Pneumococcal Vaccine*

Visanu Thamlikitkul, M.D., M.Sc.

"An Ounce of Prevention is Worth a Pound of Cure"

Benjamin Franklin's Aphorism

Streptococcus pneumoniae is a common cause of community-acquired pneumonia, meningitis, bacteraemia and otitis media.[1-4] The incidence rate of pneumococcal diseases is estimated to be as low as 0.4 to 6 cases per 1,000 people per year in the United States and Sweden to 90 per 1,000 per year among South African gold miners.[5-8] Conditions and persons at increased risk of pneumococcal infections are young children, the elderly and patients with chronic pulmonary disease, chronic heart disease, chronic alcoholism, cirrhosis, asplenia, sickle cell disease, multiple myeloma, lymphoproliferative diseases, renal failure, nephrotic syndrome and other immune suppressed states.[4,9-17] Untreated invasive pneumococcal disease such as pneumococcal meningitis is almost always fatal. The mortality rate of pneumococcal bacteraemia, meningitis and pneumonia in the antibiotic era is still high, at approximately 15 to 33 per cent, depending upon the spectrum of the disease and underlying conditions.[2,4,18,19] In addition, penicillin-resistant and multiply-resistant pneumococci, first reported in 1967,[20] have now been identified in various parts of the world; prevalence ranges from 1 to 16 per cent.[21] This phenomenon is worrisome and it may create a problem for antibiotic treatment of pneumococcal infections, especially pneumococcal meningitis, in the near future.

The pathogenicity of *Streptococcus pneumoniae* is related primarily to its capsular polysaccharides which are believed to be a virulence factor. Currently there are 83 known serotypes of *Streptococcus pneumoniae* classified by the difference of capsular polysaccharides.[22] Cross reactions of capsular polysaccharides among some individual serotypes have been detected.[22]

Host defense against *Streptococcus pneumoniae* – encapsulated bacteria depends on the host's ability to develop opsonising antibody, the presence of a functioning spleen and the ability of leukocytes to phagocytise opsonised bacteria. Acquired immunity of type-specific antibody also appears after pneumococcal infection; recurrent systemic infections with the same serotypes are rare except in immunosuppressed hosts.[23] This observation suggests that anticapsular antibody is protective, type-specific and long lasting.

The concept of immunoprophylaxis for pneumococcal disease began prior to the antibiotic era in 1911 when Wright *et al*[24] injected whole-cell pneumococci into South African gold miners among whom pneumococcal pneumonia was endemic and was a major cause of morbidity and mortality. The results favoured some protective effect but were not verified by subsequent statistical analyses done by Maynard.[25,26] In 1930 pneumococcal capsular polysaccharide was found to induce specific antibody response in humans;[27] since then, capsular polysaccharide has been used for pneumococcal vaccine.

PNEUMOCOCCAL VACCINE FORMULATION

Since the antibody response to pneumococcal capsular polysaccharides is type specific, the ideal vaccine would include as many serotypes as possible. The first generation 14-valent vaccine was released in the United States in 1977. The vaccine is composed of 50 μg of each serotype 1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F and 25F.[22] This formulation is based mainly on pneumococcal serotypes causing bacteraemia in the United States and South Africa[28,29] and it covers about 80 per cent of bacteraemic pneumococcal isolates in the United States. This formulation may not be appropriate for use in other parts of the world where the distribution of pneumococcal serotypes is different. For example,

*From the Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

serotype 5 is the most common isolate in Israel,[30] but it is not included in the 14-valent vaccine. Furthermore, this formulation may not prevent pneumococcal pneumonia because 35 to 46 per cent of pneumococcal serotypes isolated from pneumococcal pneumonia patients in the United States are not included in the vaccine[31] and bacteraemia is found in only 25 to 33 per cent of pneumococcal pneumonia cases.[18,32-35]

