Chapter

100

Epidemiology of Pneumococcal Disease and Efficacy of Polysaccharide Vaccines in Adults

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Pneumococcal pneumonia and invasive pneumococcal disease (IPD) remain a considerable cause of morbidity and mortality, with recent data showing a continued unacceptably high social and economic burden. *Streptococcus pneumoniae* can be isolated from 5-10% of healthy adults and 20-40% of healthy children[1]. Infection can result in a variety of clinical syndromes with meningitis, pneumonia, and sepsis among the most critical. It is also responsible for 30-50% of all community-acquired pneumonias,[2,3] with a fatality rate of 7-35% for bacteremic pneumococcal pneumonia.[4] Vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV23) is an important preventive strategy in the United States.

Epidemiology of Pneumococcal Disease in the United States

Each year, pneumococcal infections are responsible for 6 million cases of otitis media, 3000 cases of meningitis, and an incident rate of pneumonia of 23-33 cases per 100,000 population[5]. The very young and older adults are at high risk. Indeed, adults who are 65 years of age or older are extremely susceptible to IPD with an estimated 350,000 to 620,000 hospitalizations per year (Fig. 1)[6]. The fatality rate from IPD for patients in this age group is 7.2 per 100,000 population and 1 per 100,000 population for children ≤ 1 year of age[5].

Risk Factors

In addition to age, others at high risk for infection include Blacks, Native Americans[7, 8] and Alaska natives,[9] as well as persons with certain medical and immunocompromised conditions, such as chronic heart or lung disease, HIV, or cancer[5]. A report from the Centers for Disease Control and Prevention (CDC) compiled from data collected during 1999 and 2000 shows the dramatic effects of chronic illness and increasing age on the incidence of IPD (Figs 2A and B). Persons with chronic conditions have a 2 to 8 fold increased risk of death from IPD; this risk was higher for Blacks than for Whites.[10] Adults in long-term care facilities are particularly at risk for IPD, as residents often suffer from a number of chronic illnesses[4].

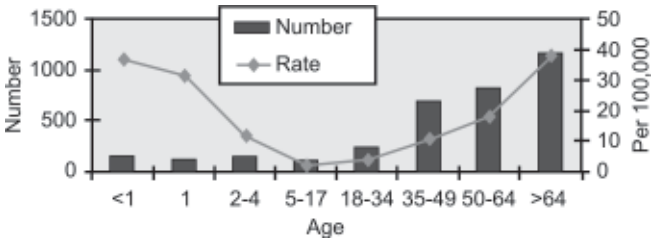


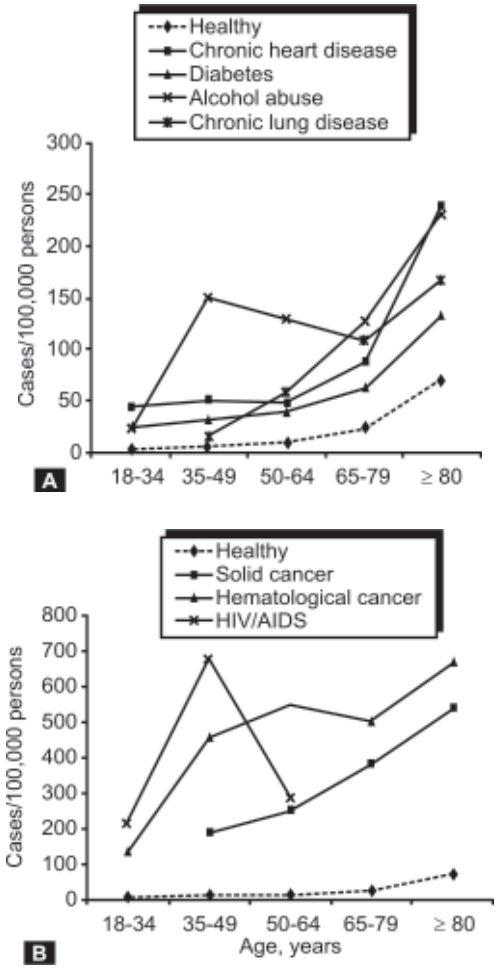
Fig. 1: Age-related IPD

Source: Centers for Disease Control and Prevention the Active Bacterial Core Surveillance Report 2004

Cigarette smoking has been identified as a strong independent behavioral risk factor for IPD in immunocompetent adults 18 to 64 years of age with an odds ratio for current smokers of 4.1 (95% CI: 2.4–7.3, P<.001)[11].

