Developing New Pneumococcal Vaccines Indicated for Adults for US licensure

Pre-meeting Package

for

VRBPAC

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Background

Streptococcus pneumonia is an important cause of morbidity and mortality in the United States disproportionately affecting children ≤ 5 years and the elderly. Published data for the period 1995-1998 showed that, although young children were at highest risk from invasive disease caused by *Streptococcus pneumoniae*, most cases of invasive pneumococcal disease and most deaths from pneumococcal disease occurred in adults (Robinson KA *et al.,* 2001). *Streptococcus pneumonia* is the most common cause of community-acquired pneumonia (CAP) among persons ≥ 65 years of age in the United States, resulting in hospitalizations and deaths (Kaplan V *et al.,* 2002; File TM, 2003). Within this age group, persons living in long term care facilities are at a higher risk for invasive pneumococcal disease and death compared to older adults living in the community (Kupronis BA *et al.*, 2003). In the elderly, the majority of cases of pneumococcal pneumonia are not associated with documented bacteremia (Ruiz-Gonzales A *et al.*, 1999; Fry *et al.,* 2002).

The risk of invasive pneumococcal disease is also higher in certain ethnic groups as compared to Caucasians. For example, in 1997-1998, the annual incidence of IPD was 56 per 100,000 for Navajos aged 18-64 years (compared to 10 per 100,000 for white persons aged 18-64 years) and 190 per 100,000 for Navajos aged ≥ 65 years (compared to 57 per 100,000 for white persons aged ≥ 65 years) (Watt JP *et al.,* 2004).

Immunocompromised individuals, those with chronic illness, and smokers are also at increased risk for invasive pneumococcal disease (Whitney CG, *et al.,* 2001). In addition, even though

antimicrobial therapy has resulted in reduced morbidity and mortality rates associated with invasive pneumococcal disease, the prevalence of multi-antimicrobial resistance among *Streptococcus pneumoniae* continues to increase worldwide (Vanderkooi OG *et al.*, 2005).

With the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in the US, the burden of invasive pneumococcal disease (IPD) has declined in children ≤ 5 years and disease rates also fell in adults (Whitney *et al.*, 2003). Population-based data from the Active Bacterial Core Surveillance (ABCs) Network indicate that the incidence of vaccine type IPD incidence in children aged < 5 years has declined by 94% (4.6 per 100,000 in 2003 vs 80 per 100,000 in 1998-1999). For persons aged ≥ 5 years, invasive disease incidence due to vaccine serotypes decreased by 62%, with the largest absolute rate reduction occurring among persons ≥ 65 years (33.6 cases per 100,000 in 1998-1999 versus 11.9 cases per 100,000 in 2003). Total IPD incidence declined by 29% and the majority of absolute rate reduction occurred among those aged ≥ 65 years in ABC surveillance areas (60.1 per 100,000 in 1998-1999 vs 41.7 per 100,000 in 2003). In contrast, the incidence of IPD caused by the 16 serotypes included in the 23-valent pneumococcal polysaccharide vaccine and not in PCV7 among persons aged ≥ 5 years increased 11% from 1998-1999 to 2003. Data showed that PCV7 prevented more than twice as many vaccine type IPD cases in 2003 through indirect effects on pneumococcal transmission than through a direct effect of protecting vaccinated children (MMWR 2005). With the introduction of PCV7, vaccine-type IPD rates have also sharply declined among Alaskan Native children < 5 years of age to levels equal to those in non-Natives. Moreover, in Alaskan

Native adults, a 40% decline in vaccine type IPD was observed (Hennessey TW *et al.*, 2005, in press). PCV7 use has resulted in a similar decline in IPD among US black children and adults (Flannery B *et al.*, 2004). Of note, these surveillance data were derived from assessments through the year 2003. Because the epidemiology of pneumococcal disease continues to change, VRBPAC members will be provided with an update on the U.S. rates of pneumococcal disease in adults at the VRBPAC meeting by e representative of the Centers for Disease Control and Prevention(CDC).