The second generation 23-valent pneumococcal vaccine has been licensed in the United States since 1983. It includes 25 μg of each serotype 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.[22] This formulation covers 88 per cent of the types causing adult bacteraemia and meningitis in the United States, nearly 100 per cent of the types causing childhood bacteraemia and meningitis in the United States, 85 per cent of the types causing acute otitis media in the United States, 94 per cent of the types causing meningitis worldwide, 92 per cent of blood isolates from the WHO collection and 86 per cent of CSF isolates from the WHO collection.[3,22,36] The antibody response to 25 μg of the 23-valent polysaccharide antigen vaccine is comparable to that of a 50-μg dose of 14-valent vaccine.[37]

ANTIBODY RESPONSE TO PNEUMOCOCCAL VACCINE

Administration of pneumococcal vaccine to healthy middle-aged persons is followed by the appearance of type-specific antibodies which reach peak levels in two to six weeks, continue at these levels for five to eight months and then slowly decrease to 33-50 per cent of peak levels for five to eight years.[36,38] A two-fold increase in antibody levels of postimmunisation, generally to levels of 250 to 300 ng per ml, has been observed in most immune-competent persons.[39] The real protective antibody level is unknown. The level of 300 ng per ml has been considered to be protective because nearly all vaccinated patients who develop pneumococcal diseases with vaccine types are found to have antibody levels lower than 300 ng per ml.[40]

Particular attention has been directed towards the antibody response of persons at increased risk of pneumococcal infections. Pneumococcal vaccine fails to induce antibody response to most serotypes in young children of less than two years, of age.[41] The antibody response in healthy elderly persons is not different from that in young adults.[23,31,42] Patients with chronic pulmonary disease appear to have high prevaccination antibody titres to most pneumococcal serotypes included in the vaccine and the antibody response is similar to normal subjects.[43] Several investigators have found that antibodies to several types among asplenic persons, including patients with sickle-cell disease, are less than normal; however, the absolute peak levels usually exceed 300 ng per ml.[44,45] Antibody response to vaccine in well-controlled insulin-dependent diabetics has been reported to be equal to that in healthy adults.[46] Patients with chronic renal failure on haemodialysis, renal transplant patients and patients with nephrotic syndrome tend to have subnormal antibody response.[15,47-49] Patients with multiple myeloma have profoundly reduced antibody response to the vaccine.[50] Patients with Hodgkin's disease prior to treatment respond to vaccine normally,[51] but they respond poorly when the vaccine is given during chemotherapy and radiation therapy.[51,52] However, if the vaccine is given at least 10 to 14 days before initiation of chemotherapy and radiation therapy, the antibody response is comparable to that of normal controls regardless of the stage of the disease.[51] The duration of vaccine-induced antibody in most of these immunosuppressed persons is unknown but may be shorter than that in normal persons.[40]

CLINICAL TRIALS OF PNEUMOCOCCAL VACCINE

Ekwuzel *et al*[53] reported the results of a clinical trial of bivalent polysaccharide vaccine on a civilian conservation corps in Massachusetts in 1938. Over 29,000 subjects received the vaccine and another 41,000 served as a control group. The incidence of lobar pneumonia and death from lobar pneumonia was statistically less in the immunised group.

The protective effects of bivalent, trivalent and tetravalent pneumococcal vaccines were also demonstrated in clinical trials conducted by MacLeod *et al*[54] among young male recruits at an Army Air Force technical school and Kaufman[55] among ambulatory institutionalised people.

Smit *et al*[56] conducted a randomised controlled trial on 1,523 South African gold miners using 6- and 12-valent vaccines compared with 3,171 controls. The vaccine had no effect during the first 14 days. Beyond 14 days, 76 and 92 per cent reductions in pneumococcal cases were found in the groups receiving 6- and 12-valent vaccine respectively.

Austrian *et al*[8] also reported an 82.3 per cent reduction in pneumococcal bacteraemia among South African gold miners who received 13-valent vaccine when compared with the control group in a randomised controlled trial.