Available Vaccines for Pneumococcal Disease

Although more than 90 serotypes of *S. pneumoniae* have been identified, the 7-valent conjugated pneumococcal vaccine (PCV7) for children covers more than 80% of isolates obtained from children less than 5 years of age. Since the introduction of this vaccine in 2000, the incidence of IPD not only decreased in children, but has apparently reduced the incidence of IPD in adults as well. In 2001, the incidence of IPD was reduced by 69%



Figs 2A and B: Age-specific incidence of IPD in healthy adults ≥ 18-year-old compared with adults with chronic illnesses or immunocompromised conditions[10]

in children; a concurrent incident disease reduction of 32% was observed in adults 20–39 years of age, 8% in adults 40-64 years of age, and 18% for adults 65 years of age and older. In the oldest cohort, there was a 22% decrease associated with the 7-valent vaccine-related serotypes: however, this was offset slightly by a 5% increase for non-vaccine related serotypes.[12]

PPV23, which is available for adults, contains purified antigens from 23 different serotypes shown to account for about 85-90% of bacteremic infections in adults in the United States[4,13]. The serotype-specific protective effect of PPV23 and PPV14 (no longer in use) was assessed in a prospective, hospital-based, case-controlled study of 1054 adults (predominantly white; median age of 69 years of age). The aggregate protective effect for IPD was 56% for all patients, 61% for immunocompetent patients (n = 808), and 21% for immunocompromised patients (n = 175). The vaccine was not effective against serotypes not included in the vaccine. The case fatality rate, however, was similar among vaccinated and non-vaccinated patients[13].

A systematic review of randomized trials (from 1976 to 1998) of various polyvalent PPV vaccines in immunocompetent adults led to a meta-analysis of 14 trials of 48,837 patients[3]. Overall, PPV vaccines decreased the incidence of definite pneumococcal pneumonia by 71%, presumptive pneumococcal pneumonia by 40% and mortality due to pneumonia by 32%. PPV vaccination did not prevent all-cause pneumonia or death. A subgroup analysis of patients older than 55 years of age lacked the statistical power to show differences in outcomes with vaccination; however, there was a trend toward a reduced risk of definitive pneumococcal pneumonia (odds ratio 0.58 [0.18–1.0] and mortality due to pneumonia (odds ration 0.69 [0.28–1.27]).

Outcomes in High-risk and Older Populations

A comprehensive 14 year surveillance study assessed the efficacy of the PPVs in high risk populations >-65 years of age) in the United States. [14] Outcomes for 2837 persons showed the overall protection efficacy for serotypes included in the vaccine was 57% (95% CI: 45-66%). Efficacy for immunocompetent older adults >-65 years of age was 75% (95% CI: 57–85%). For persons with various immunocompromised clinical conditions including diabetes mellitus, and chronic heart and lung diseases, who were considered high-risk, the estimated vaccine efficacy was considerably lower, ranging from 0% to approximately 65%. Of interest, it was observed that protection did not decline over time.

The incidence of IPD in patients infected with HIV has been reported to be 46 to 100 fold higher than in the general population. The introduction of highly active antiretroviral therapy (HAART) and the more widespread use of PPV23 may impact the incidence of IPD in this population. A prospective, case-controlled study of 142 episodes of disease in 122 Spanish HIV-infected adults showed that the incidence of pneumococcal bacteremia was significantly reduced by 2.9 fold in the current era of HAART compared to that in the pre-HAART era (8.2 episodes per 1000 patient years vs 24.1 episodes per 1000 patient years, respectively, P=.010)[15] in patients administered PPV23. In an earlier study that stratified HIV infected individuals by CD4 cell count, only 24% of persons with ≤ 500 CD4 cells responded to PPV compared with 75% of persons with CD4 >500 and 92% of healthy controls. Therefore, the authors suggested that pneumococcal vaccine should be administered when HIV is first diagnosed[16].

