

Pneumococcal Vaccination and Revaccination of Older Adults

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INTRODUCTION

“... [pneumonia] is the special enemy of old age.”
Sir William Osler (103)

Streptococcus pneumoniae is the leading cause of bacterial pneumonia (71, 74, 75, 102, 115, 125) and bacterial meningitis (132, 135) in the United States, resulting in 175,000 hospitalizations and 7,000 to 12,500 deaths annually (41).

S. pneumoniae primarily causes respiratory infections, including otitis media, sinusitis, and pneumonia. Groups at increased risk of pneumococcal infection include the very young, the elderly, the immunocompromised, smokers, and certain other demographic groups (28, 41, 60, 98, 117). As individuals advance in age, pneumococci cause increasing attack rates of pneumonia, bacteremia, and mortality (9, 11, 15, 24, 41, 42, 60, 82, 96, 110, 117, 126). Older age has long been recognized as a risk factor for infection, leading Sir William Osler to comment on pneumonia in old age 100 years ago as “a friend of the elderly,” “a special enemy of old age,” and “. . . the natural end of elderly people” (103). Even in long-term-care facilities, the pneumococcus remains the most frequently implicated bacterium causing pneumonia (74). Because the elderly population, usually defined as age >65 years, is expected to triple by 2050, the disease burden in this group becomes a critical public health issue.

Epidemiologic studies evaluating rates of pneumococcal disease often refer to rates of invasive pneumococcal disease (IPD), defined by culturing *S. pneumoniae* from a sterile bodily

site. IPD is usually a sequel to pneumococcal pneumonia, although only 15 to 30% of pneumonia cases are associated with IPD (24). The case fatality rate of IPD rises from around 20% for those aged 65 years or older to as much as 40% for those aged 85 years or older (11, 15, 24, 56, 77, 82, 110, 145).

Pneumococcal Vaccine

In light of an increased risk of pneumococcal disease with advancing age, the costs associated with infection, and the rising rates of drug resistance, vaccination has emerged as a public health priority (146). Data from 1998 indicating 24% of pneumococcal strains were resistant to penicillin underscore the problem of antibiotic resistance (149). In older adults, even higher rates of drug resistance may be found (23).

Pneumococcal vaccination using whole-cell inactivated pneumococcal preparations dates back to trials in the early 1900s in South African miners (150). Several excellent reviews have been published on this topic (6, 7, 25, 40). The currently used 23-valent vaccine, containing 25 µg each of 23 purified capsular polysaccharide (CP) antigens, was licensed in 1983. Although there are at least 90 serotypes of *S. pneumoniae* (54), the 23 serotypes in the present vaccine cause 85 to 90% of invasive infections in the United States, as well as comprising the most common drug resistant types (23, 77, 82, 84, 110, 117, 141, 149).

Vaccine Effectiveness

Despite convincing reports in certain cohorts, controversy still exists over the effectiveness of the pneumococcal polysaccharide vaccine (PPV) in older subjects. Observational studies consistently indicate 50 to 70% aggregate effectiveness in pre-

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venting IPD in elderly persons among serotypes found in the PPV (13, 22, 25, 36, 93, 94, 133).

Distinct from IPD, protection against nonbacteremic pneumonia is more difficult to demonstrate, particularly in older persons (43, 63, 79, 101, 137). Conflicting prospective data have been attributed to methodological problems, such as the poor sensitivity of tests to diagnose pneumococcal pneumonia and inadequate power to distinguish differences in outcome (39). Based upon its reduction of IPD, PPV is cost-effective, or even cost saving (4, 94, 139). The Advisory Committee on Immunization Practices published updated recommendations regarding PPV in 1997 that continue to include vaccinating all adults aged 65 or older (28). Adherence to these universal recommendations has been low; it is estimated that 50% of adults ≥ 65 years have never received the vaccine (1, 27, 58, 108, 138). The vaccination rates in long-term-care facilities may be even lower (72).

Vaccine Safety

PPV safety, including that with simultaneous influenza vaccination, has been well documented among older persons (57, 95, 101, 129, 144). The primary side effects are local reactions at the injection site. The presence of prevaccination antibodies has been associated with increased local reactions (58, 68, 129). Revaccination is also safe, although associated with a higher frequency of symptoms at the administration site (58).

VACCINE IMMUNOGENICITY

Antibody Measurement

Antibody responses to PPV have been studied as surrogate markers of vaccine protection. Serotype-specific pneumococcal (CP) antibody mediates protection (21, 50, 66, 69, 83, 90, 137). However, characterization of this specificity of anti-CP antibodies has been problematic. Early studies used less specific techniques that may limit their applicability. Antibodies to cell wall polysaccharide (CWP) are not protective against infection, as opposed to antibodies against CPs (17, 85, 90, 97, 143, 148). The early antibody assay methods are now considered less specific because they did not differentiate anti-CWP antibodies from protective anti-CP antibodies (91). Assays that incorporate a step for absorption of antibodies to CWP have allowed a more accurate measure of the relevant antibodies to CPs (65, 91, 136).

Several other technical limitations have been reported. Many early studies used a radioimmunoassay antibody method that did not discriminate among immunoglobulin classes. Also, antibody cross-reactions to CP may occur among *Streptococcus* species (70). Postvaccination antibodies are less cross-reactive than prevaccine antibodies (140). Recently, non-type-specific antibody has been identified even after anti-CWP antibody absorption, which may be due to antibody to contaminants in the PPV preparation (29, 30, 151). Absorbing antibodies to CWP and other contaminants, using a reliable enzyme-linked immunosorbent assay (ELISA), and the development of a standard reference serum (112), have contributed to more reliable anti-CP antibody measurements. In this review, there-

fore, we place more weight on data using the more specific current methods.

Studies of immunogenicity have primarily focused on quantitative measures of anti-CP antibody levels. Measures of function are as important, if not more important, in predicting protection against pneumococcal infection than is simple antibody quantification. Several assays have been developed to measure antibody functions including avidity, opsonophagocytosis (OPA), and models of passive protection. The lack of standardization of functional assays hinders comparisons of data.

Defining Antibody Response to PPV

Defining protective anti-CP antibody responses to vaccination remains elusive. Most importantly, no specific antibody level is known to correlate with reduced pneumococcal disease. This circumstance contrasts with that of vaccination for *Haemophilus influenzae* type b, a monovalent polysaccharide vaccine, where threshold levels of protective polysaccharide antibody have been described (62). In addition, factors other than antibody concentration contribute to disease susceptibility. Antibodies to the CPs for each serotype may differ in its capacity to bind and promote opsonization. Heterogeneity among populations studied offers yet another confounding variable. Even in geriatric populations, studies have focused on groups as disparate as relatively younger male veterans with a mean age of 65 years or female nursing home residents with a mean age of 89 years (87, 121). Finally, antibody responses have been reported in a variety of ways (antibody fold increase [FI], antibody concentration [geometric mean concentration {GMC}], threshold antibody level or antibody function), and these differences have added to the complexity of comparing and interpreting studies. Even in young, healthy subjects, a protective antibody response to vaccination remains undefined (44).

Antibody Levels in Unvaccinated Subjects

To compare antibody responses to vaccination, knowledge of anti-CP antibody concentrations before vaccination is useful. Most studies indicate that older adults have similar prevaccine levels to those of younger cohorts (5, 26, 33, 67, 87, 120–122, 124, 127, 130). Certain nonvaccine factors may influence the concentration of antibodies to CPs. Smoking is associated with increased prevaccination levels, at least in men (130). Smoking may predispose to increased pneumococcal exposure through respiratory infection or colonization. Several studies have reported that prevaccine levels in women are lower than in men (5, 120, 130). A more recent study, however, provided evidence against lower prevaccine levels in women. In a trial in which 39 of the 46 subjects were female nursing home residents, prevaccine levels were similar to those in younger adults (121). Although gender-specific evaluation was not reported, the study might suggest that the higher prevaccine antibody levels previously observed are a marker for cigarette use, rather than a gender difference.