Vaccines to protect adults against *S. pneumoniae* diseases

Following controlled clinical trials of a single dose of pneumococcal polysaccharide vaccine in healthy South African gold miners in the 1970s (Austrian R *et al.*, 1976), a 14-valent pneumococcal polysaccharide vaccine was licensed in the United States in 1977, and subsequently replaced by a 23-valent vaccine in 1983. The current PS vaccine contains a mixture of purified polysaccharides from 23 of the most prevalent serotypes of *S. pneumoniae* accounting for approximately 85% of pneumococcal infections. The 23-valent polysaccharide vaccine was licensed for use in persons 50 years of age and older. The Advisory Committee on Immunization Practices (ACIP) recommends that all people age 65 years or older, and persons aged 2-64 years with certain high risk conditions be immunized against *S. pneumonia* using the 23-valent vaccine (MMWR 1997). ACIP also recommends that children 2 through 5 years of age who are at high risk for pneumococcal infection due to an underlying medical condition (e.g., asplenia, HIV, nephrotic syndrome) also receive PCV7 at least 2 months prior to 23-valent vaccine (MMWR 2000).

Although efficacy of the polysaccharide vaccines against bacteremic pneumonia was clearly demonstrated in South African gold miners, its effectiveness in other high-risk populations has been controversial. In a meta-analysis of randomized controlled studies (RCT) evaluating efficacy of the polysaccharide vaccine in adults, the vaccine was shown to have a protective effect for bacteremic pneumonia and presumptive pneumococcal pneumonia in low-risk groups, but no clear protective effect for any pneumococcal disease related outcomes in high-risk persons (Fine MJ, *et al.*, 1994). In another more recent systematic review, estimates of efficacy for invasive diseases ranged from 46-59% in 13 observational studies and -4 to 63% in 9 RCTs; no consistent vaccine effect was observed for all-cause pneumonia (Conaty S *et al.,* 2004).

In a retrospective cohort study of over 47,000 members of a health maintenance organization who were 65 years of age and older, receipt of the polysaccharide vaccine was associated with a reduction in bacteremic disease of 44% (95%CI: 7%-67%), but a slightly elevated risk of hospitalization due to community acquired pneumonia, and no effect on outpatient pneumonia (Jackson LA *et al.*, 2003).

A prospectively designed, controlled, randomized trial of 23-valent polysaccharide vaccine among HIV-infected people in Uganda showed no evidence of efficacy for any outcome, but rather a significant increase in all cause pneumonia, and increased rates, though not significant, for invasive disease due to vaccine serogroups (15 vs. 7), and all pneumococcal events (20 vs. 14) (French N *et al;* 2000). These findings suggest possible harmful effects of vaccination in this

population. As this study was conducted among people who were not receiving highly active antiretroviral treatment (HAART), the results may not be directly applicable to the HIV-infected population in the U.S.

Current rates of pneumococcal vaccination coverage in the adult and the elderly in the United States have remained suboptimal (Ehresmann KR *et al.* 2001). Only limited data regarding the duration of antibody responses after vaccination are available. Data show that antibody levels to the vaccine increase within 1 week after vaccination and remain greater than pre-vaccination levels for > 5 years in healthy adults; however, in the elderly and in persons with underlying illness, immune responses to polysaccharide vaccine may be more limited and antibody concentrations may decrease more rapidly following vaccination (Musher DM *et al.*, 1993; Davidson M, *et al.*, 1994; Rodriquez-Barradas MC, 1996; Sankilampi U, 1997; Rubins JB, 1998). In addition, some data suggest that immune responses are lower after revaccination with 23-valent pneumococcal vaccine than after an initial dose (Mufson MA *et al.*, 1991; Borgoño JM *et al.,* 1978; Linnemann GC *et al.,* 1986). The quantity of antibodies that correlate with protection against pneumococcal disease in the adult population is at present not known. Hence, it is uncertain if lower antibody levels attained by the elderly in response to the polysaccharide vaccine result in inferior protection in this population.

Wyeth's 7-valent pneumococcal conjugate vaccine (Prevnar™) was licensed by FDA to protect children less than 2 years of age against invasive pneumococcal disease caused by the seven serotypes included in the vaccine, i.e., 4, 6B, 9V, 14, 18C,

19F and 23F. Capsular polysaccharides from these serotypes are coupled to a non-toxic cross-reacting mutant diphtheria toxin molecule (CRM197). The prophylactic efficacy of Prevnar™ against invasive disease (bacteremia and meningitis) was demonstrated in a large field efficacy study, conducted at Northern California Kaiser Permanente health care system. A high level of efficacy in preventing vaccine serotype invasive pneumococcal disease was demonstrated in the primary analysis [100% (95% CI 75, 100%)]. Similarly, efficacy in preventing invasive disease due to all pneumococcal serotypes was 90% (95% CI 58,99%) (Black S *et al.,* 2000).

