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Pneumococcal Polysaccharide Vaccines: Indications, Efficacy and Recommendations

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***Streptococcus pneumoniae* is the primary cause of community-acquired pneumonia, meningitis in adults and otitis media in infants and children and the third cause of meningitis in infants and children. Despite the availability of effective therapeutic agents against this pathogen, mortality has remained high, particularly for infections complicated by bacteremia. For many years, there has been a plea for vaccination. The first steps, using whole bacterial vaccines, were taken during the early decades of this century in the gold mining camps of South Africa, where pneumonia was endemic. The efficacy of purified pneumococcal polysaccharide vaccines has since been demonstrated in young adults, such as gold miners and military recruits, as well as for several other groups at risk, such as institutionalized elderly, patients with sickle cell anemia or those who have undergone a splenectomy, and elderly patients with underlying conditions such as chronic obstructive pulmonary disease and chronic cardiovascular disease, but not in infants and severely immunocompromised patients. Serological studies on the immune response to inoculation of pneumococcal polysaccharide antigens have demonstrated a severely impaired antibody response in the last two groups. Therefore, development of more highly immunogenic vaccines, e.g. by linking pneumococcal polysaccharides or parts of them to protein carriers, should be continued in an attempt to offer adequate protection to those who are insufficiently protected by the current 23-valent polysaccharide vaccine. Opportunities to immunize other patients who are at risk for pneumococcal infection and are capable of responding to the current vaccine should not be missed.**

The First Pneumococcal Vaccines (1911–1950)

The use of pneumococcal vaccines dates back to 1911, before identification of the various serotypes (Table 1). At that time, Wright investigated the potential of whole bacterial vaccines as a means of preventing epidemic pneumonia among South African gold miners (1). The trials were carried out there because pneumococcal pneumonia was endemic among the natives who lived close together in the barracks near the gold mines. Although the results of these trials indicated that the vaccine could prevent pneumonia, the many flaws in design, particularly the lack of statistical soundness and microbiological evaluations, precluded any conclusions. After identification of the diverse pneumococcal serotypes, the studies of Lister and Ordnan in South Africa between 1930 and 1934 showed that immunization with a polyvalent pneumococcal vaccine containing killed pneumococci types 1, 2, 3, 7, 12 and 14 could reduce the incidence of pneumonia caused by these same types (2). The discovery in 1930 of the immunogenicity of pneumococcal polysaccharides in man by Francis and Tillett (3) led to the replacement of killed whole bacterial vaccines by vaccines of partially purified capsular material (4). Between 1933 and 1937, the ability of a vaccine composed of two types of partially purified pneumococcal polysaccharides to prevent pneumonia in volunteers of the American Civilian Conservation Corps was investigated by Ekwurzel et al. (5), who found fewer cases of pneumonia in inoculated subjects than in controls. The ability of a tetravalent vaccine of pneumococcal polysaccharides types 1, 2, 5 and 7 to prevent pneumonia in a population of army pilot trainees was clearly demonstrated by MacLeod et al. (6) during World War II. Four cases of pneumonia associated with the pneumococcal types in the vaccine developed in 8586 recipients, all within 2 weeks of the injec-

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tion. In contrast, 26 cases were noted in 8449 control subjects, 23 of which occurred two weeks or longer after injection with a placebo. Thus, the vaccine was 86 % effective in preventing pneumonia due to vaccine-related serotypes, a very significant difference ($p = 0.0001$).

A study on the efficacy of a pneumococcal vaccine consisting of purified polysaccharide material from serotypes 1, 2, and 3 in the institutionalized elderly, carried out by Kaufman a few years later (7), yielded three cases of pneumonia caused by the pneumococcal types in the vaccine among the 99 patients with pneumonia from the immunized group and 33 cases of pneumonia caused by these types among 227 patients with pneumonia in the control group (30.3 per 1000 and 145.3 per 1000, respectively, $p = 0.0001$).

In the years following World War II, Heidelberger, MacLeod and their associates showed that it was possible to combine six purified pneumococcal polysaccharides into a single vaccine and that most of the healthy volunteers responded to all six components of the vaccine (8–10). Subsequently, they observed that half-maximum levels of the antibody – defined as half of the peak levels which appeared 2–6 weeks after vaccination – persisted for 5–8 years after a single subcutaneous injection (11). Two such 6-valent vaccines of pneumococcal polysaccharides became commercially available in the late 1940s, but their introduction coincided with the emerging view that penicillin is effective in dealing with pneumococcal infection. Thus, although there was clear evidence of their efficacy, these vaccines were seldom used and in the early 1950s the first generation of pneumococcal polysaccharide vaccines was taken off the market.