Outcomes in Older Adults

The effectiveness of vaccination for pneumococcal disease in older adults remains controversial as many prospective clinical trials have not documented a significant reduction in the risk of pneumonia or mortality by PPV, although positive trends have been observed. Overall, studies of older adults have been limited by the inability to adequately power the study because of the relatively low number of vaccinated subjects[17-19].

Nevertheless, several studies involving large numbers of older adults have evaluated outcomes of pneumococcal vaccination in the community setting and found that there are benefits from vaccination. For example, a large retrospective cohort study assessed 47,365 healthcare data base members 65 years of age and older over a 3-year period. Primary outcomes included hospitalization for community-acquired pneumonia, pneumonia in patients who were not hospitalized, and pneumococcal bacteremia. Prior administration of PPV was associated with a 44% decrease in pneumococcal bacteremia (hazard ratio, 0.56; P=.03), but was also associated with a small elevated risk of hospitalization for pneumonia ((hazard ratio, 1.14, P=.02]. Vaccination did not affect the risk of outpatient pneumonia (hazard ratio, 1.04: 95% CI [0.33–0.93])[6].

A large prospective cohort study in persons aged[3] ≥ 65 years in Sweden assessed the effectiveness of PPV23 in reducing hospitalizations and deaths[20, 21]. Enrollees could also receive the influenza vaccine. Thirty-nine percent of the population was vaccinated during an 8-week campaign 76,177 received both vaccines and 841 received PPV23 only. After 1 year of follow-up, the incidence of hospitalization for pneumonia was 22% lower in the group vaccinated (RR 0.78; P<.0001) compared to the unvaccinated group. The risk of IPD was also significantly reduced by 54% (RR: 0.46; P=.007). For the group that was vaccinated, the risk of dying of pneumonia while hospitalized was 45% lower (RR 0.55; P<.0001). The authors concluded that pneumococcal (and influenza) vaccination significantly decrease the number of hospitalizations and mortality in older adults.

The potential benefit of vaccination against pneumococcal disease is of particular interest in the older population with serious underlying medical conditions. In a 2-year retrospective study of 1898 persons ≥ 65 years of age with diagnosed chronic lung disease , vaccination with PPV23 significantly reduced hospitalization due to pneumonia and influenza by 43% (P=.005) compared with unvaccinated persons. Additionally, mortality from all causes was reduced by 29% (P=.008)[22].

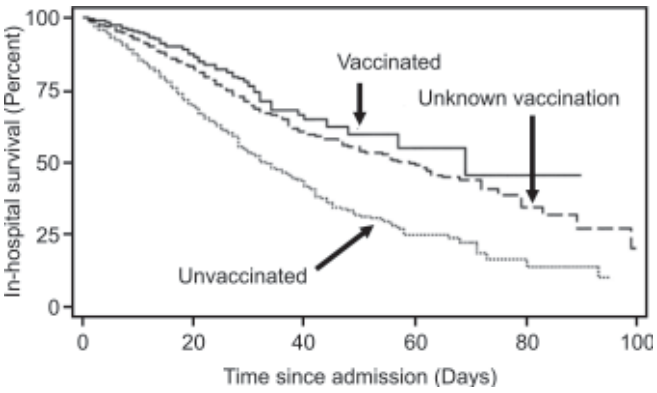


Fig. 3: In-hospital survival of patients hospitalized for community-acquired pneumonia by prior pneumococcal vaccination status[23]

In the United States, healthcare organizations covering large numbers of patients have an interest in clarifying whether pneumococcal vaccination confers health benefits to their members. Therefore, a prospective observational study was conducted at 109 community and teaching hospitals to assess the effects of prior pneumococcal vaccination on adults hospitalized for community-acquired pneumonia[23]. Between 1999 and 2003, 62,918 adults with a mean age of 72 years were hospitalized for community acquired pneumonia; only 12% had documented pneumococcal vaccination, 23% were unvaccinated and the rest were of unknown status. Patients with a record of vaccination were less likely to die in-hospital than were those in the unvaccinated group (Fig. 3). In patients with prior vaccination, the risk of respiratory failure was reduced by 33%; this group also had a reduced risk of other complications such as acute renal failure, cardiac arrest and sepsis syndrome, and median length of hospital stay was shortened by 2 days (P<.001). The authors concluded that PPV23 provides potential health and economic advantages which reinforce the goals of compliance with vaccine recommendations for adults in the United States.