TABLE 1. Peak immunogenicity of PPV in older adults

Study	Subjects	Controls ^b	Peak measurement	Antibody response to CP in older adults after PPV
Musher et al. (91)	<i>n</i> = 11; male; mean age, 62 yr; chronic bronchitis	Healthy, young	4–6 wk	Similar to young with “trend” toward lower levels; decreased response to 1/5 serotypes ^a
Musher et al. (87)	<i>n</i> = 8; male	None	1 mo	78% positive reactions at 1 mo, up from 30% prior to PPV ^c
Hedlund et al. (51)	<i>n</i> = 65; 48% male; mean age, 67 yr; discharged from Swedish hospital with CAP ^f	27 age-matched subjects seen by infectious disease department	3–4 wk	Similar to control; combining all subjects and antibodies, those >68 yr had diminished response (<i>P</i> = 0.01) and FI ^g (<i>P</i> = 0.04) relative to those ≤68 yr
Konradsen (64)	<i>n</i> = 15; mean age, 63 yr; Denmark	None	1 mo	Response to all six serotypes (<i>P</i> < 0.01 for each type); combining the response for all serotypes for each patient, 73% of subjects had higher concentrations at 1 mo (<i>P</i> < 0.01)
Musher et al. (86)	<i>n</i> = 33; age, ≥ 70 yr; from 118 subjects with mean age of 51 yr gender not specified	Subset of subjects <70 years	4–6 wk	Similar to control
Sankilampi et al. (127)	<i>n</i> = 350; 219 females mean age, 76 yr; Finnish	None	Mean, 35 days	Response present for all age cohorts (65–74 yr, 75–84 yr, ≥85 yr); in women, postvaccination antibody concentration less for 3/6 types ^d
Sankilampi et al. (128)	<i>n</i> = 62; subset of 1996 study; mean age, 72 yr; ambulatory; Finnish	None	1 mo	Response to all six serotypes (<i>P</i> < 0.001); FI range for serotypes, 2.6 to 7.7×
Rubins et al. (123, 124) ^d	<i>n</i> = 53, male; mean age, 71 yr; veterans	28 younger staff members	1 mo	Response to all 23 serotypes (<i>P</i> < 0.001); response less than that of young subjects for 1/7 serotypes (<i>P</i> < 0.01); 20% of older versus 0% of younger subjects identified as poor responders (<i>P</i> = 0.05); Median response (2 FI) was to 14/23 serotypes
Romero Steiner et al. (121)	<i>n</i> = 46; 39 women; mean age, 86 yr; nursing home residents	<i>n</i> = 12; mean age, 37 yr	2–3 wk	Response to all 5 serotypes ^d (no <i>P</i> specified); response significantly lower for 2/5 types compared to that of young subjects ^d ; fewer 2 FI compared to young for 2/5 types ^d
Jackson et al. (57)	Subset of 901 subjects between 50 and 74 yr; <i>n</i> = 54 post-PPV; <i>n</i> = 60 pre-PPV	None	1 mo	Subjects responded to initial PPV ^e
Hedlund et al. (50)	<i>n</i> = 50 of a total of 150; mean age, 71 yr; recent CAP from Sweden; patients had recurrent CAP	Those without recurrent CAP	4 wk	Combined and type-specific antibodies appear to show good peak responses; at 3 yr, combined antibody approaching prevaccine level (not statistically compared); subjects with 4 FI response had lower chance of recurrent CAP (<i>P</i> = 0.02)
Carson et al. (26)	<i>n</i> = 29; 13 females; mean age, 80 yr; veterans	Young, healthy	4 wk	Antibody response similar in older and younger subjects

^a Statistically significant at *P* < 0.05 level unless otherwise specified.

^b Not necessarily defined by author as controls. In this context, the controls are the subjects whose antibody responses to vaccination are being compared to those of the older adults.

^c Defined as number of subjects with detectable type-specific antibodies (eight subjects multiplied by eight serotypes for 64 total possible positive reactions).

^d Results of two studies on the same population presented together.

^e Data derived from table. Although antibody to CP numerically higher in group after PPV compared with that prior to PPV, it is unclear if these are the same subjects. Statistical comparison not provided.

^f CAP, community-acquired pneumonia.

^g FI, fold increase.

Initial Antibody Responses in Older Adults

Over two dozen studies have been published detailing PPV immunogenicity in older adults (5, 26, 33, 37, 38, 50, 51, 55, 57, 61, 64, 67, 73, 80, 85, 87, 91, 111, 120–124, 127, 128, 131, 133). Despite considerable heterogeneity among groups with regard to age, gender, comorbidities, country of origin, serotypes assessed, and definition of anti-CP antibody responses, most studies reach a similar conclusion: older adults mount an antibody response to PPV. As early as 1947, data indicated that pneumococcal polysaccharides were immunogenic in older adults (61). Kaufman administered a PPV with two or three serotypes to subjects who were mostly older than 50 years. Using mouse models of passive protection, he demonstrated that post vaccination serum was more protective than prevac-

cination serum. Subsequent studies of anti-CP antibodies without absorption of anti-CWP antibodies showed uniformly strong responses among serotypes studied (38, 55, 67, 80, 85, 131). With the advent of more specific ELISA techniques and absorption of antibody to CWPs, it was found that subjects rarely mount an antibody response to all serotypes in the vaccine. For example, Rubins and colleagues demonstrated that a group of older men mounted a median 2 FI in anti-CP antibodies to only 14 of the 23 vaccine serotypes (123).

Table 1 summarizes recent immunogenicity studies in older adults that use ELISA techniques for antibody determination. Caution must be exercised in comparisons, as there has been a lack of standardization among assays employed. When compared to those of younger individuals, most of the evidence

TABLE 2. Antibody duration after PPV in older adults

Study	Population	Duration ^b	Antibody to CP after PPV
Mufson et al. (80) ^a	<i>n</i> = 15; mean age, 69 yr; community	6 yr	Half of peak on average
Davidson et al. (33) ^a	<i>n</i> = 9; age, ≥65 yr; Alaskan natives	Mean, 7.4 yr ^c	48% of elderly with suboptimal levels, compared to 22% of group <65 yr ^d
Musher et al. (87)	<i>n</i> = 8; mean age, 65 yr; veterans	6 yr	Prevaccine, 30% positive antibody reactions; 1 mo, 78% positive reactions; 6 yr, 58% positive reactions ^e
Konradsen (64)	<i>n</i> = 15; mean age 63 yr; healthy	5 yr	20% of subjects with higher combined antibody at 5 yr, compared to 73% at peak
Sankilampi et al. (128)	<i>n</i> = 62; mean age, 72 yr; general population	3 yr	Antibody statistically same as baseline at 5 yr; 50% of subjects with detectable type-specific antibodies at 5 yr
Rubins et al. (124)	<i>n</i> = 53; mean age, 71 yr; veterans	16 mo	At 3 yr, combined GMC ^g 38% of 1 mo peak (statistically not different); 4/6 type-specific antibodies above prevaccine levels at 3 yr; estimated 7.7 yr before all type-specific antibody at prevaccine level
Hedlund et al. (50)	<i>n</i> = 150; mean age, 71 yr; recent CAP ^f and matched controls	3 yr	Combined GMC at 16 mo slightly lower than at 1 mo Combined GMC at 3 yr approaching prevaccine level (not statistically compared)

^a Absorption of anti-CP antibodies not performed.

^b Interval between PPV administration and immunogenicity evaluation.

^c Mean of entire population, time since revaccination for subset ≥65 years not provided.

^d Suboptimal defined as <500 ng of antibody nitrogen/ml.

^e Positive reactions defined as number of subjects with detectable type specific antibodies (eight subjects multiplied by eight serotypes for 64 total possible positive reactions).

^f CAP, community-acquired pneumonia.

^g GMC, geometric mean concentration.

supports comparable anti-CP antibody responses to PPV in older persons (26, 73, 86, 91, 124). Even with advanced age, individuals seem to retain the ability to quantitatively respond to PPV. For example, in an immunogenicity study by Carson and colleagues, 29 male and female ambulatory veterans with a mean age of 80 years were given a PPV (26). The anti-CP antibody responses to the five serotypes assayed were similar to those of young healthy controls when measured at 1 month. Comparable immunogenicity has been demonstrated in other studies as well (86, 124).

Some have suggested hyporesponsiveness in older individuals by subgroup analysis (33, 51). For example, Hedlund et al. studied the anti-CP antibody responses after PPV in older patients recently hospitalized for community-acquired pneumonia and compared these to those of age-matched outpatients in the infectious disease clinic (51). In a subgroup analysis of all subjects older than 68 years, compared to those younger than 68 years, the combined GMC of all antibody to CP was significantly less than that of the younger group. Rubins et al. concluded that older adults responded as well as did a younger cohort but that 20% of older patients were nonresponders as defined by a <2 FI to two of seven serotype-specific anti-CP antibodies (124). In a study comparing mostly female nursing home residents to young controls by Romero-Steiner et al. (121), the GMC for two of five serotype-specific CPs antibodies (6B and 19F) were less in the older group. The diminished immunogenicity seen in the older group in this study may be attributable to their very advanced age, comorbidity, and/or female gender. Thus, PPV is characterized by significant immunogenicity, at least initially, in most older persons compared to that in younger controls.

Duration of PPV Protection

In a retrospective case-control study of bacteremic pneumococcal infection by Shapiro and colleagues, protection declined with increasing interval from vaccination, and the decline was

most rapid in the oldest cohort (133). After 5 years, protection against invasive disease caused by vaccine serotypes in those <55 years old was still 85% (confidence interval [CI], 62 to 94%). For subjects 65 to 74 years old, effectiveness was 58% (CI, -2 to 83%), while in those ≥85 years old, effectiveness was -13% (CI, -174 to 54%), indicating no protection in the oldest cohort. In contrast, Butler and colleagues, using an indirect cohort method, did not confirm decreased protection with increasing interval from PPV (22). More evidence is needed to firmly establish to what degree protection declines as the interval from vaccination increases and how this decrease in protection relates to antibody levels.

If antibodies to CPs serve as markers for protection, then the longevity of the response may define the duration of protection. Protection against infection is likely to diminish when vaccine-induced antibodies decline below a certain level. Without definitive clinical studies, CPs antibodies may be a useful surrogate marker. Table 2 summarizes studies assessing the duration of anti-CP antibody responses in older adults (50, 64, 91, 124, 128). Two early studies without absorption of anti-CWP antibodies revealed comparable antibody declines in older adults 5 to 7 years after vaccination (33, 80). Two larger, more recent European studies demonstrated that 3 years after PPV, some type-specific antibodies had declined to prevaccine levels, presumably resulting in diminished clinical protection (50, 128). The study by Sankilampi and colleagues evaluated anti-CP antibodies in 62 outpatients 3 years after PPV (128). At 3 years, antibodies to two of the six serotype-specific anti-CPs were at prevaccine levels. Antibody to serotype 14 attained the highest peak levels after vaccination. Assuming a constant rate of decline, the authors extrapolated that antibody to serotype 14 would reach prevaccine levels in 7.7 years. From these data on ambulatory older persons, it is reasonable to assume that the duration of antibodies to CPs after PPV ranges from less than 3 years to as much as 8 years.

