution.

The study subjects were classified according to their smoking status (126). Current smokers reported having smoked at least 100 cigarettes in their lifetime and still smoked, or had quit smoking within the preceding year. Former smokers had smoked at least 100 cigarettes in their lifetime but had quit smoking more than one year earlier. Subjects who had smoked less than 100 cigarettes or who had never smoked were considered never to have smoked. For former and never smokers, exposure to environmental tobacco smoke was determined.

1.4. Analytic methods

Summary odds ratios adjusting for frequency-matched variables (age and study area) were calculated using the Mantel-Haenszel method (127). To control for confounding and identify independent risk factors, we used unconditional logistic regression. After assessing two-way interactions and collinearity among variables, the hierarchical backward elimination technique was used to determine the best fit for the model (128). The likelihood ratio test was used to assess the statistical significance of each variable. Adjusted population-attributable risks were calculated for independent risk factors in the multivariable model (129), and the presence of dose-response relations was investigated.

2. Population-based surveillance analysis of the relation between HIV and invasive pneumococcal disease (II)

2.1. Population-based surveillance

Cases of invasive pneumococcal disease in residents of San Francisco County, California were identified prospectively through active, laboratory-based surveillance. Project personnel contacted all of the 13 clinical microbiology laboratories in the county biweekly. They reviewed medical records by using a standard case report form to obtain demographic and limited clinical information, including HIV antibody status. *S. pneumoniae* isolates were identified by standard methods and serotyped at the CDC (130). All laboratories were audited at least bimonthly to ensure completeness of reporting. Active surveillance for invasive pneumococcal disease, as part of the California Emerging Infections Program, was approved by the California Committee for the Protection of Human Subjects and by the Institutional Review Board of the University of California, Berkeley.

2.2. Case definitions

A case of invasive pneumococcal disease was defined as an illness in which *S. pneumoniae* was isolated from a normally sterile site (such as blood or cerebrospinal fluid) in a surveillance area resident between October, 1994, and June, 1997. Recurrent disease was defined as isolation of *S. pneumoniae* from a normally sterile site more than 7 days after the original episode. Cases of AIDS were defined according to the CDC revised case definition (131).

2.3. Calculation of incidence rates and trend analysis

Incidence rates were calculated using the U.S. Bureau of Census population estimates. To calculate the incidence of invasive pneumococcal disease among persons with AIDS, we used as denominator the number of persons living with AIDS during each month of the study that was reported to the San Francisco Department of Public Health's AIDS Office. To evaluate secular trends, rates of pneumococcal disease in patients with AIDS and in those without known HIV-infection were calculated twice: for each 3-month period from October 1994 through June 1997 and for three consecutive periods of peak respiratory infection (October to March). Because HIV infection is not reportable in California, exact denominator information for those patients who were HIV-seropositive without AIDS was not available. These persons were excluded from the analyses of trends.

2.4. Statistical analysis

Proportions were compared by using the chi-square test, and continuous variables by using the Kruskal-Wallis test. For the first event of pneumococcal disease, rate ratios and 95% confidence intervals adjusted for age, race/ethnicity and sex (where appropriate) were calculated by using Poisson regression (132). To identify predictors for death and of recurrence of pneumococcal illness in multivariable analysis, we used Poisson regression models (133). We also used a Poisson regression model to evaluate whether the observed changes in the incidence of pneumococcal disease in persons with AIDS were statistically significant. In addition to the individual-level analyses, we performed ecological analyses to determine the association between census population variables (median household income, proportion of black population) and disease incidence according to census tract by using a Poisson model .

3. Investigation and control of an outbreak of multidrug-resistant pneumococcal disease in a nursing home (III)

3.1. Background

On February 16, 1996, the Centers for Disease Control and Prevention received notification that three residents of a long-term care facility had been hospitalized with pneumococcal bacteremia within a five-day period; two had died of rapidly progressing illness that did not respond to intravenous cefuroxime therapy. Initial susceptibility testing indicated that all isolates were inter-

mediate to penicillin and cefotaxime (minimum inhibitory concentration, 1.0 mg/mL for both by E-test), resistant to trimethoprim-sulfamethoxazole and erythromycin, and were susceptible only to vancomycin. The clinical microbiology laboratory of the community hospital had routinely screened all sterile-site *S. pneumoniae* isolates for antimicrobial resistance since January 1995, but no resistant isolates had been identified previously in the community.

3.2. Epidemiologic investigation

We defined a case as an illness with radiographically documented pneumonia occurring in a resident of nursing home between February 6 and 20, 1996 (the outbreak period). A carrier was defined as a resident without lower respiratory illness from whom the outbreak strain was isolated by nasopharyngeal-swab culture. To determine the extent of spread of the outbreak strain within the nursing home, we obtained nasopharyngeal swabs for culture from residents and employees before interventions were carried out and evaluated the effect of interventions in two follow-up nasopharyngeal surveys. To identify factors associated with colonization and disease in a retrospective cohort study, we compared attack rates among colonized residents with those among non-colonized residents, and attack rates among residents who had pneumonia with those among asymptomatic residents. Information from medical charts was obtained with a standard form.

3.3. Laboratory methods

Nasopharyngeal secretions were obtained with sterile calcium alginate swabs, inoculated directly onto blood agar plates, and incubated overnight. *S. pneumoniae* isolates were serotyped by quellung reaction and tested for antimicrobial susceptibility by broth-microdilution (130). For each drug tested, isolates were defined as susceptible, intermediate or resistant according to cut-off points defined by the National Committee for Clinical Laboratory Standards (134). Multidrug-resistant isolates were compared by pulsed-field gel electrophoresis after digestion with *Sma*I. The similarity of isolates was assessed by comparing the migration distances of DNA fragments (135).

3.4. Statistical analysis

Relative risks and 95 percent confidence intervals were calculated and adjusted by the Mantel-Haenszel method. P-values were calculated with Fisher's two-tailed exact test. To evaluate transmission between residents, we used a binomial probability model.

3.5. Interventions

On February 17, 1996, pneumococcal polysaccharide vaccine was given to 71 nonhospitalized residents who had no documentation of prior vaccination. Eleven employees with chronic illnesses were also vaccinated. Because there were four additional cases of pneumonia during the next three days, all residents were given penicillin (500mg three times daily) or ofloxacin (400mg twice a day for 12 residents with reported penicillin allergy) for one week beginning on February 20. Two employees who were colonized with the outbreak strain recieved a combination of rifampin (600mg daily) and ofloxacin (400mg twice daily) for one week.

RESULTS

1. Risk factors for invasive pneumococcal disease in immunocompetent nonelderly adults (I)

1.1. Characteristics of case-patients and controls

Between January 1995 and May 1996, surveillance identified a total of 2888 cases of invasive pneumococcal disease of which 1248 (43 percent) occurred among persons aged 18 to 64 years. The annual incidence per 100,000 ranged from 7.5 in Toronto to 21.8 in Baltimore. In Atlanta and Baltimore, where surveillance data concerning race were available, the rates were 5 to 8 times as high among blacks as among non-blacks, and 1.7 times as high among men as among women.

Among the 228 patients enrolled, 23.2% of case-patients had chronic illnesses and the proportion increased to 43.7% for patients who were aged 50 to 64 years. When persons classified as alcoholics were included, 28% of case-patients had an indication for pneumococcal vaccine (1). Current smokers accounted for 58 percent of all patients, 57 percent of the 164 patients who did not have an indication for the receipt of pneumococcal vaccine, and 24 percent of the control subjects. Patients were as likely as control subjects to be former smokers, but the average time since patients had stopped smoking was 11.3 years as compared with 17.0 years for the control subjects (P=0.005). Among 318 nonsmokers, 33 percent of patients and 17 percent of control subjects were exposed to environmental tobacco smoke.

1.2. Stratified analysis

After adjustment for age and study area, current smoking was strongly associated with pneumococcal disease (Table 5). Passive smoking was also associated with illness but the point estimate was lower. Other characteristics associated with pneumococcal disease included chronic illnesses, particularly COPD and cirrhosis, heavy alcohol use, living with children under the age of six years who attended day-care centers, and characteristics associated with low socioeconomic status (low educational level and low income, lack of health insurance, and household crowding).

1.3. Multivariable analysis

The independent risk factors included in the final model are shown in (Table 6). Patients were 4.1 times as likely as controls to be current smokers (95% CI, 2.4–7.3). Nonsmoking patients were 2.5 times as likely to be exposed to environmental tobacco smoke as non-smoking controls (95% CI, 1.2–5.1). The presence of chronic illness was a significant independent risk factor. In addition, male sex, black race, and low level of education were significantly associated with pneumococcal disease. Patients were 3.0 times as likely as control subjects to live in a household with young children who were in day care (95% CI, 1.5–6.2). The population attributable risks for independent risk factors in the multivariable model were 51% for cigarette smoking, 17% for passive smoking (among nonsmokers), 14% for chronic illness, and 11% for living with young children who were in day-care.