A double-blind controlled study of 14-valent vaccine was performed on 11,958 adult residents of New Guinea.[57] The incidence of pneumococcal infections documented by blood culture and lung aspirate in the vaccinated group was reduced by 84 per cent and the mortality from pneumonia was also reduced by 44 per cent.

Two randomised controlled trials of pneumococcal vaccine among 7,000 elderly persons in the United

States have been conducted.[23] The results showed no difference between the vaccinated and the control groups in terms of the incidence of pneumonia, mortality and the rate of isolation of vaccine type pneumococci. However, there was a statistically significant difference in their seroconversion rate. The explanation for not detecting vaccine effectiveness in these studies would be the lack of adequate sample size. It is estimated that given the annual incidence of pneumococcal diseases in the elderly population of 25 per 100,000, a sample size of 481,858 is needed to detect a 50 per cent protective effect.[58] Therefore, a randomised controlled trial among such a population may not be feasible to perform and an ethical issue should be considered, because the vaccine has already been licensed. Several investigators have proposed alternatives to a randomised controlled study. Broome *et al*[59,60] conducted a retrospective study comparing the distribution of pneumococcal serotypes from the blood and CSF of vaccinated persons with those of non-vaccinated persons who developed pneumococcal diseases. The study is based on the assumption that since the vaccine is not effective against non-vaccine serotypes, an effective vaccine should reduce the proportion of vaccine to non-vaccine serotypes in vaccinated persons compared with that in non-vaccinated recipients. They found 49 to 60 per cent reductions in vaccine type pneumococcal isolates in vaccinated patients older than 10 years. A case control study conducted by Shapiro *et al*[61] showed that the protective effect of pneumococcal vaccine in preventing systemic pneumococcal infections was 77 per cent for adult patients at moderately increased risk, i.e. those with chronic obstructive pulmonary disease, chronic alcoholism, diabetes mellitus, chronic renal failure and congestive heart failure, and 70 per cent for all patients 55 years or older. The vaccine had no protective effect in patients at high risk for pneumococcal infections, i.e. those with asplenia, dysglobulinaemia, renal transplantation, nephrotic syndrome, haematologic malignancies, metastatic cancer, systemic lupus erythematosus and drug-induced immunosuppression.

Three randomised controlled trials have been carried out to assess the effectiveness of 14-valent vaccine in preventing acute respiratory infections in children of six months to five years of age.[62-64] Two of the trials showed a reduction in the incidence of acute respiratory infections in children older than 17 months[62] and two years.[63] However, a larger study[64] did not demonstrate any protective effect of the vaccine.

At least eight clinical trials have been conducted to examine the benefit of pneumococcal vaccine in preventing otitis media in children.[63-71] Most of them failed to show a reduction in the incidence of acute otitis media in children younger than two years of age. However, two studies found a decrease in episodes of recurrent otitis media in older children and a reduction in vaccine type pneumococcal otitis media.[68,71]

ADVERSE REACTIONS TO PNEUMOCOCCAL VACCINE

Pneumococcal polysaccharide vaccine is quite safe. Although local reactions of local discomfort, erythema and induration may develop in up to 40 per cent of the vaccinees, they are generally mild and self-limited.[8,72,73] Low-grade fever of one to two days' duration has been noted in 3 to 7 per cent of the cases. Severe self-limited reactions of high fever, chills, headache, skin rash and arthralgia are very uncommon.[74] Reimmunisation within five years may increase the risk of severe adverse reactions.[75] No cases of Guillain Barre syndrome or permanent neurological sequale or death from the vaccine have been described. Pneumococcal vaccine and influenza vaccine may be injected simultaneously into separate sites without causing any interference in the antibody response.[72,76] Data on the safety of the vaccine during pregnancy are not available.