The Second Generation of Pneumococcal Polysaccharide Vaccines (1960–1991)

Because studies of invasive pneumococcal disease provided clear evidence that despite the administration of penicillin the mortality rate remained high (12, 13), interest in the prevention of pneumococcal disease revived in the mid-1960s. After the safety and antigenicity of 50 μg doses of six monovalent vaccines consisting of purified pneumococcal polysaccharides had been demonstrated in healthy volunteers, the six components were combined to form a 6-valent vaccine. In addition, another polyvalent vaccine containing 13 pneumococcal polysaccharides was developed (Table 1). Prospective trials of vaccination that will be discussed in the next paragraphs are summarized in Table 2.

Trials with Polyvalent Vaccines. Since pneumococcal pneumonia was still epidemic among novice gold miners in South Africa, with a putative incidence of 90–200 cases per 1000 man-years, this population was considered ideal for testing the vaccines. In the first randomized controlled double-blind trial involving 12000 novice gold miners (14), the incidence of pneumonia presumably caused by the pneumococcal types represented in the 13-valent vaccine was 78.5 % less than that observed for control gold miners ($p < 0.0001$) and the incidence of proven bacteremia caused by vaccine-related pneumococci was reduced by 82.3 % ($p < 0.0001$). The incidence of pneumonia diagnosed solely on the basis of an infiltrate on the chest x-ray, without regard to any bacteriological considerations, was 52.7 % lower in the vaccinated group ($p < 0.0001$) compared to the control cohort. A subsequent trial in South Africa (15) involved 1523 subjects who received either a 6-valent or a 12-valent pneumococcal vaccine and 3171 controls. There was a 76 % reduction among vaccinees in the incidence of pneumonia caused by the pneumococcal types in the 6-valent pneumococcal vaccine ($p < 0.0001$) and a 92 % reduction in the group that received the 12-valent vaccine ($p < 0.004$) (15).

A trial with a 14-valent polysaccharide vaccine in Papua New Guinea, where pneumonia is endemic, showed a significant decrease in vaccine-related bacteremia as well as mortality for pneumonia in vaccinees compared to controls (16).

In 1978, a 14-valent pneumococcal vaccine, containing capsular polysaccharides of pneumococcal types 1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F and 25, was licensed in the US. The vaccine was recommended for adults at risk for pneumococcal infections, notably the elderly, patients with specific underlying conditions such as asplenia, and those with a variety of chronic systemic illnesses. The populations used to evaluate the efficacy of the vaccine had been restricted to healthy adults who were likely to respond to pneumococcal vaccination with appropriate antibody levels (14–17). At the time, no data on the efficacy of the vaccine in high-risk individuals was available. Furthermore, it was not clear whether the vaccine afforded protection to infants.

Infants. Although discussion of vaccination data pertaining to infants is beyond the scope of this

Table 1: Danish and American designations for 84 serotypes of *Streptococcus pneumoniae,* and their use in a pneumococcal polysaccharide vaccine.

Danish	American	Vaccine	Danish	American	Vaccine
1	1	+	20	20	*
2	2	+	21	21	–
3	3	+	22F	22	*
4	4	+	22A	63	–
5	5	+	23F	23	+
6A	6	†	23A	46	–
6B	26	*	23B	64	–
7F	51	+	24F	24	–
7A	7	–	24A	65	–
7B	48	–	24B	60	–
7C	50	–	25A	–	–
8	8	+	25F	25	–
9A	33	–	27	27	–
9L	49	–	28F	28	–
9N	9	+	29	29	–
9V	68	*	31	31	–
10F	10	–	32F	32	–
10A	34	*	32A	70	–
11F	11	–	33A	40	–
11A	43	*	33B	42	–
11B	76	–	33C	39	–
11C	53	–	33F	70	+
12F	12	+	34	41	–
12A	83	–	35A	47, 62	–
13	13	–	35F	35	–
14	14	+	35B	66	–
15F	15	–	35C	61	–
15A	30	–	36	36	–
15B	54	*	37	37	–
15C	77	–	38	71	–
16F	16	–	39	69	–
16A	85	–	40	45	–
17F	17	*	41F	38	–
17A	78	–	41A	74	–
18F	18	–	42	80	–
18A	44	–	43	75	–
18B	55	–	44	81	–
18C	56	+	45	72	–
19F	19	+	46	73	–
19A	57	*	47F	52	–
19B	58	–	47A	84	–
19C	59	–	48	82	–

+ Indicates a type present in both the 14- and 23-valent vaccine, * a type present in only the 23-valent vaccine, and † a type only in the 14-valent vaccine; – not used.