Table 6. Independent risk factors for invasive pneumococcal disease among immunocompetent adults aged 18 to 64 years

Covariate	Odds Ratio * and (95 % CI)	P value
Male sex	2.7 (1.7–4.3)	< 0.001
Black race	3.4 (2.0–5.6)	< 0.001
Chronic illness†	2.6 (1.4–5.1)	0.005
Smoking status		
Current smoker	4.1 (2.4–7.3)	<0.001
Former smoker	1.1 (0.5–2.2)	0.91
Passive smoke exposure	2.5 (1.2–5.1)	0.01
Never smoked	1.0	
Level of education		
Did not finish high school	2.8 (1.3–5.9)	0.007
High school graduate	2.0 (1.2–3.4)	0.006
College graduate	1.0	
Children in the household		
<6 years and in daycare	3.0 (1.5–6.2)	0.003
<6 years, not in day care	1.0 (0.5–2.0)	0.99
No children <6 years	1.0	

* Odds ratios and 95% CI from an unconditional logistic regression analysis adjusted for age, study site, and all other variables in the table. Hosmer and Lemeshow goodness-of-fit statistic for the model = 8.30; 8 d.f. (P = 0.41)

† "Chronic illness" was defined as one or more of the following conditions: COPD including chronic bronchitis and emphysema, chronic heart failure, cirrhosis, or diabetes mellitus.

Table 5. Demographic, medical and socioeconomic characteristics associated with invasive pneumococcal disease in immunocompetent adults aged 18 to 64 years.

Characteristic	Case-patients (%) N=228		Control subjects (%) N=301		Odds ratio* and (95% CI*)	
Demographic/medical†						
Male gender	125	(56)	70	(29)	3.1	(2,1–4.6)
Black race	101	(44)	68	(23)	3.2	(2.1–4.8)
COPD	26	(12)	11	(4)	3.4	(1.6–7.0)
Heart failure	3	(1)	1	(0.3)	3.7	(0.4–36.1)
Cirrhosis	8	(4)	1	(0.3)	12.2	(1.5–101.7)
Diabetes	23	(10)	12	(4)	2.5	(1.2–5.1)
Asthma	32	(15)	18	(6)	2.5	(1.4–4.7)
Chronic illness	53	(23)	25	(8)	3.3	(1.9–5.5)
Vaccine indication	64	(28)	27	(9)	4.0	(2.4–6.5)
Pneumonia in past 5 years	32	(14)	20	(7)	2.3	(1.3–4.3)
URI in the past month	146	(64)	128	(43)	2.4	(1.7–3.5)
Educational attainment§						
Did not finish high school	52	(25)	23	(9)	7.3	(3.8–13.9)
High school graduate	121	(57)	127	(47)	3.0	(1.9–4.7)
College graduate	38	(18)	117	(44)	1.0	
Medical insurance status						
No insurance or Medicaid	66	(29)	45	(15)	2.7	(1.7–4.2)
Private, HMO or PPO	161	(71)	256	(85)	1.0	
Household income ($)						
<15,000	56	(28)	34	(13)	3.9	(2.2–6.9)
15,000 – 45,000	99	(49)	102	(40)	2.6	(1.6–4.0)
45,000+	47	(23)	119	(47)	1.0	
Household crowding ‡	67	(31)	47	(16)	2.4	(1.6–3.8)
Smoking status ¶						
Current smoker	130	(58)	72	(24)	5.4	(3.4–8.5)
Former smoker	23	(10)	61	(21)	1.2	(0.7–2.3)
Passive smoke exposure	31	(14)	38	(13)	2.5	(1.4–4.5)
Never smoker	40	(18)	125	(42)	1.0	
Alcohol consumption						
Heavy drinker**	15	(7)	2	(1)	7.1	(1.7–30.3)
In the previous month	108	(48)	181	(60)	0.7	(0.5–1.0)
Non-drinker	103	(45)	118	(39)	1.0	
Children in the household						
Aged <6 years and in DCC	35	(15)	24	(8)	2.3	(1.3–4.1)
Aged <6 years, not in DCC	29	(13)	34	(11)	1.4	(0.8–2.4)
No children <6 years	163	(72)	240	(81)	1.0	

* Mantel-Haenszel summary odds ratio for frequency-matched data from stratified analysis (adjusted for age-group and study area only); Robins, Greenland, and Breslow 95% CI.

† "COPD" denotes chronic obstructive pulmonary disease and includes chronic bronchitis and emphysema."Chronic illness" was defined as one or more of the following conditions: chronic heart failure, COPD, cirrhosis, or diabetes. URI denotes upper respiratory infection.

§ Educational attainment was determined for 211 case-patients and 267 controls aged ≥25 years.

‡ Crowding was defined as >0.67 persons per room (75th percentile of the distribution among controls) at residence.

¶ See Methods section for smoking status definitions. Because the number of former smokers with passive smoke exposure (7 case-patients and 8 controls) was too small for consideration as an independent group, these persons were included in the "passive smoke exposure" category.

** Heavy drinking was defined as consumption of ≥25 alcoholic beverages in a week

1.4. Dose-response relations

Among current smokers, adjusted odds ratios increased steadily from 2.3 to 5.5 with increasing number of cigarettes smoked daily (P<0.001), suggesting a dose-response relationship (Figure 3). Among current and former smokers, the adjusted odds ratios increased from 1.5 to 3.2 with increasing number of pack-years of smoking (P=0.002), a finding also consistent with dose-response (Figure 4). Although former smokers were not at increased risk overall, an association was observed with length of time since quitting smoking (P=0.001). The risk of pneumoccal disease decreased by 14% per year after the subjects quit smoking returning to the level of those who had never smoked after approximately 13 years (Figure 5). Among nonsmokers, the risk increased with an increasing duration of passive exposure to smoke.

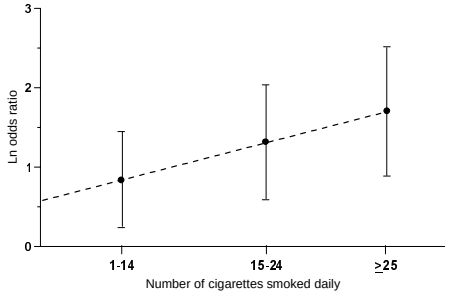

Figure 3. Relation of intensity of cigarette smoking to the risk of invasive pneumococcal disease. X-axis represents the daily number of cigarettes smoked (median of category) and Y-axis represents the adjusted parameter estimate (Ln odds ratio) and 95% CI from multiple logistic regression model (P<0.001).

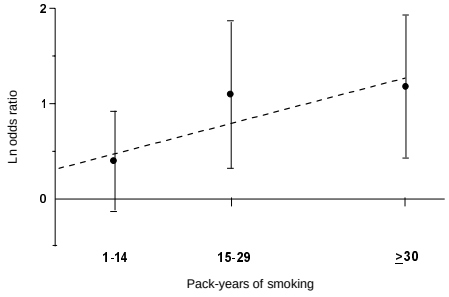

Figure 4. Relation of cumulative smoking exposure to the risk of invasive pneumococcal disease. X-axis represents pack-years of smoking (median of category) and Y-axis represents the adjusted parameter estimate (Ln odds ratio) and 95% CI from multiple logistic regression model (P=0.002).

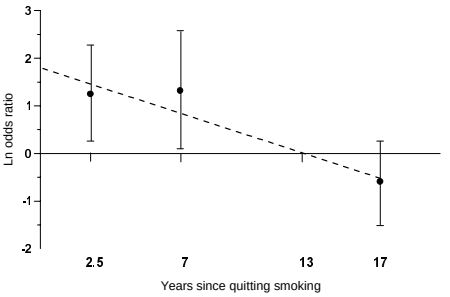

Figure 5. Relation of reversible smoking exposure to the risk of invasive pneumococcal disease. X-axis represents years since quitting smoking (median of category) and Y-axis represents the adjusted parameter estimate (Ln odds ratio) and 95% CI from multiple logistic regression model (P=0.001).

2. The epidemiologic and clinical impact of HIV on invasive pneumococcal disease (II)

2.1. All age-groups

A total of 602 cases of invasive pneumococcal disease were identified. The overall incidence was 34.0 cases per 100,000 person-years. Patients ranged in age from 2 months to 98 years (median, 45 years); 69.3% of patients were male and 12.6% died. The age-adjusted incidence rates per 100,000 person-years were 47.7 cases for male patients, 20.3 cases for female patients, 96.0 cases for black persons and 23.5 cases for nonblack persons (Figure 6). Because 99.3% of HIV-infected patients were aged 18-64 years, we restricted all subsequent analyses to those in this age group.

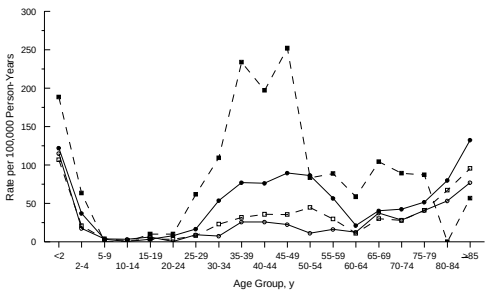

Figure 6. Incidence of invasive pneumococcal disease by age, sex and race, San Francisco, 1995–96. Black squares represent incidence among black persons, white squares represent incidence among nonblack persons, black circles represent incidence among men, and white circles represent incidence among women.