In order to increase the protection of adults and the elderly against pneumococcal disease, vaccine manufacturers have proposed vaccinating adults and the elderly with pneumococcal conjugate vaccines that contain as many as 13 pneumococcal serotypes. A potential advantage of using conjugates is that covalent linkage of PS to protein carriers convert these immunogens to T-cell dependent antigens that are better able to prime the host for boosting upon subsequent exposure to the pathogen or vaccines that contain either the glycoconjugate or the unconjugated capsular polysaccharide. Another approach for prevention of pneumococcal infections are vaccines directed against noncapsular antigens that are common to all pneumococcal serotypes, e.g., pneumococcal surface protein based vaccines (Briles DE *et al.,* 2000). Such vaccines offer the prospect of wide serotype coverage.

The purpose of the VRBPAC meeting in November 2005 is to discuss proposals and pathways for licensure of pneumococcal vaccine candidates indicated for prevention of pneumococcal disease in the adult population. Commercial sponsors will

have the opportunity to present their various proposals for pneumococcal vaccine licensure pathways for adult indications at this meeting.

In order to provide committee members with a sense of the clinical development strategies that have been proposed to CBER prior to the VRBPAC meeting, key elements of development plans are summarized below:

There have been proposals to base licensure on:

a. Non-inferiority of a single dose of pneumococcal conjugate vaccine to standard of care (23-valent pneumococcal polysaccharide vaccine) based on the opsonophagocytic antibody titer for each of the serotypes that are common to candidate vaccine and 23vPS vaccine; and

b. Demonstration of lack of hyporesponsiveness in antibody responses induced using a combined regimen of pneumococcal conjugate vaccine followed by polysaccharide vaccine.

In addition to providing evidence of non-inferiority for immune parameters, it was proposed to assess safety and lot consistency in clinical trials of pneumococcal vaccines.

It is important to note that not all clinical development plans that will be presented at the VRBPAC meeting by the various manufacturers were submitted to CBER at the time that this briefing document was prepared.

Efficacy studies

Clinical trials demonstrating preventive efficacy for clinical endpoints provide the greatest scientific rigor for evaluating pneumococcal vaccines, and represent the gold standard to support licensure of vaccines. Usually, such studies are prospective, randomized and well-controlled, and the primary efficacy endpoint is prevention of disease. Clinical disease endpoint efficacy studies may be necessary to demonstrate vaccine effectiveness for licensure purposes when the vaccine is novel, when the vaccine is the first of its kind administered to the target population, or when no accepted serological correlate of protection has been identified.

Licensure of the 14-valent pneumococcal polysaccharide vaccine was based on demonstration that the vaccine prevented pneumococcal pneumonia and bacteremia in South African gold miners (Austrian R *et al.*, 1976). This population was chosen for the clinical studies because of the high rate of pneumococcal pneumonia in that population. Additional support for licensure of the polysaccharide vaccine came from earlier clinical endpoint studies of vaccines with fewer serotypes conducted in the U.S. (PNEUMOVAX, Summary Basis of Approval).

The prophylactic efficacy of Prevnar™ against invasive disease was also demonstrated in a large field efficacy study that enrolled approximately 38,000 infants who received a 4 dose vaccine series. A high level of efficacy in preventing vaccine serotype invasive pneumococcal disease was demonstrated in the primary analysis [100% (95% CI 75, 100%)]. Similarly, efficacy in preventing invasive disease due to all

pneumococcal serotypes was 90% (95% CI 58%,99%) (Black S *et al.,* 2000).

Proposals received by FDA prior to the VRBPAC meeting have not included plans to conduct clinical endpoint efficacy studies to support licensure for use in adult populations. Rather, proposals have focused on evaluating the opsonic activity of antibodies to pneumococcus induced by vaccination and as measured in an opsonophagocytic antibody assay (OPA); opsonic activity is thought to be central to protective responses.

In this regard, the licensure of Menactra™ (quadrivalent meningococcal conjugate vaccine) offers some similarities. Menactra licensure was based on demonstration of immunologic non-inferiority to the previously licensed quadrivalent meninogococcal polysaccharide vaccine (Menomune®), for which clinical endpoint efficacy had been demonstrated for 2 of the 4 serogroups. An important difference for candidate pneumococcal conjugate vaccines is that substantially fewer serotypes may be represented than are covered by the currently licensed 23-valent polysaccharide vaccine. While immunologic non-inferiority might be demonstrated for serotypes in common, the lack of serotype coverage raises questions about how the new vaccine would be used in relation to the 23-valent vaccine, and what additional benefit afforded by the vaccine would compensate for the lack of serotype coverage.