Although PPV antibody responses have been variably de-

TABLE 3. Immunogenicity of PPV revaccination in older adults

Study	Population	Yrs since first vaccination	Antibodies to CPs after revaccination ^b
Mufson et al. (80) ^a	<i>n</i> = 15; mean age, 75 yr; community	6 yr	Mean, 1.5 FI; response less than peak after primary vaccination
Davidson et al. (33) ^a	<i>n</i> = 13; age, ≥65 yr; Alaskan natives	Mean, 7.4 yr ^c	22% suboptimal response compared with 12% in group <65 yr ^d 50% reduction of suboptimal responses; same reduction in group <65 yr and group ≥65 yr
Musher et al. (87)	<i>n</i> = 8; mean age, 71 yr; veterans	6 yr	70% positive antibody reactions; increase from 58% positive reactions prior to revaccination (78% positive reactions at peak after initial vaccine)
Jackson et al. (57)	<i>n</i> = 65; age, 50–74 yr	Median, 6 yr ^e	Numerically higher than levels before revaccination ^f (statistically not different) Levels lower than separate group post-first PPV (statistically less for 1/3 serotypes)

^a Without absorption of antibody to cell wall polysaccharide.

^b Antibody measurements taken approximately 1 month after revaccination.

^c Mean of entire population; time since revaccination for subset ≥65 years not provided.

^d Suboptimal defined as <500 ng of antibody nitrogen/ml.

^e For the entire group; mean or median since revaccination not provided for subset of older subjects studied for immunogenicity.

^f Unclear if immunogenicity data for subjects before revaccination are mutually exclusive from those for subjects after revaccination. The cohort prior to revaccination has 82 subjects, whereas the cohort after revaccination has 65 subjects.

finer, it appears that antibody duration in older persons may be shorter than previously assumed. Unfortunately none of these studies compares anti-CP antibody duration to that of younger controls. No recent data exist on antibody duration beyond 5 to 6 years in older or younger persons. Inasmuch as antibody concentration correlates with protection, a significant decrement in clinical protection might be expected as early as 3 years. However, additional clinical data are needed to correlate with the immunogenicity data to define the window of protection after PPV in older adults.

Revaccination

With declining antibodies to CPs after vaccination with PPV, the question of the role of revaccination arises. As a vaccine composed of polysaccharide antigens, the PPV induces a T-cell-independent response, and thus, an anamnestic response (i.e., “booster”) is unlikely (53, 78, 142). There are no data on the clinical effectiveness of revaccination and only limited immunogenicity data in older adults. This absence is surprising in light of the recommendations to revaccinate all adults ≥65 years if 5 or more years have passed since the first vaccination and they were <65 years at the time of the first vaccination (28).

Early data from young adults suggested revaccination several years after the initial PPV induced an antibody response to the antigens not previously given, but not to the antigens that were components of the first vaccine (14, 52, 81). Studies in other cohorts have demonstrated that if subjects had not responded to the initial PPV, they were unlikely to respond to revaccination (109, 118).

Table 3 highlights studies on PPV revaccination in older persons. The initial studies in older persons with very few subjects suggested that revaccination of older adults resulted in an antibody response similar to, or slightly less than, those to the initial PPV (33, 80). Two recent studies that absorbed sera with anti-CWP antibodies demonstrated similar results (57, 87). Musher and colleagues revaccinated eight male veterans (mean age, 71 years). He found the second vaccination induced

70% of serotype-specific antibody responses at 1 month, compared to 78% 1 month after the initial vaccination (87). In a large study evaluating the safety of revaccination, Jackson and colleagues also report immunogenicity data after revaccination of subjects 50 to 74 years old (57). Although immunogenicity was not the primary outcome, this is currently the largest published report providing immunogenicity data after revaccination. The GMC of antibody to three of the CP serotypes in the revaccinated group was less than that of the group receiving an initial vaccination. Although CPs specific antibodies rose after revaccination, it was difficult to track individual responses from the data presented.

The limited data indicate older adults mount anti-CP antibody responses to revaccination, although the responses may be less than those to the initial injection of vaccine. If true, factors that may account for the hyporesponsiveness to revaccination include age, comorbidities, or that to the initial vaccination. The subjects may simply be older and/or have more comorbidities, which would lessen their immune responsiveness. It seems less likely that aging by itself would account for this finding in light of the robust immune responses to primary vaccination in healthy older adults. However, comorbidities may be a significant factor, particularly if the subjects receiving their first vaccine were less well than the general population. The fact that a patient has already been vaccinated may indicate the presence of preexisting comorbid conditions that prompted the first vaccination. The comorbidities may have progressed since the time of the initial vaccine. Another possibility is that the first vaccination itself reduces immune responsiveness to subsequent ones. Prior antigen exposure may induce immunologic tolerance under some circumstances. The early data from young adults support this hypothesis since young healthy subjects were hyporesponsive to their second exposure to polysaccharide antigens (as discussed above). Meningococcal polysaccharide revaccination also results in hyporesponsiveness (46). Conjugate vaccine data (discussed below) further support this hypothesis.

A short interval (i.e., <1 year) between vaccinations is a

TABLE 4. Antibody function after PPV in older adults

Study	Subjects	Controls	Endpoint	Measurements after PPV	Result of functional anti-CP antibody in older adults after PPV
Musher et al. (85)	<i>n</i> = 5, men mean age, 69 yr; COPD	Healthy young men; mean age, 34 yr	OPA to 9 serotypes	1 mo	OPA increased for 8/9 types from prevaccine ($P \leq 0.01$); OPA increased less for 4/9 types compared to controls ($P \leq 0.02$)
Konradsen (64)	<i>n</i> = 15; mean age, 63 yr; Denmark	Control serum of younger subjects	Avidity for 2 serotypes	1 mo, 5 yr	Avidity same relative to controls; unchanged after 5 yr
Rubins et al. (124)	<i>n</i> = 53; men mean age, 71 yr; veterans	28 younger staff members	Avidity and OPA to 1 serotype	1 mo, 3 mo, 16 mo	OPA increased, but avidity did not, relative to prevaccine; subset of older subjects with poor antibody response also had poor OPA
Romero-Steiner et al. (121)	<i>n</i> = 46; 39 women; mean age, 86 yr; nursing home residents	<i>n</i> = 12; mean age, 37 yr	OPA to 5 serotypes; avidity for select samples; passive protection	2–3 wk	OPA less for 4/5 types compared to control prevaccine ($P < 0.05$); OPA less for 5/5 types postvaccine ($P < 0.05$); low avidity in samples with adequate antibody but low OPA; low avidity and OPA correlated with poor passive protection in mice
Carson et al. (26)	<i>n</i> = 29; 13 female; mean age, 80 yr; veterans	Young, healthy	Avidity for 2 serotypes	4 wk	Avidity increased for 1/2 types; no difference compared to young

common occurrence in both the young subjects' revaccination experience and the conjugate vaccine studies. Preexisting antibodies to CPs could be implicated. Such antibodies could bind antigens present in the subsequent vaccines and prevent their presentation to B cells. The correlation between local reactions to PPV and prevaccine anti-CP antibodies also suggests that preexisting antibodies may bind vaccine antigens (57, 68, 113, 129). Paradoxically, prevaccine antibodies in vaccine-naïve subjects predict a good antibody response (123). However, important differences may exist between the naturally occurring anti-CP antibodies present before the first administration of PPV as opposed to antibodies that develop in response to an initial vaccination (prevaccine antibodies). One possibility is the anti-CP antibodies after vaccination may be more serotype-specific than those naturally acquired. Data indicating less serotype cross-reactivity among postvaccine anti-CP antibodies compared to prevaccine anti-CP antibodies support this concept (140). Also, anti-CP antibodies found in vaccine-naïve subjects most likely developed due to natural exposure to pneumococci or to cross-reacting bacteria. This natural immune response probably involves more complex antigens, presented in a more efficient way, and thus results in increased immunogenicity upon repeat exposure to the polysaccharides in the PPV.

There is a pressing need for clinical data on effectiveness and duration of antibody responses to revaccination and multiple revaccinations. Given the T-cell-independent nature of the response to polysaccharide antigens, it is important to ascertain whether or not repeated exposures to the antigens prolong protection or whether or not the response is extinguished at some point.

Function of Antibodies to CPs after PPV

Studies have demonstrated that avidity and/or OPA correlate better with *in vivo* passive protection (59, 84, 121, 147) than do antibody levels, underscoring the importance of these functional measures. No clinical studies have correlated tests of antibody function with vaccine effectiveness. One recent

case-control study demonstrated that patients admitted either with bacteremic or nonbacteremic pneumococcal pneumonia had similar concentrations of antibodies to CPs as did controls but the OPA was diminished in patients with pneumonia, again emphasizing the importance of antibody function in protection (92).