Cost-effectiveness of Pneumococcal Vaccination

With pneumococcal bacteremia as the efficacy endpoint, the medical costs and health effects of pneumococcal vaccination versus no vaccination was assessed in older adults ≥65 years of age[24]. Analyses showed that if the 23 million unvaccinated elderly in 1993 had been vaccinated, 78, 000 years of healthy living would have been gained and US$194 million would have been saved. A subsequent study[25] in persons aged 50 to 64 years demonstrated that pneumococcal vaccination for this age group, particularly in high-risk

persons, provided both future cost savings and improved health benefits. In addition, Black race as a high-risk group showed a greater than average health and cost benefit of vaccination.

Summary

Pneumococcal pneumonia and IPD remain an important cause of morbidity and mortality in the United States. PPV23 is immunogenic and has shown efficacy in reducing IPD. Although data for reduction of pneumonia in older adults is contradictory, recent studies have suggested that vaccination may reduce hospitalization, complications, and mortality in this population. Thus, PPV23 remains a fundamental strategy for prevention of pneumococcal infection in the United States.

REFERENCES

1. Musher, Daniel M. *Streptococcus pneumoniae* In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia, PA: Elsevier 2005;2392-2412.
2. Marston BJ, Plouffe JF, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med 1997;157:1709-18.
3. Cornu C, Yzebe D, et al. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: A meta-analysis of randomized trials. Vaccine 2001;19:4780-90.
4. Whitney CG, Harper SA. Lower respiratory tract infections: Prevention using vaccines. Infect Dis Clin North Amer 2004;18:899-917.
5. Center for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections program Network, Group B *Streptococcus*, 2005-provisional. Available at: http:www.cdc.gov/ncidod/dbmd/abcs/survreports/gbs05.pdf. Accessed December 11, 2006.
6. Jackson LA, Neuzil KM, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 2003;348:1747-55.
7. Cortese MM, Wolff M, et al. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med 1992;152:2277-82.
8. Watt JP, O'Brien KL, et al. Invasive pneumococcal disease among Navajo adults, 1989-1998. Clin Infect Dis 2004;38:496-501.
9. Davidson MA, Parkinson J, et al. The epidemiology of invasive pneumococcal disease in Alaska, 1986-1990—thnic differences and opportunities for prevention. J Infect Dis 1994;170:368-76.
10. Kyaw MH, Rose CE Jr, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis 2005;192:377-86.
11. Nuorti JP, Butler JC, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000;342:681-9.
12. Whitney CG, Farley MM, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737-46.
13. Shapiro ED, Berg AT, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991; 325:1453-60.
14. Butler JC, Breiman RF, et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA 1993;270:1826-31.
15. Grau I, Pallares R, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med 2005;165:1533-40.
16. Rodriguez-Barradas MC, Musher DM, et al. Antibody to capsular polysaccharides of *Streptococcus pneumoniae* after vaccination of human immunodeficiency virus-infected subjects with 23-valent pneumococcal vaccine. J Infect Dis 1992;165:553-6.
17. Koivula I, Sten M, et al. Clinical efficacy of pneumococcal vaccine in the elderly: A randomized, single-blind population-based trial. Am J Med 1997;103:281-90.
18. Ortqvist A, Hedlund J, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. Lancet 1998;351:399-403.
19. Dear K, Holden J, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2003;4: CD000422.
20. Christenson B, Lundbergh P, et al. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: A prospective study. Lancet 2001;357:1008-11.
21. Hedlund J, Christenson B, et al. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: A 1-year follow-up. Vaccine 2003;21: 3906-11.
22. Nichol KL, Baken L, et al. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med 1999;159:2437-42.
23. Fisman DN, Abrutyn E, et al. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. Clin Infect Dis 2006;42:1093-101.
24. Sisk JE, Moskowitz AJ, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. JAMA 1997;278:1333-9.
25. Sisk JE, Whang W, et al. Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: Role of comorbid conditions and race. Ann Intern Med 2003;138:960-8.
26. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997; 46(RR-8):1-24.
27. Jackson LA, Benson P, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA 1999;281:243-8.
28. Whitney CG, Schaffner W, et al. Rethinking recommendations for use of pneumococcal vaccines in adults. Clin Infect Dis 2001;33:662-75.