2.2. Patients aged 18–64 - demographic and clinical characteristics

Persons aged 18–64 years accounted for 399 (66.3%) of all cases of invasive pneumococcal disease. Information on HIV status was available for 380 of these patients (95.2%). For 206 (54.2%) patients, HIV infection was documented in medical records; 136 (35.8%) had AIDS and 70 (18.4%) were HIV-infected but did not have AIDS when pneumococcal disease was diagnosed (Table 7). Overall, 54.5% of patients were white and 37.9% were black. The ratio of men to women was 7:1 in persons with AIDS, 4.4:1 in persons with HIV infection and 2.8:1 in persons without documented HIV infection. Persons infected with HIV were younger than those without known HIV infection (P=0.009 for the comparison of mean ages). The most common clinical syndromes associated with invasive pneumococcal disease were bacteremic pneumonia (83.9%), bacteremia without focus (10.8%) and meningitis (3.2%). The frequencies of these syndromes did not differ significantly between HIV-infected patients and those who were not known to have HIV infection.

2.3. Incidence by AIDS status, race and gender

The overall incidence of invasive pneumococcal disease for persons aged 18–64 years was 35 cases per 100,000 person-years (Table 8). The overall rate ratio for comparing men with women was 3.9 (95% CI, 2.9–5.2). Compared with

Table 7. Characteristics of 380 patients aged 18–64 years with invasive pneumococcal disease by HIV infection status, San Francisco, 1994–1996

Characteristic*	AIDS N=136		HIV seropositive N=70		Without known HIV infection N=174		All patients N=380	
Gender								
Male	119	(87.5)	57	(81.4)	128	(73.6)	304	80.0)
Female	17	(12.5)	13	(18.6)	45	(25.9)	75	(19.7)
Race/ethnicity								
White	77	(56.6)	41	(58.6)	89	(51.2)	207	(54.5)
Black	55	(40.4)	22	(31.4)	67	(38.5)	144	(37.9)
Asian/Pacific Islander	0		0		11	(6.3)	11	(2.9)
American Indian	0		0		2	(1.1)	2	(0.5)
Not specified	1	(0.7)	0		0		1	(0.3)
Unknown	3	(2.2)	7	(10)	5	(2.9)	15	(3.9)
Ethnic origin								
Hispanic	12	(8.8)	10	(14.3)	23	(13.2)	45	(11.8)
non-Hispanic	119	(87.5)	53	(75.7)	146	(83.9)	318	(83.7)
Unknown	5	(3.7)	7	(10.0)	5	(2.9)	17	(4.5)
Median age (years)	38.5		40.0		44.0		41.0	
Recurrent illness	20	(14.7)	9	(12.9)	5	(2.9)	34	(8.9)
Case-fatality ratio	16	(11.8)	3	(4.3)	15	(8.6)	34	(8.9)
Predisposing conditions								
Chronic illness†	5	(3.7)	6	(8.6)	34	(19.5)	45	(11.8)
Immunocompromised (other than HIV)‡	14	(10.3)	4	(5.7)	29	(16.7)	47	(12.4)
Alcohol misuse	27	(19.9)	16	(22.9)	71	(40.8)	114	(30.0)
Injection-drug use	57	(41.9)	26	(37.1)	23	(13.2)	106	(27.9)

* Values are expressed as no. (%) with characteristic. HIV status was unknown for 19 (4.8%) of 399 patients aged 18-64 years.
† Presence of one or more of the following conditions: chronic cardiopulmonary disease (chronic heart failure, chronic obstructive pulmonary disease), cirrhosis, diabetes mellitus, and chronic renal disease.
‡ Immunocompromising illness other than HIV infection (including leukemia, lymphoma, Hodgkins disease, multiple myeloma, generalized malignancy, nephrotic syndrome, immunosuppressive chemotherapy; and organ or bone marrow transplant).
Note: patients may have more than one predisposing condition.

Table 8. Incidence of invasive pneumococcal disease among blacks and nonblacks aged 18–64 years by gender and AIDS status, San Francisco, 1995–1996

Characteristic*	All patients		Black		Nonblack†	
	Cases	Rate per 100,000 person-years	Cases	Rate per 100,000 person-years	Cases	Rate per 100,000 person-years
	n		n		n	
Overall	343	35.0	124	127.9	204	23.1
Gender						
Male	275	54.6	93	193.0	170	37.3
Female	67	14.1	31	63.5	34	8.0
AIDS status ‡						
AIDS	117	802.9	47	2384.6	67	531.7
No HIV	149	15.7	56	60.2	88	10.2

* No data on race/ethnicity were available for 15 patients; gender was unknown for one patient.
† Because no appreciable differences were observed in rates between non-Hispanic whites and Hispanic whites, patients in these groups were combined in the analysis. Patients of other races (Asian/Pacific Islander and American Indian/Alaskan Native) were also included in the non-black category. Patients of unknown race were excluded.
‡ AIDS or not known to be HIV-infected. Information regarding AIDS status was missing for 17 patients. 60 HIV seropositive persons who did not have AIDS were excluded.

women of the same race, the rate ratios for black men and nonblack men were 3.0 (95% CI, 2.0–4.6) and 4.7 (95% CI, 3.2–6.8), respectively. When we compared black patients with nonblack patients, the rate ratio for developing pneumococcal disease was 5.4 (95% CI, 4.3–6.8), regardless of AIDS status.

Compared with persons who were not known to have HIV infection, the crude rate ratio for developing invasive pneumococcal disease for persons with AIDS was 46 (803 vs. 16 per 100,000 person-years; 95% CI, 36.0–58.9). Black patients with AIDS had the highest observed rate of pneumococcal infection (2385 per 100,000 person-years) (Figure 7). In patients with AIDS, the rate ratio for comparing black patients to non-black patients was 4.5 (95% CI, 3.1–6.5). In persons aged 18 to 64 years, 55.2% of all cases of pneumococcal disease were attributable to HIV infection (population attributable risk percent).

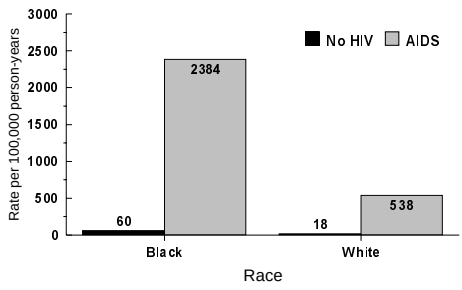

Figure 7. Incidence of invasive pneumococcal disease by race and AIDS status, San Francisco 1995–96

2.4. Mortality and recurrent infections

Thirty-four non-elderly adults (8.9%) died. Case-fatality ratios were similar according to race and sex regardless of HIV status. In multivariable analysis, the adjusted rate ratios (RR) for death were 1.8 (95% CI, 0.7–4.4) for patients with AIDS patients and 0.7 (95% CI, 0.2–2.0) for HIV-positive patients compared with patients who were not known to be HIV-infected. In multivariable analysis, HIV-infected persons were almost 5 times more likely than persons without documented HIV infection to develop recurrent pneumococcal disease.

2.5. Capsular serotypes

In patients for whom data on HIV status were available, 295 (77.6%) isolates were available for serotyping. The 23-valent polysaccharide vaccine serotypes accounted for 82.5% of isolates in HIV-infected patients and 83.0% of isolates in non-HIV-infected patients. However, only 43.8% of the isolates in HIV-infected patients were serotypes represented in the 7-valent conjugate vaccine (Figure 8).

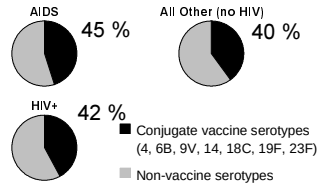

Figure 8. Proportion of serotypes causing invasive disease in adults aged 18–64 years, San Francisco.

2.6. Secular trends

Figure 9 shows the secular trends in incidence of pneumococcal disease in persons with AIDS and in those without known HIV infection.The quarterly incidence in patients with AIDS decreased from 10.6 cases to 4.2 cases per 1000 person-years from October 1994 through June 1997; this decrease was was found to be significant by Poisson regression (P=0.004): The most substantial decrease occurred from 1996 to 1997. These changes were distinct from seasonal variations: During three consecutive periods of peak respiratory infection from October 1994 through March 1997, the incidence of invasive pneumococcal disease per 1000 person-years in persons with AIDS decreased by 49.5% (P=0.01). In contrast, the incidence of pneumococcal disease in persons without known HIV infection showed only the expected seasonal variation, and no trend was observed (P>0.2). (Figure 9).

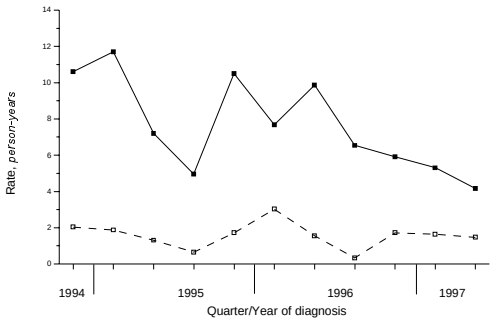

Figure 9. Incidence of invasive pneumococcal disease among persons with AIDS and those without HIV infections by quarter/year of diagnosis, San Francisco, October 1994 through June 1997. Black squares represent incidence among persons with AIDS, white squares represent incidence among persons without known HIV infection. Points represent quarterly incidence. Rates for AIDS patients are shown per 1000 person-years. For those without known HIV infection, rates are shown per 10,000 person-years.