review, some pertinent facts about the immunogenicity of the polysaccharide vaccine in this age group should nevertheless be mentioned. Infants, i.e. children under 2 years of age, exhibit different degrees of responsiveness to different pneumococcal polysaccharides. In one study, the antibody response to type 3 resembled in magnitude that seen in adults, but the responses to the four types of pneumococci most often responsible for infections in this age group, i.e. types 6A, 14, 19F and 23F, were minimal (18). As a rule, the responses to the latter serotypes remained poor until the child was about 5 years old. Another study showed that fewer than 70 % of all children under two years of age responded with a twofold rise in the relevant antibody level to vaccine polysaccharide types 4, 6A, 12F, 14 and 23F (19). Furthermore, it appeared from preimmunization data on these infants that antipneumococcal antibody levels steadily increase with age, suggesting a continuous exposure to pneumococci without an ensuing infection. For some pneumococcal sero-

Table 2: Results of prospective trials of vaccination with pneumococcal polysaccharide vaccine in adults.

Reference	Study group	Vaccine	Efficacy	Limitation of the study
Ekwurzel et al. (45)	Civilian Conservation Corps	2-valent	+	not randomized
Kaufman (47)	institutionalized elderly	3-valent	+	unexplained reduction of non-vaccine type related disease
MacLeod et al. (46)	army recruits	4-valent	+	reduced rate of pneumonia also in controls
Austrian (54)	South African mine workers	13-valent	+	
Smit et al. (55)	South African mine workers	6-valent	+	
Riley et al. (56)	Papuas > 10 years	14-valent	+	540 patients' records were lost
Austrian (20)	outpatients > 45 years old	12-valent	No	incidence of pneumococcal disease was low
Austrian (20)	institutionalized psychiatric patients	12-valent	No	incidence of pneumococcal disease was low
Simberkoff et al. (62)	veterans > 55 years with underlying disease	14-valent	No	endpoints weak; incidence of pneumococcal disease low
Gaillat et al. (63)	institutionalized elderly	14-valent	+	bacterial investigations were incomplete

types the increase was greater than for others. During the 6 months after primary immunization, antibody levels rapidly decreased to preimmunization levels; moreover, booster doses given 6 months after the primary dose did not elicit demonstrable improvement in serum levels of antibody against types 6A and 23F, and only a moderate increase in antibodies against types 14 and 19F (18). Thus, while antibody levels persist for about 5–8 years in adults (11), this certainly is not true for infants. It is unlikely that unsuccessful immunization with a polysaccharide vaccine early in life results in the development of tolerance. From this data it is clear that the polysaccharide vaccine does not elicit appropriate antibody responses in infants and therefore should not be recommended for this group at risk for pneumococcal infections.

The Elderly. The elderly, particularly those in the seventh and eighth decades, face an increased risk of developing pneumococcal disease (12, 20). The risk of death due to bacteremic pneumococcal pneumonia (12) or pneumococcal meningitis is also higher (21). Several studies have shown that in healthy elderly people the antibody response after vaccination is similar to that in younger adults (17, 19, 22).

In the United States, two double-blind randomized, controlled trials to test the efficacy of a 12-valent vaccine were carried out using elderly populations: inpatients at the psychiatric Dorothea Dix hospital in Raleigh, North Carolina, and ambulatory members of the Kaiser Permanente Health Plan who were 45 years of age and older and resided in San Fransisco, California (23). In the Dorothea Dix Hospital study, 607 subjects received the vaccine and 693 received a saline placebo injection. Among vaccinees there was no decrease in the overall frequency of pneumonia, the incidence of vaccine-type pneumonia or deaths due to pneumococcal pneumonia. There were no bacteremic episodes seen in either vaccinated subjects or controls. The only difference between the 2 groups was in seroconversion, i.e. there were no cases of radiologically confirmed vaccine-related pneumonia in vaccinees who exhibited a two-fold or greater rise in serum antibodies against a pneumococcal type present in the vaccine, whereas there were 16 such cases in the control group ($p < 0.01$). The meaning of this find-

ing in the absence of a concomitant pneumococcal isolate is uncertain, since the seroconversion could have been due to either the presence of this pneumococcal type in the nasopharynx or a cross-reaction with another microorganism, e.g. *Klebsiella* spp. or *Escherichia coli* in the gut (24). Moreover, since it is known that a secondary response to (pneumococcal) polysaccharides generally does not take place, a rise in antibody levels or "seroconversion" in a vaccinated subject may not even occur during infection with vaccine-related pneumococci.