Table 4 summarizes five studies assessing anti-CP antibody function in older adults after PPV. Again, the heterogeneity of the populations and nonstandardized assays may limit comparisons. Three studies suggested antibody avidity after PPV in immunocompetent older adults was similar to that of younger subjects (26, 64, 124). The first study to provide data suggesting older adults have antibody with lesser function after vaccination than do younger subjects was published by Musher et al. (85). They compared five older men with chronic obstructive pulmonary disease (COPD) to young controls and found lower vaccine-induced OPA in the older cohort. In contrast, Rubins and colleagues reported increased OPA, but not avidity, in both the older and younger subjects after vaccination (124). In a study of 46 nursing home residents, mostly women with a mean age of 85.5 years, Romero-Steiner and colleagues demonstrated lower OPA both before and after vaccination when compared to that in a younger cohort (121). The diminished OPA correlated with decreased passive protection. These data strongly suggest a decline in antibody function may occur in this select subset of frail elderly subjects in long-term care facilities. Whether a similar decline in functional antibodies occurs with advancing age in the general population has yet to be determined. Future studies evaluating the antibody responses to PPV should include functional characterization of the antibodies elicited.

NONPOLYSACCHARIDE VACCINES

Drawbacks of PPV

Although inexpensive, effective, and safe, the polysaccharide vaccine has drawbacks. Certain cohorts respond poorly to the PPV (3, 37, 88, 116, 118, 119), and these are often the same

TABLE 5. Immunogenicity of pneumococcal conjugate vaccine in older adults

Study	Subjects ^a	Series	Antibody to CP after PCV
Powers et al. (111)	<i>n</i> = 23; mean age, 67 yr (23 age-matched controls)	5-valent CRM ₁₉₇ ^b and then PPV after 6 mo (23 controls received PPV and then placebo at mo 6)	Similar % with 2 FI at mo 1 and 6 except lower for 1/5 serotypes (19F) at mo 6 in PCV group; in PCV subjects, minimal response except to 19F after mo 6 in PPV group
Shelly et al. (134)	<i>n</i> = 49; median age, 66 yr (healthy, young controls)	5-valent CRM ₁₉₇ and then PPV at mo 2 (controls received PPV and then placebo at mo 2)	Response same for type 6B; lower for type 14 in PCV group than in control group; only 1.2 FI in PCV group after mo 2 post-PPV; IgA by nasal secretion unchanged after vaccination
Lottenbach et al. (73)	<i>n</i> = 12; age, 50–85 yr ^c (12 age-matched controls)	5-valent CRM ₁₉₇ (controls received PPV)	Older adults appear to have antibody response to one PPV similar to that to one PCV (no statistical analysis)

^a Controls are the group to which older subjects receiving PCV are being compared (not necessarily specified as control by investigators).

^b CRM₁₉₇, mutant diphtheria toxin conjugated to pneumococcal polysaccharides.

^c No mean provided.

individuals who are predisposed to pneumococcal infection (28). Another problem is that it is uncommon for adults of any age to respond to all the vaccine serotypes (44, 123). Because the polysaccharide antigens are repeating subunits, T-cell help is not required for their recognition and cellular immunity does not develop (53, 78, 142). To counter these problems, alternative vaccines have been explored.

PCV

The most studied of the alternative vaccines are pneumococcal conjugate vaccines (PCV), in which pneumococcal polysaccharide antigens are covalently linked with immunogenic carrier proteins that bring T cells into the response. The concept of conjugation of polysaccharide to a protein arose from early work by Goebel and Avery, who demonstrated in the rabbit that immunogenicity resulted from linking saccharide haptens to protein carriers thereby inducing a T-cell-dependent response (8, 45). Theoretically, inducing immunologic memory would allow an anamnestic response to revaccination, providing longer, more durable protection against infection. Conjugate vaccines have been shown to improve pneumococcal vaccine responses in children, who typically have poor responses to PPV attributable to delayed maturation of subsets of B cells (10, 114).

The PCV has shown a marked reduction of IPD and, to a lesser extent, otitis media of children, leading to vaccine licensure in 2000 (12, 35, 104). While some data indicate that nonresponders to the polysaccharide vaccine respond better to a conjugate vaccine (89, 152), other data have not supported an improved response (1, 88). Reduction of nasopharyngeal carriage is another putative advantage of a conjugate vaccine. The reduced carriage seen in children with a *Haemophilus influenzae* type b (Hib) conjugate vaccine (49) has also been demonstrated with the PCV in children (31, 32, 76). Conjugation may also improve antibody quality. Trials with Hib conjugate vaccines have shown protection when the antibody levels were below the protective threshold for Hib polysaccharide vaccination, suggesting conjugation improves antibody effectiveness (34, 48).

While theoretically appealing, the limited data from older adults using PCV have not been promising (Table 5) (73, 111, 134). Three studies have failed to demonstrate improved immunogenicity from the conjugate vaccine in older adults, either

after one PCV dose or if a PCV is followed by a PPV. Powers et al. and Shelly et al. both compared a PCV followed by a PPV at month 6 or month 2, respectively, to PPV alone (111, 134). In both studies, the anti-CP antibody responses after the first PCV were similar to those of the control group receiving only a PPV. The subsequent administration of PPV provided no additional antibody response, with the exception to that of serotype 19 in the Powers study. However, no overall improved immunogenicity was evident because the initial response to the serotype 19 antigen in the PCV was poor. Lottenbach and colleagues compared one injection of PCV to one of PPV in older subjects (73). Although not compared statistically, there appeared to be no improved immunogenicity from one dose of the PCV compared to one dose of the PPV. An important limitation in all three studies is that only one injection of PCV was administered. PCV repeat vaccinations might provide a booster response, and in theory, vaccine strategies might include a series of PCV inoculations, as is done with other vaccines like tetanus. In infants, a significant booster response is seen after the fourth PCV (35). Whether the lower polysaccharide antigen doses used in conjugate vaccines contribute to hyporesponsiveness in adults remains unknown.

Even if the PCV eventually proves more immunogenic and/or more protective in adults, important drawbacks will still exist. The PCV may be more costly, a series of injections may be required, and only a limited number of capsular antigens are available in the current formulations. Because a broader range of serotypes is implicated in IPD in adults than in children, susceptibility to nonvaccine serotypes would not be eliminated by conjugate vaccines (47, 117). Administration of the PPV in addition to a PCV series might resolve the issue but would require the additional time and expense of another injection. It is also not yet clear whether the use of particular serotypes in two forms (polysaccharide and conjugate) might result in antigenic competition that might interfere with generating an antibody response.

Nonconjugate PPV

Also under development are the pneumococcal protein vaccines which are composed of noncapsular virulence factors. Possible advantages are the potential to protect against all serotypes and to stimulate immunologic memory. Some pneumococcal proteins that are candidates include pneumococcal

surface protein A (PspA), pneumolysin, pneumococcal surface adhesin A (PsaA), PspC, and others (2, 19, 20, 105–107). Although there are no published reports of these protein based vaccines being used in elderly adults, PspA is the furthest along in development. Encouraging early results indicate recombinant PspA elicits an antibody response in humans that confers passive protection in mice (18). Combining pneumococcal proteins in a vaccine has been proposed as a way to provide even broader protection (16, 100).

CONCLUSION

Extensive studies of the polyvalent PPV demonstrate good immunogenicity in older adults, generally comparable to that in younger subjects, although certain cohorts respond less well. The levels of the anti-CP antibody responses appear to wane as early as three years after vaccination. In older persons, revaccination also induces an antibody response, although it may not be as pronounced as that to the initial vaccination. More information on the immunogenicity and durability of response to revaccination is critically needed. Because antibody function may serve as a better marker of clinical protection, future studies should include correlates of antibody function such as OPA or passive protection. The PPV provides incomplete protection against infection, which may be worse in groups most prone to pneumococcal disease. More research into immunogenic conjugate and protein-based vaccines is needed. However, for now, because of its low cost and proven effectiveness, the use of the PPV should be a public health priority, especially in older adults.