Clinical endpoint efficacy data are likely to be difficult to obtain for pneumococcal vaccine candidates indicated for an adult population. Trials evaluating invasive pneumococcal disease in adults and in the elderly are complicated because of low and declining incidence of invasive pneumococcal

disease in the U.S. population, and thus, such studies would likely require large sample sizes. In addition, the 23-valent pneumococcal polysaccharide vaccine is currently recommended for immunization of adults ≥ 65 years and for high risk populations in the U.S. Therefore, if clinical endpoint studies are to be performed to support licensure of a new pneumococcal vaccine, such studies would likely need to be designed as: a) non-inferiority studies, using 23-valent pneumococcal conjugate vaccine in the comparator group, or b) controlled studies, using placebo or an unrelated control vaccine. In the former scenario, vaccine manufacturers may not view such studies as feasible because of the sample sizes, resources, and time required. The latter scenario would likely require conducting studies in a population for whom the 23-valent pneumococcal polysaccharide vaccine is not currently recommended (e.g., healthy adults aged ≤ 65 years). Other scenarios of interest but particularly difficult to evaluate in clinical endpoint studies include c) use of the candidate vaccine on a background of polysaccharide vaccine among the elderly, who may have already received the polysaccharide vaccine; d) use of the candidate vaccine prior to the polysaccharide vaccine.

Clinical trials demonstrating effectiveness of a new pneumococcal candidate vaccine against Community Acquired Pneumonia (CAP) as the clinical endpoint in an efficacy study might provide a clear advantage of that vaccine compared to the current polysaccharide vaccine, as the effectiveness of polysaccharide vaccine to protect against CAP remains uncertain. In the past, low specificity and sensitivity of diagnostic criteria resulted in uncertain etiological diagnoses making sample size estimates for such trials

difficult to ascertain. For example, false positives in the vaccine group would lower the efficacy estimate as well as increase the sample size needed to show any level of efficacy. Recent development of antigen tests may be helpful for the establishment of pneumococcal etiology in adult community acquired pneumonia, thus facilitating clinical endpoint definitions (Stralin K *et al.,* 2004). The use of non-specific inflammatory markers such as C-reactive protein and procalcitonin have also been proposed as methods to increase the specificity of the X-ray diagnosis of bacterial pneumonia (Klugman K, 2005; Madhi SA *et al.*, 2005). Greater specificity in the diagnosis of CAP due to *Streptococcus pneumoniae* in vaccine trials would result in more manageable sample sizes and higher efficacy estimates for a truly effective vaccine.

In order to more fully evaluate the regulatory options on which to base licensure of new pneumococcal vaccines for the adult population, CBER biostatisticians have estimated sample sizes for efficacy trials under various assumptions of efficacy, for invasive disease, community acquired pneumonia, and presumptive pneumococcal pneumonia in the adult population. An approach outlined in a few examples which follow, considers placebo-controlled studies conducted in the moderately high-risk populations of 50-64 year olds. Although the licensed polysaccharide vaccine (PNEUMOVAX23, Merck) is labeled for routine use in adults age 50 years and older, a universal recommendation by the Advisory Committee on Immunization Practices of the CDC for use in persons younger than 65 years has not been made.

In the following examples the duration of follow-up for detection of cases of disease was limited to 2.5 years, since

sponsors would likely be reluctant to plan trials requiring several years to complete. Also, 90% power was used to limit to a reasonable level the probability of a failed trial due to inadequate sample size. Extending follow-up to detect more cases of disease, or reducing power (e.g., 80%), would also reduce the sample size.

The examples provided below are not intended to be precise estimates, but are intended to provide a general idea of the magnitude of clinical studies using various endpoints.

1. Invasive Disease:

   As noted above, rates of invasive pneumococcal disease in the U.S. have been falling since the introduction of PCV7 due to indirect effects. Among 40-64 year olds, published estimates of invasive disease rates for 2001 approximated 20/100,000 (Whitney *et al.*, 2003). Although rates of invasive disease in this age group may have fallen further, the reduction in rate has been less pronounced in the 50-64 year old age group (Flannery B *et al.*, 2004). Thus, it may still be reasonable to assume a background rate of ~25/100,000 for a population of 50-64 years old adults overrepresented by persons from certain risk groups (smokers, Native Americans, African Americans), and that such a population could be enrolled into a vaccine study. Assuming also 1:1 randomization (vaccine:placebo), serotype specific coverage of 60% (e.g., multivalent conjugate) or 85% (e.g., protein based vaccine), and serotype specific vaccine efficacy ranging from 70-90%, estimated sample sizes are shown in the table below.