In the Kaiser Permanente Medical Center study, 6782 randomly selected subjects received the 12-valent vaccine and 6818 individuals of similar age received a saline placebo. No reduction was seen in the group of vaccinees in the overall incidence of pneumonia, the incidence of vaccine-type pneumococcal pneumonia or deaths associated with pneumonia compared to control subjects. There were four bacteremic episodes, all occurring in controls. Although the difference in bacteremia was suggestive of the vaccine's efficacy, it did not reach significance. As in the Dorothea Dix study, the only difference between the two groups was a reduction in pneumonia in vaccinees who exhibited seroconversion. The incidence of serologically and radiologically confirmed pneumonia due to a vaccine-related pneumococcal type was 4 for the vaccinated group and 20 for the control group, i.e. there was an 80 % reduction in the vaccinated group ($p = 0.002$).

A similar trial was unable to show efficacy of a 14-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia or bronchitis for 2295 high-risk veterans, i.e. patients over 55 years of age with chronic cardiac, pulmonary, renal or hepatic disease, alcoholism or diabetes mellitus (25). Episodes of proven or probable pneumococcal pneumonia or bronchitis occurred in 27 of the 1150 placebo recipients (2.3 %) and 36 of the 1145 vaccine recipients (3.1 %); therefore, the difference in the incidence of clinical disease was insignificant. Vaccine-related *Streptococcus pneumoniae* strains were observed in 11 placebo recipients (1.0 %) and 13 vaccine recipients (1.1 %), which also is not a significant difference.

The only positive findings for an elderly population were reported by Gaillat et al. (26). They showed convincing evidence for the efficacy of the 14-valent vaccine in a controlled randomized trial involving 1686 French elderly subjects (mean age 74 years) living in institutions. Vaccine efficacy was determined by comparing the incidence of pneumonia in vaccinated subjects and controls. In total, 31 of the 749 controls and 9 of the 937 vaccinated individuals developed pneumonia ($p = 0.0001$), i.e. a 77.1 % decrease in incidence. However, the lack of microbiological examinations and serotyping in the majority of cases weakened the strength of this study.

On the basis of these prospective trials, one had to conclude that evidence of the vaccine's efficacy in the elderly was tenuous. There was, however, one question unanswered: given the incidence of vaccine-type pneumonia, would these trials be capable of detecting a difference in pneumococcal disease between vaccinees and controls? The incidence of vaccine-type pneumococci-related pneumonia for the control group of the Kaiser Permanente study was only 1.1 case per 1000 patient-years (23), whereas the incidence of vaccine-type pneumococcal pneumonia and bronchitis for the control group of the veterans study was 3.1 cases per 1000 patient-years (25). In contrast, the incidence of putative pneumococcal pneumonia among the South African mine workers (14, 15) was between 30 and 60 cases per 1000 man-years for the control group, and the incidence of pneumonia for the placebo group of the French study was 20 cases per 1000 patient-years (26). On the basis of the low incidences reported for the US studies, Austrian estimated that one had to study a cohort of well over 100,000 subjects (23) in order to avoid a type II error, i.e. the possibility of failing to prove efficacy due to inadequate sample size. The power of the veterans study (25) to detect a 65 % reduction in the occurrence of proven bacteremic pneumococcal infection was only 6 % (27). Therefore, the risk of a type II error was significant for all previous US studies. In addition, it also became clear that studies covering a population of 100,000 subjects could not readily be executed. Moreover, the ethical constraints on withholding a licensed product hampered further evaluation of vaccine efficacy in high-risk populations by means of randomized clinical trials. In view of these considerations, alternative methods had to be sought.

Epidemiologists at the Centers for Disease Control (CDC) reasoned that, since the vaccine is only effective against the 14 polysaccharide types that it contains and not against other types, one would expect a reduction in the incidence of vaccine-type pneumococcal infections in vaccinated subjects compared to that in unvaccinated subjects (28). They compared the serotypes of 35 isolates of *Streptococcus pneumoniae* isolated from blood or cerebrospinal fluid from immuno-

Table 3: Populations in whom vaccination with the current pneumococcal vaccine is recommended.

Children over two years of age
Asplenia
Sickle cell disease
Malignant lymphoma[a,c]
Nephrotic syndrome
Recurrent pneumococcal meningitis with or without a cerebrospinal fluid leak
Asymptomatic or symptomatic HIV infection
Bone marrow recipient[c]
Immunoglobulin deficiency[b]
Classical complement pathway deficiency
Adults
Asplenia
Sickle cell disease
Malignant lymphoma[a,c]
Cirrhosis of the liver[d]
Bone marrow recipient
Recurrent pneumococcal meningitis with or without cerebrospinal fluid leak
Institutionalized elderly people (older than 65 years)
Elderly with chronic cardiovascular, obstructive pulmonary or renal disease
Asymptomatic or symptomatic HIV infection