REFERENCES

- Ahmed, F., M. C. Steinhoff, M. C. Rodriguez-Barradas, R. G. Hamilton, D. M. Musher, and K. E. Nelson. 1996. Effect of human immunodeficiency virus type 1 infection on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomized trial. *J. Infect. Dis.* **173**: 83–90.
- Alexander, J. E., R. A. Lock, C. C. Peeters, J. T. Poolman, P. W. Andrew, T. J. Mitchell, D. Hansman, and J. C. Paton. 1994. Immunization of mice with pneumolysin toxoid confers a significant degree of protection against at least nine serotypes of *Streptococcus pneumoniae*. *Infect. Immun.* **62**: 5683–5688.
- Ambrosino, D. M., G. R. Siber, B. A. Chilmonczyk, J. B. Jernberg, and R. W. Finberg. 1987. An immunodeficiency characterized by impaired antibody responses to polysaccharides. *N. Engl. J. Med.* **316**:790–793.
- Ament, A., R. Baltussen, G. Duru, C. Rigaud-Bully, D. de Graeve, A. Ortqvist, B. Jonsson, J. Verhaegen, J. Gaillat, P. Christie, A. S. Cifre, D. Vivas, C. Loiseau, and D. S. Fedson. 2000. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 western European countries. *Clin. Infect. Dis.* **31**:444–450.
- Ammann, A. J., G. Schiffman, and R. Austrian. 1980. The antibody responses to pneumococcal capsular polysaccharides in aged individuals. *Proc. Soc. Exp. Biol. Med.* **164**:312–316.
- Austrian, R. 1999. A brief history of pneumococcal vaccines. *Drugs Aging* **15**(Suppl. 1):1–10.
- Austrian, R. 1981. Some observations on the pneumococcus and on the current status of pneumococcal disease and its prevention. *Rev. Infect. Dis.* **3**(Suppl. 1):S1–S17.
- Avery, O. T., and W. F. Goebel. 1931. Chemo-immunological studies on conjugated carbohydrate-protein. V. The immunological specificity of an antigen prepared by combining the capsular polysaccharide of type III pneumococcus with foreign protein. *J. Exp. Med.* **54**:437–447.
- Baik, L., G. C. Curhan, E. B. Rimm, A. Bendich, W. C. Willett, and W. W. Fawzi. 2000. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. *Arch. Intern. Med.* **160**:3082–3088.
- Barrett, D. J., J. W. Sleasman, D. A. Schatz, and M. Steinitz. 1992. Human anti-pneumococcal polysaccharide antibodies are secreted by the CD5– B cell lineage. *Cell. Immunol.* **143**:66–79.
- Bennett, N. M., J. Buffington, and F. M. LaForce. 1992. Pneumococcal bacteremia in Monroe County, New York. *Am. J. Public Health* **82**:1513–1516.
- Black, S., H. Shinefield, B. Fireman, E. Lewis, P. Ray, J. R. Hansen, L. Elvin, K. M. Ensor, J. Hackell, G. Siber, F. Malinoski, D. Madore, I. Chang, R. Kohberger, W. Watson, R. Austrian, K. Edwards et al. 2000. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr. Infect. Dis. J.* **19**:187–195.
- Bolan, G., C. V. Broome, R. R. Facklam, B. D. Plikaytis, D. W. Fraser, and W. F. Schlech III. 1986. Pneumococcal vaccine efficacy in selected populations in the United States. *Ann. Intern. Med.* **104**:1–6.
- Borgono, J. M., A. A. McLean, P. P. Vella, A. F. Woodhour, I. Canepa, W. L. Davidson, and M. R. Hilleman. 1978. Vaccination and revaccination with polyvalent pneumococcal polysaccharide vaccines in adults and infants. *Proc. Soc. Exp. Biol. Med.* **157**:148–154.
- Breiman, R. F., J. S. Spika, V. J. Navarro, P. M. Darden, and C. P. Darby. 1990. Pneumococcal bacteremia in Charleston County, South Carolina. A decade later. *Arch. Intern. Med.* **150**:1401–1405.
- Briles, D. E., E. Ades, J. C. Paton, J. S. Sampson, G. M. Carlone, R. C. Huebner, A. Virolainen, E. Swiatlo, and S. K. Hollingshead. 2000. Intranasal immunization of mice with a mixture of the pneumococcal proteins PsaA and PspA is highly protective against nasopharyngeal carriage of *Streptococcus pneumoniae*. *Infect. Immun.* **68**:796–800.
- Briles, D. E., C. Forman, J. C. Horowitz, J. E. Volanakis, W. H. Benjamin, Jr., L. S. McDaniel, J. Eldridge, and J. Brooks. 1989. Antipneumococcal effects of C-reactive protein and monoclonal antibodies to pneumococcal cell wall and capsular antigens. *Infect. Immun.* **57**:1457–1464.
- Briles, D. E., S. K. Hollingshead, J. King, A. Swift, P. A. Braun, M. K. Park, L. M. Ferguson, M. H. Nahm, and G. S. Nabors. 2000. Immunization of humans with recombinant pneumococcal surface protein A (rPspA) elicits antibodies that passively protect mice from fatal infection with *Streptococcus pneumoniae* bearing heterologous PspA. *J. Infect. Dis.* **182**:1694–1701.
- Briles, D. E., S. K. Hollingshead, E. Swiatlo, A. Brooks-Walter, A. Szalai, A. Virolainen, L. S. McDaniel, K. A. Benton, P. White, K. Prellner, A. Hermansson, P. C. Aerts, H. Van Dijk, and M. J. Crain. 1997. PspA and PspC: their potential for use as pneumococcal vaccines. *Microb. Drug Resist.* **3**:401–408.
- Briles, D. E., R. C. Tart, E. Swiatlo, J. P. Dillard, P. Smith, K. A. Benton, B. A. Ralph, A. Brooks-Walter, M. J. Crain, S. K. Hollingshead, and L. S. McDaniel. 1998. Pneumococcal diversity: considerations for new vaccine strategies with emphasis on pneumococcal surface protein A (PspA). *Clin. Microbiol. Rev.* **11**:645–657.
- Bruyn, G. A., B. J. Zegers, and R. van Furth. 1992. Mechanisms of host defense against infection with *Streptococcus pneumoniae*. *Clin. Infect. Dis.* **14**:251–262.
- Butler, J. C., R. F. Breiman, J. F. Campbell, H. B. Lipman, C. V. Broome, and R. R. Facklam. 1993. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* **270**:1826–1831.
- Butler, J. C., J. Hofmann, M. S. Cetron, J. A. Elliott, R. R. Facklam, and R. F. Breiman. 1996. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance Syst. *J. Infect. Dis.* **174**:986–993.
- Butler, J. C., and A. Schuchat. 1999. Epidemiology of pneumococcal infections in the elderly. *Drugs Aging* **15**(Suppl. 1):11–19.
- Butler, J. C., E. D. Shapiro, and G. M. Carlone. 1999. Pneumococcal vaccines: history, current status, and future directions. *Am. J. Med.* **107**: 69S–76S.
- Carson, P. J., K. L. Nichol, J. O'Brien, P. Hilo, and E. N. Janoff. 2000. Immune function and vaccine responses in healthy advanced elderly patients. *Arch. Intern. Med.* **160**:2017–2024.
- Centers for Disease Control and Prevention. 2001. Influenza and pneumococcal vaccination levels among persons aged > or = 65 years—United States, 1999. *Morb. Mortal. Wkly. Rep.* **50**:532–537.
- Centers for Disease Control and Prevention. 1997. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb. Mortal. Wkly. Rep.* **46**(RR-08):1–24.
- Concepcion, N. F., and C. E. Frasch. 2001. Pneumococcal type 22f polysaccharide absorption improves the specificity of a pneumococcal-polysaccharide enzyme-linked immunosorbent assay. *Clin. Diagn. Lab. Immunol.* **8**:266–272.
- Coughlin, R. T., A. C. White, C. A. Anderson, G. M. Carlone, D. L. Klein, and J. Treanor. 1998. Characterization of pneumococcal specific antibodies in healthy unvaccinated adults. *Vaccine* **16**:1761–1767.
- Dagan, R., R. Melamed, M. Muallem, L. Piglansky, D. Greenberg, O. Abramson, P. M. Mendelman, N. Bohidar, and P. Yagupsky. 1996. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. *J. Infect. Dis.* **174**: 1271–1278.
- Dagan, R., M. Muallem, R. Melamed, O. Leroy, and P. Yagupsky. 1997. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. *Pediatr. Infect. Dis. J.* **16**:1060–1064.