Sample size estimates are also provided using a higher background rate, 50/100,000, as it may be possible to identify a population at greater risk, either outside the U.S., or a special population within the U.S.

Table 1. Sample size estimates for invasive disease endpoint for various assumptions of efficacy

Background Event Rate* /100,000/yr	Serotype coverage of candidate vaccine	Assumed serotype specific Efficacy	Lower 95% CI	Sample size per group
25	60%	70%	38%	82,000
		80%	46%	59,000
		90%	50%	44,000
	85%	70%	38%	58,000
		80%	46%	42,000
		90%	50%	31,000
50	60%	70%	38%	41,000
		80%	46%	30,000
		90%	50%	22,000
	85%	70%	38%	29,000
		80%	46%	21,000
		90%	50%	16,000

Assumptions: ~90% power, 1:1 randomization, placebo or inactive control, 2.5 years mean follow-up for case ascertainment.
* Assumed background event rate for all pneumococcal invasive disease
Stata statistical software used to generate sample size.

2. Community Acquired Pneumonia (CAP):

Published information for age-specific, population-based rates of all cause community acquired pneumonia is sparse. The rate of hospitalization discharges for CAP in the 40-64 year age group in a U.S. population has been estimated at 270/100,000 (Marston BJ, 1997); this figure could be rounded up to a rate of ~300/100,000 for the older age range of 50-64 years. Assuming that 30% of hospitalizations for CAP are due to pneumococcus, and the

proportion covered by vaccine serotypes is 60%, one might expect about 50 cases of CAP per 100,000 individuals 50-64 years old which are due to vaccine serotypes. Sample size estimates based on a higher estimate of the rate of CAP are also provided in the table below.

Table 2. Sample size estimates for community acquired pneumonia endpoint for various assumptions of efficacy

Event Rate for CAP (all causes) /10^5/yr	CAP due to all *S. pneumo* /10^5/yr	Serotypes covered by candidate vaccine	Assumed Efficacy For CAP due to Vaccine Serotype	Efficacy for All CAP	Lower 95% CI for All CAP	Sample size per group
300	100	60%	70%	13%	5%	166,318
			80%	14%	6%	126,368
			90%	22%	9%	54,438
		85%	70%	18%	7%	81,030
			80%	20%	8%	61,353
			90%	23%	10%	47,935
600	200	60%	70%	13%	5%	82,577
			80%	14%	6%	62,747
			90%	22%	9%	27,039
		85%	70%	18%	7%	40,241
			80%	20%	8%	30,472
			90%	23%	10%	23,810

Assumptions: 90% power, 1:1 randomization, placebo or inactive control, 2.5 years mean follow-up for case ascertainment.
Stata statistical software used to generate sample sizes.

Although sample sizes for an endpoint of hospitalized CAP would be quite large, the trials could be conducted simply, using computerized hospital discharge databases, and with few additional resources for diagnosis and case evaluation. Including cases of CAP diagnosed in an outpatient setting would result in higher background rates. The type of trial described for all cause CAP, sometimes referred to as an effectiveness trial, would necessarily have a much lower

efficacy estimate for prevention of CAP, than for the specific endpoint of CAP due to vaccine serotype specific *Streptococcus pneumoniae*.

Approval of FluMist® (influenza vaccine live, intranasal) for use in adults was supported by demonstration of efficacy for all cause influenza-like illness syndromes during influenza season. Efficacy estimates for these influenza-like illnesses, not confirmed by virus culture, ranged from 10.9% to 23.7%. These data were considered substantial evidence of a protective effect to support use in adults; licensure of FluMist® was also supported by a study demonstrating a high level of efficacy for culture-confirmed influenza illness in a pediatric population.

In the pediatric otitis media trials of PCV7 (Prevnar™), efficacy for all cause otitis media in the NCKP trial, using office visit diagnoses from the computerized databases, was 6-7% (Black S, *et al.*, 2000). Serotype specific efficacy was subsequently demonstrated in the Finnish trial (Escola J *et al.*, 2001) that used tympanocentesis and culture for diagnosis [efficacy estimate, 57%, (95%CI: 44%, 67%)]. Data from both trials supported licensure of Prevnar™ for the prevention of otitis media.

CAP would be an important endpoint to evaluate for the purpose of public health recommendations and could provide clinical evidence of benefit afforded by a vaccine for licensure purposes.