[a] Recommended also when splenectomy has not been performed.
[b] Except in case of IgA deficiency.
[c] Post-vaccination antibody level should be checked.
[d] Only when additional risk factor is present.

compromised vaccinees with those of 392 isolates from unvaccinated individuals of the general population. In the group over 10 years of age, 50 % of the 24 isolates of the vaccinated group were vaccine types, whereas 66 % of the 330 isolates from the unvaccinated subjects were vaccine types, i.e. an efficacy of 60 %. In the group of 2–10 year olds, 91 % of the 11 isolates from vaccinated infants were vaccine types, whereas 73 % of the 62 isolates from unvaccinated infants were vaccine types, i.e. an efficacy of 0 %. When only immunocompromised patients were considered, the efficacy was also 0 %. In a follow-up study of the CDC data, now excluding immunocompromised patients and patients under 2 years of age, Bolan and co-workers (29) estimated the overall efficacy of pneumococcal vaccine for patients with bacteremia to be 64 %; for those over 65 years of age with diabetes mellitus, chronic heart disease, pulmonary disease or no underlying illnesses, the efficacy was 61 %.

Shapiro and Clemens (30) used yet another method to evaluate the efficacy of the pneumococcal vaccine, namely the case-control design. In their study they assembled two groups of patients: a case group of patients with systemic pneumococcal infections and a control group of patients without pneumococcal infections. They then compared the frequencies of antecedent immunization with pneumococcal vaccine for the two groups. They found 6 antecedent pneumococcal vaccinations for the case group of 90 patients and 16 vaccinations for the 90 matched controls, indicating a protective efficacy for the vaccine of 67 %; after adjusting for age, the efficacy for the vaccine was 70 % for healthy patients who were 55 years or older. Forrester et al. (31) conducted a similar carefully executed study using a group of 89 veterans with documented pneumococcal bacteremia and a matched control group, but they found no significant differences in vaccination rates between bacteremic patients (29 %) and controls (24 %). Furthermore, the serotypes of 65 % of the blood isolates from nonvaccinated bacteremic patients were included in the vaccine compared to 69 % of those from vaccinated bacteremic patients. More recently, Sims et al. (32) reported the results of a large multicenter case-control study focused on elderly patients in which positive cultures of *Streptococcus pneumoniae* from otherwise sterile body fluids were used as endpoint. Eight per cent of the patients and 20.8 % of the controls had received the pneumococcal vaccine, indicating a 70 % clinical effectiveness for the vaccine in this population of immunocompetent elderly.

Asplenia. Although the risk of serious infection after splenectomy is low (about 7.16 cases per 100

person-years (33)), the course is sometimes fulminant resulting in a high mortality (34). Retrospective studies have indicated that the incidence of serious pneumococcal disease in splenectomized patients increases with the severity of the underlying disease, from 1.4 % for patients who have undergone splenectomy because of trauma to 11.5 % and 24.8 % for splenectomized patients with "reticuloendotheliosis" or thalassemia major, respectively (35). A study on splenectomized Rochester residents (33) showed that patients with hematological diseases were twice as likely to develop a serious pneumococcal infection as patients who were splenectomized because of trauma; for patients with a malignant neoplasm the chance was even five times greater.

The purpose of immunizing these patients is to increase the level of type-specific anticapsular antibodies in order to enhance clearance of pneumococci from the bloodstream in the liver by Kupffer cells (24). Immunogenicity data indicates that splenectomized children and adults are able to achieve both a quantitatively (36–38) and qualitatively (39, 40) normal antibody response to the pneumococcal vaccine. In one study, three-fold increases in antibody levels were observed for 11 of the 12 antigens measured in asplenic patients compared to 8 of 12 antigens measured in normal controls (38). However, since subnormal immune responses have been reported by others (41, R. van Furth et al., unpublished observations), sometimes restricted to a few serotypes (42), vaccination should take place 2 weeks before surgery if the splenectomy is elective.

Sickle Cell Anemia. Robinson and Watson (46) were the first to document the marked prevalence of pneumococcal meningitis in children with sickle cell anemia. The risk that these children will develop a severe pneumococcal infection is about 600 times greater than that for healthy children. The highest risk occurs between the ages of 6 months and three years; for children over six years of age, the risk gradually decreases. Similar quantitative serologic responses have been reported for children and young adults with sickle cell disease. These patients have qualitative, i.e. immunoglobulin class-specific, antibody responses similar to those found in normal individuals (44, 45). In a prospective controlled but non-randomized study Amman et al. demonstrated the efficacy of the vaccine in children and young adults with sickle cell disease or after splenectomy (46). Unfortunately, most pneumococcal infections in patients with sickle cell disease occur before the age of two. Since children between 0 and two years exhibit a poor antibody response to pneumococcal polysaccharide antigens, recent recommendations for these children include (1) penicillin prophylaxis between 6 months and 5 years (this has been shown to be very effective in preventing pneumococcal disease (47) and (2) pneumococcal vaccination at two years of age.