RECOMMENDATIONS

The American College of Physicians[77] and the American Academy of Pediatrics' Committee on Infectious Diseases[78] have made the following recommendations with regard to the use of pneumococcal vaccine:

The vaccine is recommended for all persons aged 65 years or older, patients with chronic underlying conditions, i.e. congenital or acquired heart disease, particularly with congestive heart failure, asthma, obstructive pulmonary disease, alcoholism, diabetes mellitus and conditions associated with immunosuppression such as sickle-cell disease, anatomic asplenia, renal failure, multiple myeloma, lymphoma, drug-induced immunosuppression related to cancer chemotherapy and transplantation. At present, pneumococcal vaccine is not recommended for pregnant women unless the risk is high; then it should be given after the first trimester.

The vaccine is recommended for children two years of age or older who have sickle-cell disease, functional or anatomical asplenia, nephrotic syndrome and Hodgkin's disease prior to cytoreduction therapy. Routine repeated administration of pneumococcal vaccine is not currently recommended. However, revaccination may be justified in certain children at high risk of overwhelming pneumococcal sepsis such as those with asplenia and sickle-cell disease. Persons who have received the 14-valent pneumococcal vaccine should not be revaccinated with the 23-valent vaccine simply to broaden protection since the modest increase in protection does not outweigh the pos-

sible increased risk of adverse reactions.

It should be kept in mind that the aforementioned statements are recommended for people in the United States. The extent to which these recommendations are applicable to the population in other parts of the world is not known, although the 23-valent vaccine has included pneumococcal serotypes that cause diseases worldwide. Several indications for pneumococcal vaccination that have appeared in the recommendations have never been proven to be valid in a well-designed study. Therefore, each community has a direct responsibility to adopt or adapt these recommendations according to its own health policy.