Whereas the overall incidence in persons aged 18–64 years decreased markedly from 1995 to 1998 because of the decline in HIV-infected cases, the incidence in elderly persons did not decrease (Figure 10).

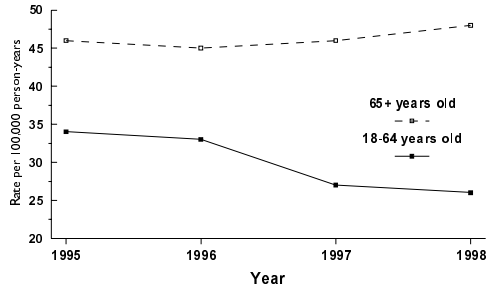

Figure 10. Annual incidence of invasive pneumococcal disease in nonelderly and elderly adults, San Francisco, 1995 through 1998

2.7. Socioeconomic factors

We analyzed the incidence rates for cases of pneumococcal disease in persons aged 18–64 years by median household income of the residence census tract and by race/ethnicity. In black persons, the incidence per 100,000 person-years decreased almost linearly from 113.0 cases in census tracts with incomes less than $15,000 to 34.2 cases in tracts with incomes more than $45,000. For nonblack persons, the rates per 100,000 person-years decreased similarly, from 61.6 cases to 15.8 cases (Figure 11). In a Poisson model, both median household income (P<0.001), and black race (P<0.001) were highly significant in determining the incidence rate of pneumococcal disease. The highest rates of disease occurred in a few inner-city census tracts with median household incomes less than $20,000. Homeless persons, who accounted for 14% of cases, were excluded from the census tract analysis.

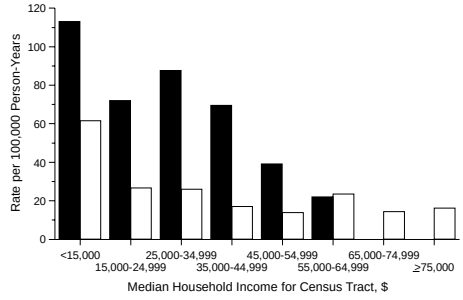

Figure 11. Incidence of invasive pneumococcal disease in black and nonblack persons by median household income of census tract of residence. Black bars represent incidence among black persons and white bars represent incidence among nonblack persons

3. Institutional outbreak of multidrug-resistant pneumococcal disease (III)

3.1. Epidemiologic characteristics of the outbreak

The nursing home in which the outbreak occurred is a 100-bed single story building with two wings. The 84 residents at the time of the outbreak ranged in age from 48 to 101 years (median, 85 years). Ninety-two percent were at least 65 years old; 81% were women, and 93% were white. There were 78 employees (median age, 41 years).

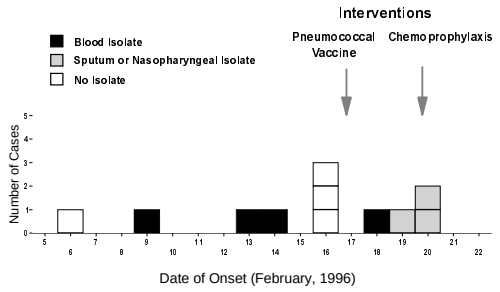

Figure 12. Cases of pneumonia among nursing home residents by date of onset of illness

During the outbreak, 11 residents had illness that met the case definition giving an attack rate of 13 percent (Figure 12). The 11 patients were similar to residents who were not ill in mean age, race and sex. All 11 patients had lobar consolidation evident on chest radiography, and none had symptoms suggestive of meningitis. Multidrug-resistant *S. pneumoniae*, serotype 23F was isolated from the blood of four patients and from respiratory tract of three. Three patients, all with bacteremia, died (case-fatality ratio, 27 percent). Only 3 residents (4%) had had pneumococcal vaccination, although 60 of the 84 residents (71%) had received influenza vaccine during the fall of 1995. No cases were identified among the nursing staff.

3.2. Nasopharyngeal carriage studies

Before any interventions were undertaken, the outbreak strain was isolated from nasopharyngeal specimens from 17 of the 74 residents tested (23 percent), including 3 who subsequently developed pneumonia, and 2 of the 69 employees tested (3 %) (Table 9). All other pneumococcal isolates that were recovered were sensitive to penicillin. In the second nasopharyngeal- culture survey, conducted after the completion of chemoprophylaxis, serotype 23F was recovered from three residents and none of the employees. Five weeks later, two residents were still colonized. All multidrug-resistant isolates from blood, sputum and nasopharyngeal specimens had identical patterns of antimicrobial susceptibility and were indistinguishable from one another by pulsed-field gel electrophoresis.

Table 9. Nasopharyngeal Carriage of *S. pneumoniae* Among Nursing Home Residents and Employees in Three Consecutive Culture Surveys, February–March, 1996.

Group	No. of carriers (rate of carriage [%])		
	Before intervention* (Feb 17)	After intervention (Feb 28)	5-week follow-up (Mar 26)
Residents			
No. tested	74	68	71
Any *S. pneumoniae*	20 (27)	3 (4)	3 (4)
MDRSP, 23F	17 (23)†	3 (4)‡	2 (3)§
Nursing staff			
No. tested	69	59	52
Any *S. pneumoniae*	12 (17)	3 (5)	3 (6)
MDRSP, 23F	2 (3)	0 ¶	0

* Pneumococcal polysaccharide vaccine was administered immediately after nasopharyngeal specimens were collected on February 17, 1996. Residents were given antibiotics from February 20 to 27, 1996.

† Three of these residents developed pneumonia after nasopharyngeal specimens were collected.

‡ Two of these three carriers were new acquisitions, compared to before intervention. P=0.002 for the comparison of number of carriers with the number before intervention (paired McNemar' test).

§ The outbreak strain was recovered from one of these residents before intervention but not immediately after intervention; the other resident was colonized with the outbreak strain in all three nasopharyngeal surveys.

¶ Only two employees who were colonized with the outbreak strain were treated with antibiotics from March 1 to 7; they were re-cultured on March 11, 1996.

3.3. Risk factors for colonization and disease

Seventy-eight residents were enrolled in the cohort study; 25 were considered colonized with the outbreak strain (11 case-patients and 14 asymptomatic carriers). The colonization rates (64% vs. 28%; relative risk, 2.3; 95% CI, 1.3 to 4.2) and attack rates of disease (36% vs. 10%; relative risk, 3.6; 95% CI, 1.2 to 10.8) were higher

among residents who were taking antibiotics at the time of onset of illness (or at the time of culturing for residents who were not ill) than among those who had not taken antibiotics within the previous 2 months. Disease was more likely to develop in residents who had been hospitalized in the previous year, who had had pneumonia in the previous year, or who needed assistance when taking oral medications than those who did not have these characteristics. Colonization and attack rates were similar among residents of each wing and among residents in single and double occupancy rooms. On the basis of the binomial probability model, there was no clustering of colonized residents in double rooms.

Analysis of interactions between the staff and residents identified two bedridden patients and two other patients who lived in single rooms and had had no contacts with other residents or visitors after January 1, 1996. Both colonized employees provided direct patient care. Between January 1 and February 17, one was in charge of administering medications to every resident on both wings twice per shift. From January 18 to February 13, 1996, she had a febrile respiratory illness which was treated with amoxicillin, but she continued working while ill.

DISCUSSION

Collectively, the three original studies (I to III) provide information about the epidemiologic characteristics of invasive pneumococcal disease in three distinct adult populations: immunocompetent nonelderly adults, HIV-infected persons and elderly residents of long-term care facilities. The key new evidence these studies contribute include identifying cigarette smoking and exposure to environmental tobacco smoke as major new risk factors for invasive pneumococcal disease in immunocompetent adults and quantifying the large population-attributable risks associated with these exposures (I), quantifying the impact of HIV on the epidemiologic pattern of pneumococcal disease incidence and documenting the decreasing trend in the incidence of invasive pneumococcal infections in AIDS patients (II) and; confirming in an elderly population the associations of prior antimicrobial use with colonization and disease due to multi-drug resistant *S. pneumoniae*, as well as providing experience about the effectiveness of control measures during an outbreak in an institutional setting (III).

The epidemiologic data from studies I to III update those included the 1997 ACIP statement concerning prevention of pneumococcal disease in the above populations (1). The first part of this discussion summarizes the specific findings of each study and evaluates reasons for the recent epidemiologic developments identified in these studies. Because the study designs and epidemiologic methods differ between the studies, each study (i.e., population-based case-control study, population-based surveillance analysis, ecological analysis and a retrospective cohort study) has specific strengths as well as potential weaknesses that influence the generalizability of the findings. The second part examines the general public health policy implications of these epidemiologic trends for preventing pneumococcal disease, and their relation to current vaccination recommendations in each target group (1). Finally, unresolved issues and future directions in preventing pneumococcal disease in adults are considered.