Hodgkin's Disease. About 10 % of children with Hodgkin's disease experience infection with *Streptococcus pneumoniae* after undergoing splenectomy and immunosuppressive therapy (48). By means of ELISA studies, we found that these patients had a significantly poorer response to vaccination with pneumococcal polysaccharide vaccines (49). Others have also shown that after treatment patients with Hodgkin's disease exhibit a profound impairment of their immune response to a 12-valent pneumococcal polysaccharide vaccine (50), which correlated with the intensity of treatment for Hodgkin's disease. The response improved with time but often did not return to normal until four years after discontinuation of the combination therapy. Patients with Hodgkin's disease who are immunized prior to the institution of immunosuppressive therapy are capable of responding to pneumococcal polysaccharides (51, 52). In both treated and untreated Hodgkin's disease, the antibody response was unrelated to the stage of the disease and the absence or presence of the spleen.

The immune response to pneumococcal vaccine of splenectomized patients with various hematological disorders, including lymphomas, has been found to depend on the underlying disease (53). Patients with non-malignant hematological disorders responded in 90 % of all cases with a rise in antibody titers, comparable to those found in normal subjects; for patients with hematological malignancies, an appropriate antibody response occurred in only 60 % of the cases. These findings correlate well with our data on antibody concentrations (49) in diverse groups of splenectomized patients as well as with the clinical observation that splenectomized patients with underlying disease are more likely to develop overwhelming infection (33, 35).

Multiple Myeloma. These patients face an increased risk of acquiring pneumococcal infection (54). Patients with multiple myeloma are characterized by an impairment of polyclonal immunoglobulin synthesis and an inability to form antibody resulting in secondary hypogammaglobulinemia (55). These patients also exhibit a severely

impaired immune response to pneumococcal vaccine (56).

Bone Marrow Recipients. In these patients there is an increased incidence and severity of pneumococcal disease; in addition, the mortality rate is markedly higher (57). Bone marrow transplantation may result in a combined IgG2 and IgG4 deficiency, and these patients are particularly susceptible to pneumococcal infections (58). Infections occur even when the IgM and IgG levels are normal or high; however, pneumococcal antibody levels remain very low, suggesting an imbalance of the cellular mechanisms regulating IgM and IgG production or an immunological immaturity as in infants. Our findings regarding post-vaccination antibody concentrations in these patients indicate a poor response to pneumococcal polysaccharide vaccines (49). Others have reported that pneumococcal vaccination of recipients of bone marrow transplants with the 12-valent pneumococcal polysaccharide vaccine yielded significantly lower post-immunization antibody levels for each serotype than in normal controls (59). Nowadays, bone marrow recipients are protected against Gram-positive infections by prophylaxis with oral antibiotics.

Human Immunodeficiency Virus (HIV) Seropositivity. For patients with AIDS the incidence of severe pneumococcal infections is quite high, pneumococcal pneumonia being the most common bacterial infection of the lung in these patients (60–62). HIV-infected individuals also seem to be at risk for bacterial infections, including pneumococcal pneumonia, before either AIDS or severe HIV-related symptoms develop (63). Acute bacterial infections, especially *Streptococcus pneumoniae* and *Salmonella typhimurium,* are causing at least a quarter of HIV-related medical admissions to the largest hospital in east Africa (64). In addition, nosocomial infections with penicillin-resistant pneumococci have been reported in patients with AIDS (65). Patients with AIDS have also been shown to have an impaired antibody response to pneumococcal vaccine (66), an observation that makes them less suitable candidates for vaccination. Studies on the antibody response to pneumococcal vaccine in asymptomatic HIV-infected subjects or those with persistent generalized lymphadenopathy have yielded conflicting results (66–68). Immunization with the vaccine had no adverse effects in these patients (66).

Nephrotic Syndrome. Young patients with nephrotic syndrome are prone to pneumococcal infections, including childhood peritonitis. Children with steroid-responsive nephrotic syndrome who are receiving glucocorticosteroids or who are not treated also respond normally to vaccination with pneumococcal polysaccharide vaccines (37). Children who are steroid-resistant have significantly lower antibody levels before and after vaccination than normal controls (37). Immunization of patients with active nephrotic syndrome using pneumococcal polysaccharides of types 3 and 19 resulted in a significant increase in the levels of serum IgM antibody against both types; however, only the IgG antibody against one of the two types rose (69). The duration of protective antibody levels after vaccination of patients with nephrotic syndrome is unknown but is probably short. Adults with nephrotic syndrome are not known to be at increased risk for pneumococcal infection.