REFERENCES

1. McFarlane JT, Finch RG, Ward MJ, Macrae AD. Hospital study of community-acquired pneumonia. Lancet 1982; 2:255-8.
2. Schlech WF III, Ward JI, Band JD, *et al.* Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study. JAMA 1985; 253:1749-54.
3. Austrian R, Howie VM, Ploussard JH. The bacteriology of otitis media. Johns Hopkins Med J 1977; 141:104-11.
4. Gransden WR, Eykyn S, Phillips I. Pneumococcal bacteremia: 325 episodes diagnosed at St. Thomas's hospital. Br Med J 1985; 290:505-8.
5. Schwartz JS. Pneumococcal vaccine: Clinical efficacy and effectiveness. Ann Intern Med 1982; 96:208-20.
6. Centers for Disease Control. Update: Pneumococcal polysaccharide vaccine usage – United States. Ann Intern Med 1984; 101:348-50.
7. Burman LA, Norrby R, Trollfor S. Invasive pneumococcal infections: Incidence, predisposing factors and prognosis. Rev Infect Dis 1985; 7:133-41.
8. Austrian R, Douglas RM, Schiffman C, *et al.* Prevention of pneumococcal pneumonia by vaccination. Trans Assoc Am Phys 1976; 89:184-94.
9. Gray BM, Converse GM III, Dillon HC Jr. Epidemiologic studies of *Streptococcus pneumoniae* in infants. Acquisition, carriage and infection during the first 24 months of life. J Infect Dis 1980; 142: 923-33.
10. Valenti WM, Jeuzer M, Bentley DW. Type specific pneumococcal respiratory diseases in the elderly and chronically ill. Am Rev Respir Dis 1978; 117:233-8.
11. King H, Shumacker HB Jr. Splenic studies: Susceptibility to infection after splenectomy performed in infancy. Ann Surg 1973; 136:239-42.
12. Bisno AL. Hyposplenism and overwhelming pneumococcal infection: A reappraisal. Am J Med Sci 1971; 262:101-7.
13. Notter DT, Grossman PL, Rosenberg SA, Remington JS. Infections in patients with Hodgkin's disease: A clinical study of 300 consecutive adult patients. Rev Infect Dis 1980; 2:761-80.
14. Keane WF, Shapiro FL, Raij L. Incidence and type of infections occurring in 455 chronic hemodialysis patients. Trans Am Soc Artif Intern Organs 1977; 23:41-7.
15. Linnemann CC Jr, First MR. Risk of pneumococcal infection in renal transplant patients. JAMA 1979; 241:2619-21.
16. Meyers BR, Hirschmann SZ, Axelrod JA. Current patterns of infection in multiple myeloma. Am J Med 1972; 52:87-92.
17. Folland D, Armstrong D, Seides S, Blevins A. Pneumococcal bacteremia in patients with neoplastic diseases. Cancer 1974; 23: 845-9.
18. Austrian R, Gold J. Pneumococcal bacteremia with special reference to bacteremic pneumococcal pneumonia. Ann Intern Med 1964; 60:759-70.
19. Mufson MA, Kruss DM, Wasil RE, Metzger WI. Capsular types and outcomes of bacteremic pneumococcal disease in the antibiotic era. Arch Intern Med 1974; 134: 505-10.
20. Hansman D, Bullen MM. A resistant pneumococcus. Lancet 1967; 2:164-5.
21. Centers for disease control. Multiply resistant pneumococcus – Colorado. Morbid Mortal Weekly Rep 1981; 30:197-8.
22. Robbins JB, Austrian R, Lee CJ, *et al.* Considerations for formulating the second generation pneumococcal capsular polysaccharide vaccine with emphasis on cross-reactive types within groups. J Infect Dis 1983; 148:1136-59.
23. Roberts RD. *Streptococcus pneumoniae.* In: Mandell GL, Douglas RG Jr, Bennett JE, eds, Principles and practice of infectious diseases. New York: John Wiley & Son, 1985:1142-52.
24. Wright AE, Parry Morgan WP, Colebrook E, Dodgson RW. Observations on prophylactic innoculations against pneumococcal infections and on the results which have been achieved by it. Lancet 1914; 87:1-10, 87-95.
25. Maynard GD. An inquiry into etiology, manifestations and prevention of pneumonia amongst natives on the rand from tropical areas. Publications of the South African Institution for Medical Research 1913; 1:1-101.
26. Maynard GD. Pneumonia innoculation experiment No III. Med J S Afr 1915; 11:36-8.
27. Francis T, Tillet WS. Cutaneous reactions in pneumonia: The development of antibodies following the intradermal injection of type specific polysaccharides. J Exp Med 1930; 52:573-85.
28. Austrian R. Surveillance of pneumococcal infection for field trials of polyvalent pneumococcal vaccines. Report DAB-VDP-12-84. Bethesda, Maryland: National Institutes of Health, 1980:1-84.
29. Austrian R. Some observations on the pneumococcus and on the current status of pneumococcal disease and its prevention. Rev Infect Dis 1981; 3 (suppl):S1-17.
30. Schlaeffer F, Rosenheck S, Baumgarten-Kleiner A, *et al.* Pneumococcal infections among immunised and splenectomised patients in Israel. J Infect 1985; 10:38-42.
31. Bentley DW. Pneumococcal vaccine in the institutionalized elderly: Review of past and recent studies. Rev Infect Dis 1981; 3 (suppl):S61-70.
32. Austrian R, Winston AL. The efficacy of pen V in the treatment of mild and moderately severe pneumococcal pneumonia. Am J Med Sci 1956; 232:624-8.
33. U.S. Congress, Office of Technology Assessment. A review of selected federal vaccine and immunization policies. Washington, D.C.: U.S. Government Printing Office, 1979.
34. Cecil RL, Baldwin HS, Larsen NP. Lobar pneumonia, a clinical and bacteriologic study of two thousand typed cases. Arch Intern Med 1927; 40:253-80.
35. Tilghman RC, Finland M. Clinical significance of bacteremia in pneumococcal pneumonia. Arch Intern Med 1937; 59: 602-19.
36. Heidelberger M, McCleod CM, Dilapi MM. The human antibody response to simultaneous injections of six specific polysaccharides of pneumococcus. J Exp Med 1948; 88:369-72.
37. Pankey G, Schiffman G. The immunogenicity and reactogenicity of a 22-valent pneumococcal vaccine. Clin Res 1982; 20: 376A.
38. Heidelberger M, DiLapi MM, Siegal M, Walter AW. Persistence of antibodies in human subjects injected with pneumococcal polysaccharides. J Immunol 1950; 65:535-41.
39. Mufson MR, Krause HE, Tarrant CJ, *et al.* Polyvalent pneumococcal vaccine given alone and in combination with bivalent influenza vaccine. Proc Soc Exp Biol Med 1980; 163:498-503.
40. Landesman SH, Schiffman G. Assessment of the antibody response to pneumococcal vaccine in high risk population. Rev Infect Dis 1981; 3(suppl):S184-96.
41. Sell SH, Wright PF, Vaughn WK, *et al.* Clinical studies of pneumococcal vaccines in