33. Davidson, M., L. R. Bulkow, J. Grabman, A. J. Parkinson, C. Chamblee, W. W. Williams, A. P. Lanier, and G. Schiffman. 1994. Immunogenicity of pneumococcal revaccination in patients with chronic disease. *Arch. Intern. Med.* **154**:2209–2214.
34. Eskola, J., H. Kayhty, A. K. Takala, H. Peltola, P. R. Ronnberg, E. Kela, E. Pekkanen, P. H. McVerry, and P. H. Makela. 1990. A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive *Haemophilus influenzae* type b disease. *N. Engl. J. Med.* **323**:1381–1387.
35. Eskola, J., T. Kilpi, A. Palmu, J. Jokinen, J. Haapakoski, E. Herva, A. Takala, H. Kayhty, P. Karma, R. Kohberger, G. Siber, and P. H. Makela. 2001. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N. Engl. J. Med.* **344**:403–409.
36. Farr, B. M., B. L. Johnston, D. K. Cobb, M. J. Fisch, T. P. Germanson, K. A. Adal, and A. M. Anglim. 1995. Preventing pneumococcal bacteremia in patients at risk. Results of a matched case-control study. *Arch. Intern. Med.* **155**:2336–2340.
37. Fata, F. T., B. C. Herzlich, G. Schiffman, and A. L. Ast. 1996. Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B12 levels. *Ann. Intern. Med.* **124**:299–304.
38. Fattal-German, M., J. Taillandier, D. Mathieu, and B. Bizzi. 1991. Pneumococcal vaccination of elderly individuals. *Vaccine* **9**:542–544.
39. Fedson, D. S. 1999. The clinical effectiveness of pneumococcal vaccination: a brief review. *Vaccine* **17**(Suppl. 1):S85–S90.
40. Fedson, D. S., D. M. Musher, and J. Eskola. 1999. Pneumococcal vaccine, p. 553–607. *In* S. A. Plotkin and W. A. Orenstein (ed.), *Vaccines*, 3rd ed. W. B. Saunders Company, Philadelphia, Pa.
41. Feikin, D. R., A. Schuchat, M. Koleczak, N. L. Barrett, L. H. Harrison, L. Lefkowitz, A. McGeer, M. M. Farley, D. J. Vugia, C. Lexau, K. R. Stefek, J. E. Patterson, and J. H. Jorgensen. 2000. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. *Am. J. Public Health* **90**:223–229.
42. Gaillat, J. 1998. Epidemiology of systemic *Streptococcus pneumoniae* infections. *Presse Med.* **27**(Suppl. 1):9–16.
43. Gaillat, J., D. Zmirou, M. R. Mallaret, D. Rouhan, J. P. Bru, J. P. Stahl, P. Delormas, and M. Micoud. 1985. Clinical trial of an antipneumococcal vaccine in elderly subjects living in institutions. *Rev. Epidemiol. Sante Publique* **33**:437–444.
44. Go, E. S., and Z. K. Ballas. 1996. Anti-pneumococcal antibody response in normal subjects: a meta-analysis. *J. Allergy Clin. Immunol.* **98**:205–215.
45. Goebel, W. F. 1939. Studies on antibacterial immunity induced by artificial antigens. I. Immunity to experimental pneumococcal infection with an antigen containing cellobiuronic acid. *J. Exp. Med.* **69**:353–364.
46. Granoff, D. M., R. K. Gupta, R. B. Belshe, and E. L. Anderson. 1998. Induction of immunologic refractoriness in adults by meningococcal C polysaccharide vaccination. *J. Infect. Dis.* **178**:870–874.
47. Hausdorff, W. P., J. Bryant, P. R. Paradiso, and G. R. Siber. 2000. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin. Infect. Dis.* **30**:100–121.
48. Heath, P. T., R. Booy, H. J. Azzopardi, M. P. Slack, J. Bowen-Morris, H. Griffiths, M. E. Ramsay, J. J. Deeks, and E. R. Moxon. 2000. Antibody concentration and clinical protection after Hib conjugate vaccination in the United Kingdom. *JAMA* **284**:2334–2340.
49. Heath, P. T., J. Bowen-Morris, D. Griffiths, H. Griffiths, D. W. Crook, and E. R. Moxon. 1997. Antibody persistence and *Haemophilus influenzae* type b carriage after infant immunisation with PRP-T. *Arch. Dis. Child.* **77**:488–492.
50. Hedlund, J., A. Ortvist, H. B. Konradsen, and M. Kalin. 2000. Recurrence of pneumonia in relation to the antibody response after pneumococcal vaccination in middle-aged and elderly adults. *Scand. J. Infect. Dis.* **32**:281–286.
51. Hedlund, J. U., M. E. Kalin, A. B. Ortvist, and J. Henrichsen. 1994. Antibody response to pneumococcal vaccine in middle-aged and elderly patients recently treated for pneumonia. *Arch. Intern. Med.* **154**:1961–1965.
52. Heidelberger, M., M. M. Dilapi, M. Siegel, and A. W. Walter. 1950. Persistence of antibodies in human subjects injected with pneumococcal polysaccharides. *J. Immunol.* **65**:535–541.
53. Heilmann, C. 1990. Human B and T lymphocyte responses to vaccination with pneumococcal polysaccharides. *APMIS Suppl.* **15**:1–23.
54. Henrichsen, J. 1995. Six newly recognized types of *Streptococcus pneumoniae*. *J. Clin. Microbiol.* **33**:2759–2762.
55. Hilleman, M. R., A. J. Carlson, Jr., A. A. McLean, P. P. Vella, R. E. Weibel, and A. F. Woodhour. 1981. *Streptococcus pneumoniae* polysaccharide vaccine: age and dose responses, safety, persistence of antibody, revaccination, and simultaneous administration of pneumococcal and influenza vaccines. *Rev. Infect. Dis.* **3**(Suppl.):S31–S42.
56. Hook, E. W., III, C. A. Horton, and D. R. Schaberg. 1983. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. *JAMA* **249**:1055–1057.
57. Jackson, L. A., P. Benson, V. P. Sneller, J. C. Butler, R. S. Thompson, R. T. Chen, L. S. Lewis, G. Carlone, F. DeStefano, P. Holder, T. Lezhava, and W. W. Williams. 1999. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* **281**:243–248.
58. Janes, G. R., D. K. Blackman, J. C. Bolen, L. A. Kamimoto, L. Rhodes, L. S. Caplan, M. R. Nadel, S. L. Tomar, J. F. Lando, S. M. Greby, J. A. Singleton, R. A. Strikas, and K. G. Wooten. 1999. Surveillance for use of preventive health-care services by older adults, 1995–1997. *Morb. Mortal. Wkly. Rep. CDC Surveill. Summ.* **48**:51–88.
59. Johnson, S. E., L. Rubin, S. Romero-Steiner, J. K. Dykes, L. B. Pais, A. Rizvi, E. Ades, and G. M. Carlone. 1999. Correlation of opsonophagocytosis and passive protection assays using human antipneumococcal antibodies in an infant mouse model of bacteremia for *Streptococcus pneumoniae*. *J. Infect. Dis.* **180**:133–140.
60. Kalin, M., A. Ortvist, M. Almela, E. Aufwerber, R. Dwyer, B. Henriques, C. Jorup, I. Julander, T. J. Marrie, M. A. Mufson, R. Riquelme, A. Thalmé, A. Torres, and M. A. Woodhead. 2000. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. *J. Infect. Dis.* **182**:840–847.
61. Kaufman, P. 1947. Pneumonia in old age. Active immunization against pneumonia with pneumococcus polysaccharide: results of a six year study. *Arch. Intern. Med.* **79**:518–531.
62. Kayhty, H., H. Peltola, V. Karanko, and P. H. Makela. 1983. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J. Infect. Dis.* **147**:1100.
63. Koivuola, I., M. Sten, M. Leinonen, and P. H. Makela. 1997. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. *Am. J. Med.* **103**:281–290.
64. Konradsen, H. B. 1995. Quantity and avidity of pneumococcal antibodies before and up to five years after pneumococcal vaccination of elderly persons. *Clin. Infect. Dis.* **21**:616–620.
65. Koskela, M. 1987. Serum antibodies to pneumococcal C polysaccharide in children: response to acute pneumococcal otitis media or to vaccination. *Pediatr. Infect. Dis. J.* **6**:519–526.
66. Landesman, S. H., and G. Schiffman. 1981. Assessment of the antibody response to pneumococcal vaccine in high-risk populations. *Rev. Infect. Dis.* **3**(Suppl.):S184–S197.
67. Landesman, S. H., P. M. Smith, and G. Schiffman. 1983. Pneumococcal vaccine in elderly patients with COPD. *Chest* **84**:433–435.
68. Lawrence, E. M., K. M. Edwards, G. Schiffman, J. M. Thompson, W. K. Vaughn, and P. F. Wright. 1983. Pneumococcal vaccine in normal children. Primary and secondary vaccination. *Am. J. Dis. Child.* **137**:846–850.
69. Lee, C. J., S. D. Banks, and J. P. Li. 1991. Virulence, immunity, and vaccine related to *Streptococcus pneumoniae*. *Crit. Rev. Microbiol.* **18**:89–114.
70. Lee, C. J., K. Koizumi, J. Henrichsen, B. Perch, C. S. Lin, and W. Egan. 1984. Capsular polysaccharides of nongroupable streptococci that cross-react with pneumococcal group 19. *J. Immunol.* **133**:2706–2711.
71. Lieberman, D., F. Schlaeffer, and A. Porath. 1997. Community-acquired pneumonia in old age: a prospective study of 91 patients admitted from home. *Age Ageing* **26**:69–75.
72. Loeb, M., McGeer, A., McArthur, M., Walter, S., and Simor, A. E. 1999. Risk Factors for pneumonia and other lower respiratory tract infections in elderly residents of long-term care facilities. *Arch. Intern. Med.* **159**:2058–2064.
73. Lottenbach, K. R., C. M. Mink, S. J. Barenkamp, E. L. Anderson, S. M. Homan, and D. C. Powers. 1999. Age-associated differences in immunoglobulin G1 (IgG1) and IgG2 subclass antibodies to pneumococcal polysaccharides following vaccination. *Infect. Immun.* **67**:4935–4938.
74. Marrie, T. J. 1998. Community-acquired pneumonia: epidemiology, etiology, treatment. *Infect. Dis. Clin. N. Am.* **12**:723–740.
75. Marrie, T. J. 1999. Pneumococcal pneumonia: epidemiology and clinical features. *Semin. Respir. Infect.* **14**:227–236.
76. Mbelle, N., R. E. Huebner, A. D. Wasas, A. Kimura, I. Chang, and K. P. Klugman. 1999. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J. Infect. Dis.* **180**:1171–1176.
77. Mirzanejad, Y., S. Roman, J. Talbot, L. Nicolle, et al. 1996. Pneumococcal bacteremia in two tertiary care hospitals in Winnipeg, Canada. *Chest* **109**:173–178.
78. Mond, J. J., Q. Vos, A. Lees, and C. M. Snapper. 1995. T cell independent antigens. *Curr. Opin. Immunol.* **7**:349–354.
79. Moore, R. A., P. J. Wiffen, and B. A. Lipsky. 2000. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. *BMC. Fam. Pract.* **1**:1.
80. Mufson, M. A., D. F. Hughey, C. E. Turner, and G. Schiffman. 1991. Revaccination with pneumococcal vaccine of elderly persons 6 years after primary vaccination. *Vaccine* **9**:403–407.
81. Mufson, M. A., H. E. Krause, and G. Schiffman. 1984. Reactivity and antibody responses of volunteers given two or three doses of pneumococcal vaccine. *Proc. Soc. Exp. Biol. Med.* **177**:220–225.
82. Mufson, M. A., and R. J. Stanek. 1999. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. *Am. J. Med.* **107**:34S–43S.
83. Musher, D. M. 1992. Infections caused by *Streptococcus pneumoniae*: clin-