1. Recent developments in the epidemiology of pneumococcal disease in adults

1. 1. Identifying new risk factors for invasive pneumococcal disease

Our population-based case-control study (I) provided strong evidence for the association of tobacco smoke with pneumococcal disease and established cigarette smoking as the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults. Current smokers accounted for 58% of all patients with invasive pneumococcal disease. Nonsmokers exposed to environmental tobacco smoke accounted for an additional 14% of cases, and only 28% of patients had no current exposure to smoke. Overall, we estimated that 51 % of the pneumococcal disease burden in this population group could be attributed to cigarette smoking, and that 17% of disease among nonsmokers was attributable to exposure to environmental tobacco smoke.

All case-control studies are susceptible to selection bias, misclassification of exposure status and confounding. Differences in the distribution of factors associated with both smoking and pneumococcal disease, such as chronic illness (particularly chronic lung disease), alcohol consumption, low socioeconomic status, or undiagnosed HIV infection (136), could potentially confound the association with smoking. However, adjustment for multiple demographic, medical and socioeconomic characteristics in a multivariable model did not appreciably change the crude odds ratios for smoking or other variables, suggesting that confounding by these factors was relatively minor.

Because HIV/AIDS and other immunocompromising conditions are overwhelming risk factors for invasive pneumococcal disease (1), we excluded immunocompromised persons from our case-control study to improve its efficiency. Re-

stricting the study population to immunocompetent persons provided control for potential confounding in the study design (137). Although an unknown proportion of cases and controls may have had undiagnosed HIV infection, this is unlikely to have confounded the association of smoking with pneumococcal disease. A variety of known risk factors for HIV, including study site, age, race, sex, and socioeconomic status were indirectly controlled for by inclusion in the multivariable model. The clear dose-response relations constitute additional strong evidence against potential confounding. Increased risk of pneumococcal disease was significantly associated with the number of cigarettes smoked per day, the number of pack-years of smoking and duration of exposure to ETS. In addition, increased risk of pneumococcal disease was reversible and, in former smokers, decreased with the length of time since they had quit smoking.

Although the random-digit dialing method used in identifying control subjects necessarily excludes persons without telephones (such as homeless persons), selection bias also is unlikely to account for the findings. Among selected control subjects, the proportions of blacks, smokers, and persons with certain underlying medical conditions (e.g., diabetes) were similar to those among adults in the general population of the surveillance areas (126), suggesting that the sample was representative. Because of the data regarding chronic illnesses and alcohol consumption were self-reported, it is possible that underreporting and misclassification of alcohol consumption data may have occurred, particularly among heavy drinkers.

In summary, when assessing the plausibility of a causal relationship between smoking and pneumococcal disease, the strong independent association, existence of dose-response relations, apparent lack of significant bias or confounding, consistency with findings from previous studies (20, 21, 34), and existence of plausible biologic mechanisms all suggest that a causative role of smoking in the pathogenesis of pneumococcal infections is highly plausible (138).

Findings from both studies I and II are consistent with other studies that have found higher rates of invasive pneumococcal disease among men than women and among blacks compared with whites (3, 20, 21). Even after adjustment for possible confounders (particularly chronic medical conditions, smoking and socioeconomic status) in the case-control analysis (I), male sex and black race remained independent risk factors. In San Francisco (I), the rates were higher in men than in women and in black adults compared with nonblack adults, regardless of AIDS status of the subjects. Black patients with AIDS had the highest observed incidence of pneumococcal disease; this rate was 4.5-fold higher compared with nonblack AIDS patients.

It is not known why black patients with AIDS have a greater risk for pneumococcal disease than nonblack patients with AIDS but some of the difference may be explained by socioeconomic factors (37). Blacks persons may have limited access to health care, resulting in delayed diagnosis of HIV infection and less frequent use of pneumococcal vaccine, chemoprophylaxis against opportunistic infections and antiretroviral therapy (139). In a recent national survey, black persons, women, uninsured persons, and Medicaid-insured persons were shown to receive less optimal patterns of care for HIV infection (140).

In addition to black race, low socioeconomic status has consistently been identified as increasing the risk of pneumococcal disease (3, 21, 37). The case-control analysis (I) confirmed that a low socioeconomic status, as indicated by a low level of education is a strong independent risk factor for pneumococcal disease even after adjustment for other risk factors. We also found a strong inverse relationship between incidence of pneumococcal disease and the median household income of the census tracts in which the patients lived in an ecological analysis conducted in San Francisco (II). Although the relations between socioeconomic status, race and risk of disease are complex and poorly understood, it is possible that the factors that increase the risk of pneumococcal disease in blacks may not be present or are not significant in persons living in higher income areas and presumably in better living conditions. A recent study in Baltimore confirmed that black race, male sex, low median household income, and community AIDS prevalence were independently associated with increased incidence of pneumococcal disease (31).

Young children who attend day-care centers are at increased risk of pneumoccal disease (44, 45), but the risk of disease among adult family

members of children who attend day-care centers has been unknown. The increased risk of pneumococcal disease associated with living with young children who were in day-care is a new finding and probably associated with increased transmission of colonizing bacteria. This hypothesis is supported by studies that have found markedly higher carriage rates of *S. pneumoniae* in adults with preschool children in the family than in those without preschool children (29% and 6%, respectively) (141), and higher carriage rates in children attending day-care than in those not in day-care (73, 142).

1. 2. Impact of HIV on pneumococcal disease burden

In previous population-based reports, incidence rates of invasive pneumococcal disease have characteristically been high in young children and elderly persons, but low in young and middle-aged adults (Table 1, Figure 1). Our findings from population-based surveillance (II) highlight a dramatic change in the epidemiologic pattern of pneumococcal disease in a community with a high prevalence of HIV infection. An increase in the proportion of susceptible, immunocompromised persons in the population has resulted in extremely high rates of pneumococcal disease among young adults. We estimated that 55 % of the disease burden among adults aged 18–64 years and one third of all pneumococcal disease in the community could be attributed to HIV infection. Consequently, the overall incidence of invasive pneumococcal disease in San Francisco County was the highest reported in the continental United States (23, 24). We found that the risk of developing invasive pneumococcal disease was 46 times higher in persons with AIDS than in persons without known HIV infection. HIV-infected patients were predisposed to recurrences, but the case-fatality ratio was not increased in HIV-infected patients with pneumococcal disease.

The surveillance data from San Francisco (II) are the first report to document the substantial recent decrease in the incidence of invasive pneumococcal disease in persons with AIDS. In an earlier study, conducted at 10 San Francisco hospitals from 1983 to 1987, HIV-infected persons accounted for approximately one-fourth of adult cases of pneumococcal bacteremia, and the rate in patients with AIDS was estimated to be as high as 1% per year (5). HIV now accounts for a much larger proportion, more than half of cases in the community. However, the incidence in patients with AIDS patients seems to be decreasing. Coinciding with our study period, from 1994 to 1997, the incidence of certain AIDS-related opportunistic infections and deaths from these infections began to decrease substantially (54). These reductions in deaths and disease have been attributed to the effect of highly active antiretroviral therapy (HAART) (143). It is likely, therefore, that the reduction by half in the incidence of pneumococcal disease we observed in patients with AIDS also is associated with wider use of HAART. In San Francisco, the use of HAART was uncommon until the end of 1995 and then increased rapidly in 1996 and 1997 (144) coinciding with the most substantial decrease in incidence occurring in our study (Figure 10).

A limitation of our surveillance study (II) was that it did not include information on the use of antiretroviral therapy or routine chemoprophylaxis to prevent opportunistic infections. In addition, accurate data on pneumococcal vaccination status of patients were not available. Although the HIV treatment practices in San Francisco are probably comparable to those in other urban areas in the United States, differences may exist in the demographic composition of HIV-infected populations and the use of preventive services between San Francisco and other areas (145).

1.3. Institutional outbreaks and drug-resistant *S.pneumoniae*

Epidemic pneumococcal disease was common in institutional settings in the preantibiotic era (146, 147). After use of antibiotics became widespread, outbreaks were rarely reported. In the past decade, however, reports of institutional outbreaks appear to have become more frequent (69, 70). Because the rate of sporadic pneumococcal disease in nursing home residents is almost 14 times as high as that in the noninstitutionalized elderly (148), unrecognized or unreported clusters of pneumococcal disease in nursing homes may be more common than is currently believed. No routine surveillance for respiratory infections exists in long-term care facilities and treatment of these infections is commonly empiric without

microbiologic confirmation of etiology (149). Although the reasons for the apparent increase in pneumococcal outbreaks are not well understood, the emergence of multidrug-resistant strains may result in clusters becoming easier to detect, particularly if the clinical response of infections to empiric therapy declines, as was the case in the outbreak we investigated.