infants I. Reactogenicity and immunogenicity of two polyvalent polysaccharide vaccine. Rev Infect Dis 1981; 3(suppl):S97-107.
42. Ammann AJ, Schiffman G, Austrian R. The antibody response to pneumococcal capsular polysaccharides in aged individuals. Proc Soc Exp Biol Med 1980; 164: 312-6.
43. Davis AL, Aranda C, Christianson L, Schiffman G. Pneumococcal antibodies in patients with chronic obstructive pulmonary disease and their response to pneumococcal capsular polysaccharides: Preliminary results. Rev Infect Dis 1981; 3 (suppl):S183.
44. Ammann AJ, Addiego J, Wara DW, *et al.* Polyvalent pneumococcal polysaccharide immunization of patients with sickle cell anemia and patients with splenectomy. N Engl J Med 1977; 297:897-900.
45. Hosea SW, Burch CG, Brown EJ, *et al.* Impaired immune response of splenectomized patients to polyvalent pneumococcal vaccine. Lancet 1981; 1:804-7.
46. Lederman MM, Schiffman G, Rodman HM. Pneumococcal immunization in adult diabetics. Diabetes 1981; 30:119-21.
47. Linnemann CC Jr, First MR, Schiffman G. Rêsponse to pneumococcal vaccine in renal transplant and hemodialysis patients. Arch Intern Med 1981; 141:637-40.
48. Fikrig SM, Schiffman G, Philip JC, Moel DI. Antibody response to capsular polysaccharide vaccine of *Streptococcus pneumoniae* in patients with nephrotic syndrome. J Infect Dis 1978; 137:818-21.
49. Cosio FG, Giebink GS, Le CT, Schiffman G. Pneumococcal vaccination in patients with chronic renal disease and renal allograft recipients. Kidney Int 1981; 20:254-8.
50. Lazarus SM, Lederman M, Lubin M, *et al.* Pneumococcal vaccination: The response of patients with multiple myeloma. Am J Med 1980; 69:19-23.
51. Siber GR, Weitzman SA, Aisenberg AC. Antibody response of patients with Hodgkin's disease to protein and polysaccharide antigens. Rev Infect Dis 1981; 3 (suppl): S144-59.
52. Silber GR, Weitzman SA, Aisenberg AC, *et al.* Impaired antibody response to pneumococcal vaccine after treatment for Hodgkin's disease. N Engl J Med 1978; 299:442-8.
53. Ekwurzel GM, Simmon JS, Dublin H, Felton LD. Studies on immunizing substances in pneumococci viii. Report on field test to determine the prophylactic value of pneumococcal antigen. Public Hlth Rep 1938; 53:1877-93.
54. MacCleod CM, Hodges RG, Heidelberger M, Bernhard WG. Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. J Exp Med 1945; 82:445-65.
55. Kaufman P. Pneumonia in old age. Active immunization against pneumonia with pneumococcus polysaccharides: result of a six year study. Arch Intern Med 1947; 29: 518-31.
56. Smit P, Oberhozer D, Hayden-Smith S, Koornhof HJ, Hilleman MR. Protective efficacy of pneumococcal polysaccharide vaccines. JAMA 1977; 238:2613-6.
57. Riley ID, Tarr PI, Andrew M, *et al.* Immunization with polyvalent pneumococcal vaccine. Reduction of respiratory mortality in a New Guinea Highlands community. Lancet 1977; 1:1338-41.
58. Clemens JD, Shapiro ED. Resolving the pneumococcal controversy: Are there alternatives to randomized clinical trial? Rev Infect Dis 1984; 5:589-600.
59. Broome CV. Efficacy of pneumococcal polysaccharide vaccines. Rev Infect Dis 1981; 3(suppl):S82-8.
60. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: An alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 1980; 303:549-52.
61. Shapiro ED, Clemens JD. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infections. Ann Intern Med 1984; 101:325-30.
62. Riley ID, Everingham FA, Smith DE, *et al.* Immunization with a polyvalent pneumococcal vaccine: Effect on respiratory mortality in children living in the New Guinea highlands. Arch Dis Child 1981; 56:354-7.
63. Rosen C, Christensen P, Hovelins B, *et al.* Effect of pneumococcal vaccination on upper respiratory infection in children: Design of a follow up study. Scand J Infect Dis 1983; 39(suppl):39-44.
64. Douglas RM, Miles HB. Vaccination against *Streptococcus pneumoniae* in childhood: Lack of demonstrable benefit in young Australian children. J Infect Dis 1984; 149:861-9.
65. Douglas RM, Paton JC, Duncan SJ, *et al.* Antibody response to pneumococcal vaccination in children younger than 5 years of age. J Infect Dis 1983; 148:131-7.
66. Howie VM, Ploussard JH, Sloya JL. Immunization against recurrent otitis media. Ann Otol Rhinol Laryngol 1976; 85 (suppl):254-8.
67. Teele DW, Klein JO. Use of pneumococcal vaccine for recurrent acute otitis media in infants in Boston. Rev Infect Dis 1981; 3(suppl):S113-8.
68. Makela PH, Leinonen M, Pukander J, *et al.* A study of pneumococcal vaccine in prevention of clinically acute attacks of recurrent otitis media. Rev Infect Dis 1981; 3 (suppl):S124-30.
69. Sloya JL Jr, Ploussard JH, Howie VM. Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama. Rev Infect Dis 1981; 3(suppl):S119-23.
70. Wright PF, Sell SH, Vaughn WK, *et al.* Clinical studies of pneumococcal vaccines in infants. II. Efficacy and effect on nasopharyngeal carriage. Rev Infect Dis 1981; 3(suppl):S108-12.
71. Rosen C, Christensen P, Henricksen J, *et al.* Beneficial effect of pneumococcal vaccination on otitis media in children over 2 years old. Int J Pediatr Otorhinolaryngol 1984; 7:239-46.
72. Hilleman MR, Carlson AJ Jr, McLean AA, *et al. Streptococcus pneumoniae* polysaccharide vaccine: age and dose responses, safety, persistence of antibody, revaccination and simultaneous administration of pneumococcal and influenza vaccines. Rev Infect Dis 1981; 3(suppl):S31-42.
73. Bentley DW, Simon SF, Douglas RG Jr, Robertson RG. Response to pneumococcal vaccine in healthy elderly volunteers. Clin Res 1974; 22:436A.
74. Gabor EP, Seeman M. Acute febrile systemic reactions to polyvalent pneumococcal vaccine. JAMA 1979; 242:2208-9.
75. Borgono JM, McLean AA, Vella PP, *et al.* Vaccination and revaccination with polyvalent pneumococcal polysaccharide vaccines in adults and infants. Proc Soc Exp Biol Med 1978; 157:148-54.
76. DeStafano F, Goodman RA, Noble GR, *et al.* Simultaneous administration of influenza and pneumococcal vaccines. JAMA 1982; 247:2551-4.
77. Committee on Immunization, American college of Physicians. Guide for adult immunization. 1985:66-9.
78. Giebink GS. Preventing pneumococcal disease in children: recommendations for using pneumococcal vaccine. Pediatr Infect Dis 1985; 4:343-8.