- ical spectrum, pathogenesis, immunity, and treatment. *Clin. Infect. Dis.* **14**:801–807.
84. Musher, D. M., I. Alexandraki, E. A. Graviss, N. Yanbei, A. Eid, L. A. Inderias, H. M. Phan, and E. Solomon. 2000. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. *Medicine (Baltimore)* **79**:210–221.
 85. Musher, D. M., A. J. Chapman, A. Goree, S. Jonsson, D. Briles, and R. E. Baughn. 1986. Natural and vaccine-related immunity to *Streptococcus pneumoniae*. *J. Infect. Dis.* **154**:245–256.
 86. Musher, D. M., J. E. Groover, E. A. Graviss, and R. E. Baughn. 1996. The lack of association between aging and postvaccination levels of IgG antibody to capsular polysaccharides of *Streptococcus pneumoniae*. *Clin. Infect. Dis.* **22**:165–167.
 87. Musher, D. M., J. E. Groover, J. M. Rowland, D. A. Watson, J. B. Struewing, R. E. Baughn, and M. A. Mufson. 1993. Antibody to capsular polysaccharides of *Streptococcus pneumoniae*: prevalence, persistence, and response to revaccination. *Clin. Infect. Dis.* **17**:66–73.
 88. Musher, D. M., J. E. Groover, D. A. Watson, J. P. Pandey, M. C. Rodriguez-Barradas, R. E. Baughn, M. S. Pollack, E. A. Graviss, M. de Andrade, and C. I. Amos. 1997. Genetic regulation of the capacity to make immunoglobulin G to pneumococcal capsular polysaccharides. *J. Invest. Med.* **45**:57–68.
 89. Musher, D. M., J. E. Groover, D. A. Watson, M. C. Rodriguez-Barradas, and R. E. Baughn. 1998. IgG responses to protein-conjugated pneumococcal capsular polysaccharides in persons who are genetically incapable of responding to unconjugated polysaccharides. *Clin. Infect. Dis.* **27**:1487–1490.
 90. Musher, D. M., B. Johnson, Jr., and D. A. Watson. 1990. Quantitative relationship between anticapsular antibody measured by enzyme-linked immunosorbent assay or radioimmunoassay and protection of mice against challenge with *Streptococcus pneumoniae* serotype 4. *Infect. Immun.* **58**:3871–3876.
 91. Musher, D. M., M. J. Luchi, D. A. Watson, R. Hamilton, and R. E. Baughn. 1990. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and the effect of adsorption of serum with non-type-specific cell wall polysaccharide. *J. Infect. Dis.* **161**:728–735.
 92. Musher, D. M., H. M. Phan, D. A. Watson, and R. E. Baughn. 2000. Antibody to capsular polysaccharide of *Streptococcus pneumoniae* at the time of hospital admission for Pneumococcal pneumonia. *J. Infect. Dis.* **182**:158–167.
 93. Nichol, K. L. 1999. The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. *Vaccine* **17**(Suppl. 1):S91–S93.
 94. Nichol, K. L., L. Baken, J. Wuorema, and A. Nelson. 1999. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch. Intern. Med.* **159**:2437–2442.
 95. Nichol, K. L., R. MacDonald, and M. Hauge. 1997. Side effects associated with pneumococcal vaccination. *Am. J. Infect. Control* **25**:223–228.
 96. Nielsen, S. V., and J. Henrichsen. 1996. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989–94. *Epidemiol. Infect.* **117**:411–416.
 97. Nielsen, S. V., U. B. Sorensen, and J. Henrichsen. 1993. Antibodies against pneumococcal C-polysaccharide are not protective. *Microb. Pathog.* **14**:299–305.
 98. Nuorti, J. P., J. C. Butler, M. M. Farley, L. H. Harrison, A. McGeer, M. S. Kolczak, R. F. Breiman, et al. 2000. Cigarette smoking and invasive pneumococcal disease. *N. Engl. J. Med.* **342**:681–689.
 99. Reference deleted.
 100. Ogunniyi, A. D., R. L. Folland, D. E. Briles, S. K. Hollingshead, and J. C. Paton. 2000. Immunization of mice with combinations of pneumococcal virulence proteins elicits enhanced protection against challenge with *Streptococcus pneumoniae*. *Infect. Immun.* **68**:3028–3033.
 101. Ortvist, A., J. Hedlund, L. A. Burman, E. Elbel, M. Hofer, M. Leinonen, I. Lindblad, B. Sundelof, M. Kalin, et al. 1998. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet* **351**:399–403.
 102. Ortvist, A., J. Hedlund, L. Grillner, E. Jalonen, I. Kallings, M. Leinonen, and M. Kalin. 1990. Aetiology, outcome and prognostic factors in community-acquired pneumonia requiring hospitalization. *Eur. Respir. J.* **3**:1105–1113.
 103. Osler W. 1892. The principles and practice of medicine, 1st ed. D. Appleton and Company, New York, N.Y.
 104. Overturf, G. D. 2000. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. *Pediatrics* **106**:367–376.
 105. Overweg, K., A. Kerr, M. Sluiter, M. H. Jackson, T. J. Mitchell, A. P. de Jong, R. de Groot, and P. W. Hermans. 2000. The putative proteinase maturation protein A of *Streptococcus pneumoniae* is a conserved surface protein with potential to elicit protective immune responses. *Infect. Immun.* **68**:4180–4188.
 106. Paton, J. C. 1998. Novel pneumococcal surface proteins: role in virulence and vaccine potential. *Trends Microbiol.* **6**:85–88.
 107. Paton, J. C., A. M. Berry, and R. A. Lock. 1997. Molecular analysis of putative pneumococcal virulence proteins. *Microb. Drug Resist.* **3**:1–10.
 108. Petersen, R. L., K. Saag, R. B. Wallace, and B. N. Doebbeling. 1999. Influenza and pneumococcal vaccine receipt in older persons with chronic disease: a population-based study. *Med. Care* **37**:502–509.
 109. Petrasch, S., O. Kuhnemund, A. Reinacher, M. Uppenkamp, R. Reinert, W. Schmiegler, R. Lutticken, and G. Brittinger. 1997. Antibody responses of splenectomized patients with non-Hodgkin's lymphoma to immunization with polyvalent pneumococcal vaccines. *Clin. Diagn. Lab. Immunol.* **4**:635–638.
 110. Plouffe, J. F., R. F. Breiman, R. R. Facklam, et al. 1996. Bacteremia with *Streptococcus pneumoniae*. Implications for therapy and prevention. *JAMA* **275**:194–198.
 111. Powers, D. C., E. L. Anderson, K. Loffenbach, and C. M. Mink. 1996. Reactogenicity and immunogenicity of a protein-conjugated pneumococcal oligosaccharide vaccine in older adults. *J. Infect. Dis.* **173**:1014–1018.
 112. Quataert, S. A., C. S. Kirch, L. J. Wiedl, D. C. Phipps, S. Strohmeyer, C. O. Cimino, J. Skuse, and D. V. Madore. 1995. Assignment of weight-based antibody units to a human antipneumococcal standard reference serum, lot 89-S. *Clin. Diagn. Lab. Immunol.* **2**:590–597.
 113. Rigau-Perez, J. G., G. D. Overturf, L. S. Chan, J. Weiss, and D. Powars. 1983. Reactions to booster pneumococcal vaccination in patients with sickle cell disease. *Pediatr. Infect. Dis.* **2**:199–202.
 114. Rijkers, G. T., J. J. Roord, F. Koning, W. Kuis, and B. J. Zegers. 1987. Phenotypical and functional analysis of B lymphocytes of two siblings with combined immunodeficiency and defective expression of major histocompatibility complex (MHC) class II antigens on mononuclear cells. *J. Clin. Immunol.* **7**:98–106.
 115. Riquelme, R., A. Torres, M. El-Ebiary, J. P. de la Bellacasa, R. Estruch, J. Mensa, J. Fernandez-Sola, C. Hernandez, and R. Rodriguez-Roisin. 1996. Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. *Am. J. Respir. Crit. Care Med.* **154**:1450–1455.
 116. Robertson, J. D., K. Nagesh, S. N. Jowitt, M. Dougal, H. Anderson, K. Mutton, M. Zambon, and J. H. Scarffe. 2000. Immunogenicity of vaccination against influenza, *Streptococcus pneumoniae* and Haemophilus influenzae type B in patients with multiple myeloma. *Br. J. Cancer.* **82**:1261–1265.
 117. Robinson, K. A., W. Baughman, G. Rothrock, N. L. Barrett, M. Pass, C. Lexau, B. Damaske, K. Stefonek, B. Barnes, J. Patterson, E. R. Zell, A. Schuchat, and C. G. Whitney. 2001. Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995–1998: opportunities for prevention in the conjugate vaccine era. *JAMA* **285**:1729–1735.
 118. Rodriguez-Barradas, M. C., J. E. Groover, C. E. Lacke, D. W. Gump, C. J. Lahart, J. P. Pandey, and D. M. Musher. 1996. IgG antibody to pneumococcal capsular polysaccharide in human immunodeficiency virus-infected subjects: persistence of antibody in responders, revaccination in nonresponders, and relationship of immunoglobulin allotype to response. *J. Infect. Dis.* **173**:1347–1353.
 119. Rodriguez-Barradas, M. C., D. M. Musher, C. Lahart, C. Lacke, J. Groover, D. Watson, R. Baughn, T. Cate, and G. Crofoot. 1992. Antibody to capsular polysaccharides of *Streptococcus pneumoniae* after vaccination of human immunodeficiency virus-infected subjects with 23-valent pneumococcal vaccine. *J. Infect. Dis.* **165**:553–556.
 120. Roghmann, K. J., P. A. Tabloski, D. W. Bentley, and G. Schiffman. 1987. Immune response of elderly adults to pneumococcus: variation by age, sex, and functional impairment. *J. Gerontol.* **42**:265–270.
 121. Romero-Steiner, S., D. M. Musher, M. S. Cetron, L. B. Pais, J. E. Groover, A. E. Fiore, B. D. Plikaytis, and G. M. Carlone. 1999. Reduction in functional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. *Clin. Infect. Dis.* **29**:281–288.
 122. Ruben, F. L., and M. Uhrin. 1985. Specific immunoglobulin-class antibody responses in the elderly before and after 14-valent pneumococcal vaccine. *J. Infect. Dis.* **151**:845–849.
 123. Rubins, J. B., M. Alter, J. Loch, and E. N. Janoff. 1999. Determination of antibody responses of elderly adults to all 23 capsular polysaccharides after pneumococcal vaccination. *Infect. Immun.* **67**:5979–5984.
 124. Rubins, J. B., A. K. Puri, J. Loch, D. Charboneau, R. MacDonald, N. Opstad, and E. N. Janoff. 1998. Magnitude, duration, quality, and function of pneumococcal vaccine responses in elderly adults. *J. Infect. Dis.* **178**:431–440.
 125. Ruiz, M., S. Ewig, M. A. Marcos, J. A. Martinez, F. Arancibia, J. Mensa, and A. Torres. 1999. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am. J. Respir. Crit. Care Med.* **160**:397–405.
 126. Sankilampi, U., E. Herva, R. Haikala, O. Liimatainen, O. V. Renkonen, and M. Leinonen. 1997. Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. *Epidemiol. Infect.* **118**:7–15.
 127. Sankilampi, U., P. O. Honkanen, A. Bloigu, E. Herva, and M. Leinonen.