In the outbreak (III), a single multidrug-resistant pneumococcal strain was transmitted among nursing home residents and staff members. Although outbreaks caused by drug-resistant *S pneumoniae* have been reported among children (71, 72), such outbreaks have not been previously described in adult populations in the U.S. Our investigation suggested that several factors likely contributed to the high attack rate of disease and mortality, including a susceptible, unvaccinated population and high prevalence of colonization with a virulent organism. Findings of our retrospective cohort study confirmed in an elderly population those of other studies that have associated previous antibiotic use with carriage of drug-resistant *S. pneumoniae* in children (57, 71, 72) and with drug-resistant disease in children (150) and adults (75).

Exactly how and when the epidemic strain was introduced into the nursing home we studied is unknown, but our findings suggested person-to-person transmission from staff members to residents. Although few data are available about *S. pneumoniae* carriage rates in adults, the rate of asymptomatic carriage among nursing home residents (23%) was higher than that generally reported among adults (less than 10%) (66, 69, 70). After the administration of pneumococcal vaccine and antibiotics to the residents, no new cases occurred. Surprisingly, carriage was also reduced substantially despite the strain's resistance to penicillin, and we observed no recolonization during follow-up. Because it is not possible to distinguish the separate effects of antibiotics and vaccination in ending the outbreak, vaccination and chemoprophylaxis may both have had a role in reducing carriage (151). Successful eradication of resistant pneumococci from the two colonized employees by antibiotics may have eliminated the most likely source of reinfection in this relatively closed environment.

2. Implications for prevention of invasive pneumococcal disease in adults

Our epidemiologic findings have several potential implications for prevention of invasive pneumococcal infections in adults and may have relevance for identifying optimal strategies for using the pneumococcal polysaccharide vaccine in the adult groups studied (1). In particular, because the current vaccine indications do not address a substantial proportion of the disease burden in nonelderly adults. The preventive strategies with potential for reducing the incidence of pneumococcal disease in different adult target populations identified in each of the studies I to III are summarized in Table 10.

2.1. Immunocompetent, nonelderly adults

The case-control study (I) added invasive pneumococcal disease to the long list of diseases linked to active and passive smoking. However, unlike the well known chronic effects of smoking such as cancer, heart and lung disease, which may take decades to develop, the increased risk of pneumococcal disease in young adults is potentially immediate. In 1995, 47 million adult Americans, approximately one-fourth of the U.S. adult population, smoked cigarettes (152). Because of the high prevalence of smoking and the large population-attributable risk for smoking, substantial opportunities exist for prevention. We estimated that if the prevalence of cigarette smoking could be reduced from the current 25% to 15%, one of the National Health Objectives, the incidence of invasive pneumococcal disease among nonelderly adults would potentially decrease by approximately 18 percent. At the population level, this would mean approximately 4000 fewer cases in the U.S. annually (CDC, unpublished data). Because exposure to environmental tobacco smoke is widespread in both the home and the workplace (153), efforts to reduce exposure to smoke in public spaces may also result to fewer cases of pneumococcal infection.

The role of pneumococcal vaccine in preventing pneumococcal infections in smokers remains to be determined (138). Before it can be

Table 10. Summary of preventive strategies with potential for reducing pneumococcal disease burden in adults

Target groups for increased use of pneumococcal polysaccharide vaccine	Incidence per 100 000*	VE (%)†	PAR (%)‡	Other methods of prevention	PAR (%)‡
Immunocompetent adults aged 18–64 years	16			Reducing exposure to ETS	17
				Indirect effect of vaccinating children with conjugate vaccines	11
smokers? (incorporate vaccine in smoking cessation programs?)	38	56	51	Reducing prevalence of smoking	51
persons with chronic illnesses	37	65–84	14		
black persons (young adults in poor urban areas)	46–61	56	31		
HIV infected persons with CD4 counts >500 cells/mm^3	803	50	55	HAART (effectiveness 50%) (early identification of HIV)	—
Persons aged ≥65 years in LTCFs vaccination universally recommended	29	75	—	Judicious use of antibiotics to prevent outbreaks caused by DRSP	

* Incidence rates from studies I and II and reference (23).
† Vaccine and HAART effectiveness estimates from references (79, 108, 160, 161).
‡ Population attributable risks: potential for reduction in disease incidence if risk factor removed through vaccination, therapy or behavior change (on the basis of studies I and II)

defined, advisory bodies responsible for determining vaccination indications should consider several issues, including the cost-effectiveness of such intervention, duration of protection and possible need for revaccination, limitations in vaccine supply, and the fact that pneumococcal vaccine is still underused even in those groups for whom it is currently recommended (154). Because the increased risk of pneumococcal disease in former smokers persisted for over 10 years after they had quit smoking, incorporating pnemococcal vaccination into smoking–cessation programs could be considered.

Our findings confirm that the current pneumococcal polysaccharide vaccine indications for chronic medical conditions, as recommended by the ACIP (1), appear to be appropriate. In the case-control study (I), the presence of any non-immunosuppressing chronic illness was an independent risk factor for invasive pneumococcal disease. Although in our study the population attributable risk associated with chronic illnesses was relatively low because of the low prevalence of these conditions in the age-group studied (Table 10), overall, 59% of invasive pneumococcal disease in persons aged 18–64 years occurs in those who have an indication for the vaccine (23). Because the pneumococcal vaccine is effective against bacteremia among immunocompetent adults (79, 108), and because vaccination coverage among persons in this age group is even lower than in those aged ≥65 years (126), substantial reductions in disease could be achieved in nonelderly adults with chronic illnesses thorough improved use of the vaccine according to current recommendations (1). Our results also support the recommendation to evaluate persons 50 years of age for indications for pneumococcal vaccine (155), because of the increasing prevalence of risk factors with advancing age.

However, the current vaccine indications do not address a considerable proportion (41%) of cases of invasive pneumococcal disease occurring in adults. Because of the higher risk for infection in blacks persisted even after adjustment for multiple medical and socioeconomic factors, our findings also raise the question of need for broader use of polysaccharide vaccine in black persons

(31). This is particularly relevant since both non-elderly and elderly black adults are much less likely to have received pneumococcal vaccine than whites (156, 157).

2.2. HIV-infected persons.

Although limited data are available on the effectiveness of pneumococcal polysaccharide vaccine in HIV-infected persons, its use has been recommended on the basis of the high rate of disease, the apparent safety and potential benefits of the vaccine (158). Therefore, the strength of ACIP recommendation for vaccinating HIV infected persons is category "C" (Effectiveness of vaccination is not proven)(1). However, some asymptomatic HIV-infected persons respond well to pneumococcal polysaccharide vaccine; the immunologic response seems to be best in early stages of HIV infection (82, 83).

A recent clinical trial on the efficacy of 23-valent pneumococcal polysaccharide vaccine in HIV-infected adults in Uganda found no efficacy against invasive pneumococcal disease (159). However, many study subjects were in advanced stage of HIV as evidenced by over half of them being classified in WHO clinical stage 3 and almost half having CD4 counts <200 cells/mm^3. In addition, the background rate of disease was over 3 times of that in the U.S., many had recurrent disease, and mortality was extremely high (although similar) in both vaccine and placebo groups. Although the findings of this study warrant further research, they appear to have limited relevance for vaccination policy in industrialized countries because of the substantial differences in the epidemiology and treatment of HIV infection as well as epidemiology of pneumococcal disease.

In contrast, two recent observational studies and an earlier, small case-control study conducted in the U.S. found that the vaccine was effective in HIV-infected persons (160–162). A case-control study conducted in San Francisco assessed risk factors and vaccine effectiveness among 176 HIV infected patients with invasive pneumococcal disease and 327 controls matched by admitting hospital and CD4 cell count (160). In multivariate analysis, patients with invasive pneumococcal disease were more likely to be black, current smokers, and have close contact with children, all factors that were previously associated with invasive pneumococcal disease in non-HIV infected adults in our case-control study (Study I). Adjusted for these factors and CD4 counts, pneumococcal polysaccharide vaccine had an overall effectiveness of 49% (95%CI, 12–70%) against invasive disease. The adjusted vaccine effectiveness in whites was 76%, but no effectiveness was documented in blacks (160). Immunologic status at the time of vaccination may have influenced the apparent racial difference in efficacy. Because the interval from diagnosis of HIV to admission to the hospital (and enrollment to the study) was significantly shorter for blacks than whites, blacks may have been diagnosed with HIV at a later stage or may have had more rapid disease progression (139).

A cohort study based on the Adult and adolescent spectrum of HIV disease project (ASD), evaluated the effectiveness of pneumococcal vaccination against both invasive and non-invasive disease during 1990-98 by using data from >100 inpatient and outpatient facilities in 11 U.S. cities (161). Among 39,086 persons with 71,116 person-years of observation and 585 episodes of pneumococcal disease, factors associated with increased risk of pneumococcal disease included injection drug use, black race, alcoholism and low CD4 counts. Pneumococcal polysaccharide vaccine given at CD4 counts $\geq$500 cells/mm^3 was associated with significantly lower risk of pneumococcal disease (RR, 0.5; 95%CI 0.3–0.9). However, vaccination at lower CD4 counts (<500 cells/mm^3) was not associated with decreased risk.