Chronic Renal Failure. These patients have an increased risk for invasive pneumococcal disease (25); uremia is also associated with a poor prognosis for invasive pneumococcal infections (12, 13). Patients with chronic renal failure who undergo dialysis appear to have a normal or modestly subnormal antibody response to pneumococcal vaccination compared to normal subjects (70, 71). Duration of the enhanced antibody levels in patients who undergo dialysis tends to be shorter than in normal controls.

Renal Transplant Recipients. In some reports from the US, renal transplantation appeared to be a risk factor, but these recipients had also been splenectomized, a practice not common in Europe. Recent reports have failed to document an increased susceptibility to pneumococcal disease in renal transplant recipients (72). There is no indication for vaccination of these patients, except when they also undergo a splenectomy.

Cirrhosis of the Liver and Alcoholism. Although there is no conclusive evidence at hand that patients with these conditions have an increased risk for pneumococcal infection (25), they have a significantly poorer prognosis for invasive pneumococcal disease (12, 13, 73). Vaccination of these patients with pneumococcal vaccine may therefore be considered when there is an additional risk factor.

Chronic Obstructive Pulmonary Disease (COPD). Patients with COPD have both an increased susceptibility to (25, 73) and a poor prognosis for invasive pneumococcal infections (73–75), although this view has been challenged (76).

Elderly patients with COPD show high preimmunization antibody levels (77) and respond normally to vaccination (78, 79). Some patients with COPD, however, have low baseline levels of antipneumococcal capsular antibodies and may be at risk (80). The clinical efficacy of the pneumococcal polysaccharide vaccine in this population has not been studied in prospective trials. Bolan et al. (29) retrospectively demonstrated a protective efficacy of 47 % for the vaccine in a high-risk group that also included patients with COPD. Shapiro and Clemens (30) showed a significantly lower incidence in vaccinated patients with COPD; this group, however, also included patients with other chronic illnesses, such as cardiac disease, diabetes mellitus, and alcoholism.

Diabetes Mellitus. Although these patients have no increased risk for pneumococcal infection, they have a poorer prognosis for such infections (73, 75). Two studies have shown that insulin-dependent diabetics responded to the pneumococcal polysaccharide vaccine in the same manner as controls (81, 82). Vaccination of these patients may be considered when there is an additional risk factor.

Systemic Lupus Erythematosus (SLE) and Sjögren's Syndrome. For various reasons, patients with SLE are prone to infections; however, there is no evidence that indicates a higher incidence or increased severity of pneumococcal disease in these patients (83, 84). An exception should be made for patients with SLE and a concomitant C2 deficiency or splenic atrophy. Such patients should be vaccinated, since these conditions increase the risk of pneumococcal infection. Patients with lupus respond normally to the pneumococcal polysaccharide vaccine and show no change in activity of the SLE after vaccination (85).

Patients with Sjögren's syndrome do not appear to be at increased risk for pneumococcal infection. They respond normally to the vaccine (86). Patients with Sjögren's syndrome often have other disorders, such as immunoglobulin deficiencies (87) and lymphomas, and may then be considered candidates for vaccination.

Adverse Effects. The toxicity of the pneumococcal vaccine is very slight (17, 19). Adverse reactions are generally limited to mild pain and tenderness at the site of the inoculation. On rare occasions the local reaction is more severe and is associated with erythema, fever and leukocytosis.

Revaccination. Local reactions are more severe when circulating antibody levels are high, giving rise to an Arthus-type reaction. Initial studies by Heidelberger and associates (11) indicated that pneumococcal anticapsular antibodies are sustained for at least 5 years. In one study, local reactions in adults after revaccination were more severe than after initial vaccination when the interval between vaccinations was 13 months (19). Reports on revaccination of children and adults after longer intervals, including a large group of elderly subjects revaccinated at least 4 years after primary vaccination, suggest a similar incidence of such reactions (17). Therefore, it is recommended that patients who were vaccinated with the 14-valent vaccine not be revaccinated with the new 23-valent vaccine. Five years after the first vaccination, revaccination can be considered for patients who are at very high risk of fatal pneumococcal infections, e.g. asplenic patients. In the event of doubt serum should be obtained to determine the antibody levels before revaccination. The possibility of potentially poor responders, e.g. immunocompromised patients, should be considered, and if such patients exhibit a poor antibody response, then they should be revaccinated as well.