1996. Antibody response to pneumococcal capsular polysaccharide vaccine in the elderly. *J. Infect. Dis.* **173**:387–393.
128. **Sankilampi, U., P. O. Honkanen, A. Bloigu, and M. Leinonen.** 1997. Persistence of antibodies to pneumococcal capsular polysaccharide vaccine in the elderly. *J. Infect. Dis.* **176**:1100–1104.
129. **Sankilampi, U., P. O. Honkanen, R. Pyhala, and M. Leinonen.** 1997. Associations of prevaccination antibody levels with adverse reactions to pneumococcal and influenza vaccines administered simultaneously in the elderly. *Vaccine* **15**:1133–1137.
130. **Sankilampi, U., R. Isoaho, A. Bloigu, S. L. Kivela, and M. Leinonen.** 1997. Effect of age, sex and smoking habits on pneumococcal antibodies in an elderly population. *Int. J. Epidemiol.* **26**:420–427.
131. **Schouten, J.** 1981. Immune response to a 14-valent pneumococcal polysaccharide vaccine in the elderly. *Pharmatherapeutica* **3**:1–5.
132. **Schuchat, A., K. Robinson, J. D. Wenger, L. H. Harrison, M. Farley, A. L. Reingold, L. Lefkowitz, B. A. Perkins, et al.** 1997. Bacterial meningitis in the United States in 1995. *N. Engl. J. Med.* **337**:970–976.
133. **Shapiro, E. D., A. T. Berg, R. Austrian, D. Schroeder, V. Parcells, A. Margolis, R. K. Adair, and J. D. Clemens.** 1991. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N. Engl. J. Med.* **325**:1453–1460.
134. **Shelly, M. A., H. Jacoby, G. J. Riley, B. T. Graves, M. Pichichero, and J. J. Treanor.** 1997. Comparison of pneumococcal polysaccharide and CRM197-conjugated pneumococcal oligosaccharide vaccines in young and elderly adults. *Infect. Immun.* **65**:242–247.
135. **Short, W. R., and A. R. Tunkel.** 2000. Changing epidemiology of bacterial meningitis in the United States. *Curr. Infect. Dis. Rep.* **2**:327–331.
136. **Siber, G. R., C. Priehs, and D. V. Madore.** 1989. Standardization of antibody assays for measuring the response to pneumococcal infection and immunization. *Pediatr. Infect. Dis. J.* **8**:S84–91.
137. **Simberkoff, M. S., A. P. Cross, M. Al-Ibrahim, A. L. Baltch, P. J. Geiseler, J. Nadler, A. S. Richmond, R. P. Smith, G. Schiffman, D. S. Shepard, et al.** 1986. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administration Cooperative Study. *N. Engl. J. Med.* **315**:1318–1327.
138. **Singleton, J. A., S. M. Greby, K. G. Wooten, F. J. Walker, and R. Strikas.** 2000. Influenza, pneumococcal, and tetanus toxoid vaccination of adults—United States, 1993–7. *Morb. Mortal. Wkly. Rep. CDC Surveill. Summ.* **49**:39–62.
139. **Sisk, J. E., A. J. Moskowitz, W. Whang, J. D. Lin, D. S. Fedson, A. M. McBean, J. F. Plouffe, M. S. Cetron, and J. C. Butler.** 1997. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* **278**:1333–1339.
140. **Soininen, A., G. van den Dobbelen, L. Oomen, and H. Kayhty.** 2000. Are the enzyme immunoassays for antibodies to pneumococcal capsular polysaccharides serotype specific? *Clin. Diagn. Lab. Immunol.* **7**:468–476.
141. **Stanek, R. J., and M. A. Mufson.** 1995. Emergence of penicillin-resistant invasive pneumococci in a single American community. *Am. J. Med. Sci.* **310**:150–155.
142. **Stein, K. E.** 1992. Thymus-independent and thymus-dependent responses to polysaccharide antigens. *J. Infect. Dis.* **165**(Suppl. 1):S49–52.
143. **Szu, S. C., R. Schneerson, and J. B. Robbins.** 1986. Rabbit antibodies to the cell wall polysaccharide of *Streptococcus pneumoniae* fail to protect mice from lethal challenge with encapsulated pneumococci. *Infect. Immun.* **54**:448–455.
144. **Toniolo-Neto, J., L. W. Weckx, E. Halker, C. H. Lopes, R. C. de Menezes Succi, T. M. de Paiva, M. A. Ishida, and E. Forleo-Neto.** 1999. Safety of simultaneous pneumococcal and influenza vaccination in elderly patients in Brazil. *Drugs Aging* **15**(Suppl. 1):43–45.
145. **Urwin, G., M. F. Yuan, L. M. Hall, K. Brown, A. Efstratiou, and R. A. Feldman.** 1996. Pneumococcal meningitis in the North East Thames Region UK: epidemiology and molecular analysis of isolates. *Epidemiol. Infect.* **117**:95–102.
146. **U.S. Department of Health and Human Services.** 2000. Healthy people 2010. U.S. Department of Health and Human Services, Washington, D.C.
147. **Usinger, W. R., and A. H. Lucas.** 1999. Avidity as a determinant of the protective efficacy of human antibodies to pneumococcal capsular polysaccharides. *Infect. Immun.* **67**:2366–2370.
148. **Vitharsson, G., I. Jonsdottir, S. Jonsson, and H. Valdimarsson.** 1994. Opsonization and antibodies to capsular and cell wall polysaccharides of *Streptococcus pneumoniae*. *J. Infect. Dis.* **170**:592–599.
149. **Whitney, C. G., M. M. Farley, J. Hadler, L. H. Harrison, C. Lexau, A. Reingold, L. Lefkowitz, P. R. Cieslak, M. Cetron, E. R. Zell, J. H. Jorgensen, and A. Schuchat.** 2000. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N. Engl. J. Med.* **343**:1917–1924.
150. **Wright, A. E., W. Morgan, L. Colebrook, and R. W. Dodgson.** 1914. Observations on prophylactic inoculations against pneumococcus infection, and the results which have been achieved by it. *Lancet* **i**:1–10, 87–95.
151. **Yu, X., Y. Sun, C. Frasc, N. Concepcion, and M. H. Nahm.** 1999. Pneumococcal capsular polysaccharide preparations may contain non-C-polysaccharide contaminants that are immunogenic. *Clin. Diagn. Lab. Immunol.* **6**:519–524.
152. **Zielen, S., I. Buhning, N. Strnad, J. Reichenbach, and D. Hofmann.** 2000. Immunogenicity and tolerance of a 7-valent pneumococcal conjugate vaccine in nonresponders to the 23-valent pneumococcal vaccine. *Infect. Immun.* **68**:1435–1440.