Data from these two studies are consistent with pneumococcal polysaccharide vaccine providing significant protection in a subset of HIV patients (163) and support the ACIP (1) and USPHS/IDSA (164) recommendation that HIV-infected persons should be vaccinated as soon as possible after the diagnosis of HIV is confirmed (at high CD4 counts) to increase the opportunity for a functional immune response (158). For persons presenting with low CD4 counts, delaying the administration of pneumococcal vaccine until after immune restoration with HAART has been achieved might be considered (163). The effect HAART on antibody responses to pneumococcal vaccination warrants further study, as does determining the effectiveness of pneumococcal

polysaccharide vaccine when used in persons with restored immune function after treatment with HAART.

No data have been previously available on the specific effect of HAART on the risk of pneumococcal disease in HIV-infected persons. In the ASD study, use of triple therapy with antiretroviral agents was associated with a similarly lowered risk of pneumococcal disease as was vaccination (RR, 0.5; 95%CI 0.3–0.9) (161), supporting the hypothesis that increased use of HAART was the principal reason for the decline in incidence of invasive pneumococcal disease in AIDS patients in San Francisco (Study II).

Considerable reductions in the incidence of pneumococcal disease in HIV-infected adults may result from increasing use of HAART, and the decrease in HIV-attributable risk of pneumococcal disease may have a major effect on public health in communities with high prevalence of HIV. Previous analysis suggested that pneumococcal surveillance may be a sensitive epidemiologic indicator of increases in the immunosuppressed HIV-infected population in the community (6). Our data suggests that pneumococcal surveillance may also reflect decreases in this population due to response to HAART, or use of preventive services.

Because the HIV epidemic disproportionately affects persons in ethnic minority groups (54), targeted preventive efforts are needed, especially among black HIV-infected patients living in poor urban areas. To date, most efforts to increase pneumococcal vaccination coverage rates have targeted elderly persons but many HIV-infected, nonelderly adults who have access to medical care may not be vaccinated (165). In a recent surveillance study in Baltimore, the majority of pneumococcal infections in blacks occurred before age 65 years (31). Efforts to increase pneumococcal vaccination rates should therefore target young HIV-infected adults, particularly those living in poor urban areas.

2.3. Preventing drug-resistant pneumococcal infections in elderly persons

An overall strategy for preventing illness and death due to drug-resistant pneumococcal infections has been implemented in the U.S. and consists of a) improved surveillance for drug-resistant infections, b) promotion of judicious use of antibiotics, and c) increased use of pneumococcal vaccine (166). Reducing the selective pressure for drug-resistant organisms is important in limiting the spread of drug-resistant infections (167). Although several factors are likely to contribute to the spread of drug-resistant strains, many studies have consistently shown that both therapeutic and prophylactic use of antibiotics are associated with carriage and disease due to drug-resistant *S. pneumoniae*. Because antibiotics are the most commonly prescribed drugs in outpatient settings, one key strategy in decreasing the spread of resistant pneumococci is decreasing unnecessary use of antibiotics in the community (167).

S. pneumoniae is the most common cause of nursing home-acquired pneumonia (168). Because long-term care facilities are the most likely settings for outbreaks of pneumococcal disease in elderly persons, encouraging judicious use of antibiotics is an important prevention strategy also in institutional settings. Systemic antibiotic use in long-term care facilities is common and 25% to 75% of it may be inappropriate (149, 169–171). Nursing homes may therefore serve as foci for emergence of drug-resistant bacteria. Residents who are frequently transferred to and from acute care hospitals, may also provide a route for the spread of resistant strains from one facility to another. The part that colonized staff members appear to have played in transmitting the epidemic strain in the nursing home we investigated (III) highlights the importance of excluding health care providers from work when they are ill. Guidelines for optimal antimicrobial drug use in long-term care facilities are needed.

The increasing prevalence of drug-resistant *S. pneumoniae* and the potential of resistant strains to cause epidemic disease with high case-fatality among unvaccinated individuals underscores the importance of prevention by vaccination. Pneumococcal polysaccharide vaccination is efficacious and cost-effective against pneumococcal bacteremia in elderly persons (79, 107, 108, 111). However, in 1995, only 35 percent of persons 65 years of age and older reported ever having received a dose of pneumococcal vaccine in the U.S (154). In addition, the vaccine coverage among elderly blacks was lower than among elderly

whites. Vaccination coverage rates have consistently been less than 5% in all recently reported outbreaks among elderly nursing home residents (69, 70), including the outbreak we investigated.

Our investigation (Study III) highlighted the high mortality rates from pneumococcal disease among elderly persons, continuing emergence of drug-resistance, lack of effective means to reduce or prevent transmission, and the occurrence of pneumococcal outbreaks among undervaccinated nursing home residents (151). To prevent pneumococcal disease outbreaks, nursing homes should offer pneumococcal vaccine to all eligible residents and to new residents on admission to the facility. According to current recommendations, all persons aged 65 years or older should be vaccinated if their vaccination status is unknown (1; Figure 2).

3. Unresolved issues and future directions

3.1. Limitations of the pneumococcal polysaccharide vaccine

There are several limitations for using the 23-valent pneumococcal polysaccharide vaccine in preventing pneumococcal disease in adults. These limitations include limited duration of protection, particularly in elderly persons, poor immunogenicity of several capsular antigens in the vaccine, poor antibody responses in immunocompromised persons, and lack of effect on pneumococcal carriage. Furthermore, several of the poorly antigenic capsular serotypes (e.g., 6B, 23F) are also those most frequently causing invasive drug-resistant infections (8, 172). Although the precise duration of immunity is unknown, declines in serum antibody levels 3–5 years after vaccination in the elderly (86) and decreases in clinical protection (79, 108) suggest that revaccination may be indicated to provide continued protection. However, more immunogenic pneumococcal vaccines that also provide long-term immunity are clearly needed for adults and they may provide a more feasible approach to the public health problem than periodic revaccination.

3.2. Potential role of pneumococcal conjugate vaccines in adults

Because of the excellent results of the 7-valent pneumococcal conjugate vaccine efficacy trial against invasive disease (123), major changes in the epidemiology of pneumcoccal infections in children may result in the next decade from incorporation of conjugate vaccines in childhood immunization programs. However, no clinical efficacy data are currently available in adults. Although the role of pneumococcal conjugate vaccines in adults has not yet been determined, in the long term, the advantages of new pneumococcal conjugate vaccines over the polysaccharide vaccine in adults may include production of antibodies with high functional activity (119), improved protection against poorly immunogenic capsular antigens, improved immunogenicity in immunocompromised persons (173), reduction of nasopharyngeal carriage (174), and increased duration of protection due to immunologic memory after infant vaccination.

Although children who had received polysaccharide vaccine were not significantly less likely to be carriers of pneumococcus (175), conjugate vaccines may reduce nasopharyngeal carriage of the pneumococcal serotypes included in the vaccine (176). Reduction in carriage rates of *S. pneumoniae* would potentially increase the overall impact of conjugate vaccines by reducing transmission and thereby also limiting spread of drug-resistant strains. Consequently, incidence and disease burden from noninvasive infections such as nonbacteremic pneumonia and acute otitis media could also be reduced (120). Our finding that living with young children who are in day care was an independent risk factor for pneumococcal disease in adults (Study I), suggests that vaccinating children with conjugate vaccines may indirectly result in reduction of disease incidence in adults through decreased transmission (Table 10).

Conjugate vaccines should be evaluated for utility in preventing pneumococcal disease in adults at high risk including immunocompromised adults who respond poorly to the current 23-valent polysaccharide vaccine. Limited data suggests that conjugate vaccines may induce better immune responses in immunocompromised persons but no

data exist on clinical effectiveness of conjugate vaccines in this group. It may be possible to prime the immune system in adults by first administering the 7-valent conjugate vaccine. A subsequent dose of 23-valent polysaccharide vaccine could then be given to induce a booster response to the serotypes present in both vaccines and primary T-cell independent responses to the 16 serotypes that are only included in the polysaccharide vaccine (173). Additional data are needed to determine immunogenicity, safety, and clinical effectiveness of conjugate vaccines in adults, and of the above approach in HIV-infected persons.

A limitation of conjugate vaccines is that it appears possible to include only a limited number of serotypes in the vaccine. Overall, the 7-valent conjugate vaccine covers approximately 50–60% of the serotypes of invasive pneumococcal isolates in adults compared with the 80-90% coverage of the polysaccharide vaccine. Because of the broad distribution of serotypes in infected adults, use of the conjugate vaccine alone would not prevent invasive pneumococcal disease in HIV-infected persons. In study II, the distribution of pneumococcal serotypes causing illness was similar in HIV-infected patients and non-HIV-infected patients (5, 51), and 83% of the isolates were of serotypes included in the current 23-valent polysaccharide vaccine. However, serotypes included in a 7-valent pneumococcal conjugate vaccine accounted for only 44% of the isolates. These data support continuing use of the polysaccharide vaccine in adults instead of replacing it with the conjugate vaccine at this point.