Pregnancy. At present, the pneumococcal polysaccharide vaccine is not recommended for routine immunization of pregnant women, because the effects of bacterial polysaccharide vaccines on the mother and the immune response of the neonate have not been studied extensively.

Discussion and Recommendations

The above-mentioned studies lead to a number of conclusions and recommendations. From a practical point of view, one has to consider whether a particular patient belongs to one of the groups at risk and secondly, whether the patient is able to respond immunologically to polysaccharide antigens.

Healthy Individuals of Various Ages. As we have seen, young adults and the healthy elderly are responders to pneumococcal polysaccharide vaccination (17, 19), but infants are not (18, 19). Several epidemiological studies on the efficacy in infants and older children revealed no or sparse evidence of reduction of pneumococcal disease (88, 89). Prospective trials involving young healthy adults from special populations at risk have clearly proven the efficacy of the vaccine (14–16). One large prospective trial with the healthy elder-

ly (23), another with institutionalized elderly (23) and a third trial using veterans with an underlying condition were inconclusive (25), but also indicated a low risk of invasive pneumococcal disease for healthy outpatients. On the other hand, two other studies of institutionalized elderly subjects showed a significant reduction of pneumonia in vaccinees (7, 26). Therefore, on the basis of the available evidence from efficacy trials using healthy individuals of different ages, a clear indication for vaccination are crowded living conditions, such as those in military training centers, psychiatric hospitals or institutions for the mentally disabled, barracks or prisons (90). At present, until further evidence has been submitted, no clear indications exist for vaccination of the healthy elderly or infants, the former because the risk of serious pneumococcal disease is controversial and the latter because of an inadequate immune response to polysaccharide antigens.

Individuals with a Condition Predisposing to Serious Pneumococcal Disease. Prospective trials of the pneumococcal polysaccharide vaccine are scarce in these groups. One of the most important groups at risk for serious pneumococcal infection are splenectomized persons. Apart from a non-randomized clinical study of a limited number of patients (46), no epidemiological efficacy studies of splenectomized patients or patients with sickle cell anemia have been performed. The immune response in these patients, however, has been investigated extensively (36–42). Patients with a splenectomy after trauma generally respond like normal controls. Splenectomized persons with an underlying disease, e.g. Hodgkin's disease or other malignant lymphomas, respond to a lesser degree. The immune response of these patients to pneumococcal polysaccharide vaccines is poor and apparently irrespective of the presence of the spleen, but is further reduced by combination therapy. Therefore, we recommend that patients with Hodgkin's disease and other lymphomas should be immunized before treatment is started. Although there is only limited evidence that staging splenectomy impairs the immune response in Hodgkin's disease (38, 40, 42, 50, 52), we also recommend immunization before splenectomy is performed in these patients.

Other immunocompromised patients, such as patients with multiple myeloma and bone marrow recipients, are poor responders. Since their immune response is poor, vaccination of patients with multiple myeloma or bone marrow recipients as well as those treated for malignant lymphoma with the currently available pneumococcal polysaccharide vaccines is controversial. In such cases, post-vaccination antibody concentrations should be measured and if low, revaccination should be considered.

Other patients with an enhanced risk of becoming infected with pneumococci or a poorer prognosis for pneumococcal disease are elderly individuals with chronic cardiovascular, pulmonary, hepatic or renal disease. One prospective epidemiological study of veterans older than 55 years with one of the above underlying conditions did not demonstrate efficacy of the vaccine and showed an impaired immune response to the pneumococcal vaccine (25). There is, however, extensive retrospective epidemiological evidence of the efficacy of the vaccine for these groups (29, 30, 32). We therefore recommend vaccination for elderly patients with chronic cardiovascular, respiratory, renal and hepatic diseases (Table 2).

From the foregoing it is clear that large groups at risk for pneumococcal infection, e.g. infants and well-defined groups of adults, cannot be protected by means of immunization with the currently available pneumococcal polysaccharide vaccines. This lack of protection leads to new requirements for a new vaccine. First, such a vaccine must be highly immunogenic, i.e. inducing at least a two-fold increase in antibodies against all polysaccharide antigens in the vaccine. Second, the antibody levels should persist for several years. Third, the new vaccine has to be safe. Fourth, ideally, efficacy should be demonstrated in a randomized double-blind placebo-controlled study. Various strategies are being employed in an effort to develop more highly immunogenic vaccines, including covalent coupling of polysaccharides/oligosaccharides to proteins (91–94), incorporation of semisynthetic serotypes in liposomes (95) and addition of adjuvants in order to improve antigenic presentation (96–98). Among these, the conjugation of a specific pneumococcal polysaccharide to a protein-carrier, such as tetanus or diphtheria-toxoid (92), is one of the most promising approaches.

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