3.3. Improving utilization of pneumococcal polysaccharide vaccine

The 1997 ACIP recommendations for use of pneumococcal polysaccharide vaccine (1) were intended for use primarily in the U.S. because the epidemiologic features of pneumococcal disease (e.g., rates of disease and hospital admissions, and mortality) and organization of the health care system may differ in other countries. However, these recommendations have subsequently been adapted and used as the basis for national recommendations in Canada but not in many European countries (177, 178). Although the epidemiologic situation (e.g., prevalence of drug-resistance) and distribution of risk factors, such as HIV and cigarette smoking in the population may be different, the findings of studies I to III could be useful when developing policies for prevention of pneumoccal disease in industrialized countries other than the U.S.(179).

The use of pneumococcal polysaccharide vaccine in line with the ACIP also has been recommended by the American College of Physicians and Infectious Disease Society of America (155), the American Academy of Family Physicians and the American Academy of Pediatrics. In the U.S., the current target group for pneumococcal vaccination includes 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). In 1995, only 35% of persons aged ≥65 years had ever received the pneumococcal polysaccharide vaccine (154).

Although vaccination coverage has increased since the 1997 recommendations were implemented, the vaccine remains underutilized and large geographical variations exist in coverage. In 1997, the percentage of persons aged ≥65 years who reported ever receiving pneumococcal vaccination ranged from 32% to 60% (median, 46%) in different states. The vaccine coverage rates also vary by race (156). In 1997, 47% of white adults aged ≥65 years reported having received pneumococcal vaccine compared with 30% of black adults.

The underutilization of pneumococcal vaccine reflects a lack of emphasis on adult vaccination. Childhood vaccination programs, such as conjugate vaccines for *Haemophilus influenzae* type b disease, have made substantial achievements in reducing the burden of many vaccine-preventable diseases. However, childhood vaccination programs alone will not eliminate specific public health problems, such as that caused by pneumococcal disease, because a large proportion of illness and most deaths occur in adults (Figure 1; 155), and because pneumococcal disease is unlikely to disappear completely even among children immunized with the new conjugate vaccines. Therefore, vaccination programs must also be extended to adult populations at increased risk of pneumococcal disease.

Reasons for underuse of pneumococcal vaccine in adults may include lack of awareness of

the vaccine-preventable disease burden, particularly in nonelderly adults, the importance of pneumococcal disease and benefits of pneumococcal vaccination including doubts about its effectiveness (180). Better understanding of the evolving epidemiology of pneumococcal infections in adults, including assesment of disease burden and preventablility, identification of risk factors with their associated attributable risks, will help focus vaccination efforts to persons at greatest risk of pneumococcal infection and to those most likely to benefit from vaccination. These data will also help in assessing the potential impact of proposed prevention programs. Until the role of new pneumococcal vaccines in adults is defined, improved utilization of pneumococcal polysaccharide vaccine, the best available prevention tool despite its limitations, will remain a cornerstone for the public health challenge of preventing invasive pneumococcal disease in adults.

SUMMARY

Several demographic and epidemiologic developments have made an impact on the epidemiology of invasive pneumococcal infections in adults during the past decade. These trends include the increasing number of persons who are immunocompromised because of HIV/AIDS, the aging of the population and the growing number of institutionalized persons, all of which have contributed to an increasing number of persons susceptible to pneumococcal infections. The increasing prevalence of drug-resistant *S. pneumoniae* has made treatment of pneumococcal infections more difficult than before. In addition, the specific underlying conditions and other factors that increase the risk of pneumococcal disease, as well as the disease burden associated with these conditions in different adult populations have not been well defined. These developments highlight the need for updated epidemiologic data and new preventive strategies for pneumococcal disease in adults.

The three studies (I to III) in this thesis provided new information about the recent developments in the epidemiology of invasive pneumococcal disease in three distinct adult populations: immunocompetent nonelderly adults, HIV-infected persons, and elderly residents of long-term care facilities. The main findings are summarized below, and the public health policy implications of these findings for the prevention of pneumococcal disease in industrialized countries are discussed, particularly the role of pneumococcal polysaccharide vaccine.

1. We assessed the contribution of active and passive smoking and other factors to the risk of invasive pneumococcal disease and determined the population attributable risks associated with independent risk factors in a population-based case-control study (I). This study provided strong evidence for the association of tobacco smoke with pneumococcal disease and established cigarette smoking as the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults. Overall, 51 % of the pneumococcal disease burden in this population group could be attributed to cigarette smoking; 17% of disease among nonsmokers was attributable to exposure to environmental tobacco smoke. Other factors identified as independently increasing the risk of invasive pneumococcal disease included chronic medical conditions, low socioeconomic status, black race, male sex, and living with young children who were in day care.

Because of the high prevalence of smoking and the large population-attributable risk, substantial opportunities exist for prevention. We estimated that if the prevalence of cigarette smoking could be reduced from the current 25% to 15%, the incidence of invasive pneumococcal disease among nonelderly adults would potentially decrease by approximately 18 percent. Because exposure to environmental tobacco smoke is common, efforts to reduce exposure to smoke in public spaces may also result to fewer cases of pneumococcal infection.

Our findings confirmed the appropriateness of current pneumococcal polysaccharide vaccine indications for chronic medical conditions. Because most (59%) invasive pneumococcal infections in persons aged 18-64 years occur in those who have an indication for the vaccine, considerable disease reductions could be achieved in this age-group thorough improved use of the vaccine among persons with underlying chronic medical conditions. However, a substantial proportion (41%) of adult cases of invasive pneumococcal disease occur in persons who do not have an indication for the vaccine. Because the higher risk of infection in blacks persisted even after adjustment for multiple medical and socioeconomic factors, our findings also raise the question of need for broader use of pneumococcal vaccine in black persons. This issue is particularly relevant since both nonelderly and elderly black adults are much less likely to have received pneumococcal vaccine than white adults.

2. We evaluated the impact of the HIV epidemic on the rates and clinical characteristics of invasive pneumcoccal disease by conducting population-based surveillance in a community with a high prevalence of HIV (II). Our findings highlighted a dramatic change in the epidemiologic pattern of pneumococcal disease with extremely high rates among young adults. More than

half of the disease burden among adults aged 18-64 years and one third of all pneumococcal disease in the community could be attributed to HIV infection. The risk of developing invasive pneumococcal disease in persons with AIDS was 46 times higher than in persons without known HIV infection. Black AIDS patients had a 4.5-fold higher risk of infection than nonblack AIDS patients. HIV-infected patients also were predisposed to recurrences but mortality from pneumococcal disease was not increased. Our data also documented a substantial decrease in the incidence of invasive pneumococcal disease in persons with AIDS from 1994 to 1997 , likely associated with wider use of HAART.

Considerable reductions in the incidence of pneumococcal disease in HIV-infected adults may result from increasing use of HAART. The decrease in HIV-attributable risk for pneumococcal disease may have a major effect on public health in communities with high prevalence of HIV. Although limited data are available on the effectiveness of pneumococcal polysaccharide vaccine in HIV-infected persons, the vaccine appears to provide protection in a subset of HIV patients. Our findings support the recommendation that HIV-infected persons should be vaccinated as soon as possible after the diagnosis of HIV is confirmed. Efforts to increase pneumococcal vaccination rates also should target black HIV-infected adults, particularly those living in poor urban areas.

3. We studied factors associated with colonization and disease with multidrug-resistant *Streptococcus pneumoniae* in a cohort study in the context of an outbreak investigation in a nursing home (III). A single multidrug-resistant pneumococcal strain was transmitted among elderly nursing home residents and staff members. The factors that contributed to the high attack rate included a susceptible, unvaccinated institutionalized population and high rate of carriage. The epidemic ended and carriage was reduced substantially when residents were given antibiotics and pneumococcal polysaccharide vaccine. Our retrospective cohort study confirmed in an elderly population the associations of prior antimicrobial use with colonization and disease due to drug-resistant *S.pneumoniae*.

Because long-term care facilities are the most likely setting for outbreaks of pneumococcal disease in elderly persons, encouraging judicious use of antibiotics is an important strategy for preventing illness and death due to drug-resistant pneumococcal infections in institutional settings. Guidelines for optimal antimicrobial drug use in long-term care facilities are needed. The increasing prevalence of drug-resistant *S. pneumoniae* and outbreaks among undervaccinated nursing home residents underscore the importance of vaccination.

The pneumococcal polysaccharide vaccine is efficacious and cost-effective against pneumococcal bacteremia in elderly persons, but it is underused. A common factor in all reported outbreaks in nursing homes from the past decade has been that less than 5 percent of residents had been vaccinated. Our investigation highlighted the high mortality rates from pneumococcal disease among elderly persons, continuing emergence of drug-resistance and the lack of effective means to reduce or prevent transmission. Improved pneumococcal vaccine coverage among elderly residents is fundamental for preventing outbreaks of pneumococcal disease in long-term care facilities.

Better understanding of the evolving epidemiology of pneumococcal infections in adults, including the assesment of disease burden and identification of risk factors with their associated attributable risks will help in optimizing vaccination efforts and in assessing the potential impact of prevention programs. Until the role of new pneumococcal conjugate vaccines in adults is defined, improved utilization of pneumococcal polysaccharide vaccine, the best available prevention tool despite its limitations, will remain a cornerstone for the public health challenge of preventing pneumococcal disease in adults.

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