3. Presumptive pneumococcal pneumonia

By choosing appropriate clinical and radiologic criteria, pathogen-specific diagnostic criteria (e.g., sputum culture, PCR, urine antigen; Stralin K *et al*., 2004), and non-specific markers of inflammation (e.g., C-reactive protein, procalcitonin; Madhi SA, 2005), it may be possible to evaluate a clinical endpoint of community acquired pneumonia presumed due to vaccine-serotype *S. pneumoniae, or* presumptive pneumococcal pneumonia, with a fair amount of specificity. Using similar assumptions as above for CAP, a background rate of 100 pneumococcal pneumonia cases per 100,000 among persons 50-64 year old appears reasonable.

From another perspective, if most pneumococcal bacteremia in adults is associated with pneumonia, and assuming only about 15-30% of pneumococcal pneumonia is bacteremic (Butler JC & Schuchat A, 1999), and the rate of bacteremia is 25/100,000, then background rates for all pneumococcal pneumonia fall in the range of 83-166/100,000. Using 60% (or 85%) serotype coverage, and 50%-80% vaccine efficacy, and specificity of diagnosis of 80%, sample sizes were estimated, and are provided below.

Table 3. Sample size estimates for an endpoint of community acquired pneumonia due to *S. pneumoniae* of vaccine serotype for various assumptions of efficacy

Background Event Rate for Community Acquired Pneumococcal Pneumonia /100,000/yr	Serotype coverage	Assumed Efficacy for CAP due to Pneumococcal Vaccine Serotype	Lower 95% CI	Sample size per group
100	60%	50%	22%	44,608
		60%	28%	29,392
		70%	38%	20,425
		80%	46%	14,740
	85%	50%	22%	31,473
		60%	28%	20,738
		70%	38%	14,412
		80%	46%	10,401
200	60%	50%	22%	22,279
		60%	28%	14,681
		70%	38%	10,203
		80	46%	7,363
	85%	50%	22%	15,712
		60%	28%	10,354
		70%	38%	7,196
		80%	46%	5,194

Assumptions: 90% power, 1:1 randomization, placebo or inactive control, 2.5 year mean follow-up for case ascertainment.
Stata statistical software used to estimate sample sizes.

The estimates above do not account for the sensitivity and specificity of diagnostic methods used to identify serotype-specific *S. pneumoniae*.

Sample size calculations for a higher background rate of CAP due to *S. pneumoniae* are also provided. Higher background rates may be reasonable if a larger proportion of CAP is due to pneumococcus in the study population, the population is enriched with persons with additional risk factors for pneumococcal disease (e.g., history of smoking, diabetes mellitus, African or Native American descent), or if a population were identified outside or inside the U.S. with

substantially higher risk. A clinical study using a presumptive pneumococcal pneumonia endpoint could be relatively resource-intensive due to the laboratory diagnostic work-up of cases of pneumonia.

Use of pneumococcal conjugate vaccines in combination with the polysaccharide vaccine by sequential inoculations, offers the possibility of benefit from both vaccines. However, an immunologic evaluation as the basis for licensure of the combination would not be straightforward. Demonstration of a non-inferior immune response in comparison to the licensed vaccine would not be meaningful if both groups would receive the polysaccharide vaccine. While it is possible that the vaccine combination may result in an immune response that is superior by some measure to that achieved with the polysaccharide vaccine alone, it is not clear how a superior immune response should be interpreted for licensure purposes. For pneumococcal vaccines, no correlate of protection for any clinical endpoint exists, and it has not been demonstrated that antibody levels higher than levels achieved by polysaccharide vaccine alone result in greater levels of protection from pneumococcal disease.

As noted above, several studies have failed to demonstrate a positive preventive effect of the polysaccharide vaccine for pneumonia in the elderly. If one assumes that the polysaccharide vaccine does not contribute to efficacy for pneumonia, it may be possible to evaluate in the elderly the efficacy of a new vaccine on a background of polysaccharide vaccine for a pneumonia endpoint. All subjects would have access to the polysaccharide vaccine, obviating ethical concerns about withholding a recommended vaccine. Evaluation

of any added efficacy above that of the existing recommended vaccine could be highly informative from a public health perspective. Based on an observational cohort study of Medicare recipients, the rate of hospitalization for CAP among persons older than 65 years was 1830/100,000 (Kaplan V *et al.*, 2002). Thus, studies to prevent pneumonia in this population would likely be feasible, even for relatively low efficacy estimates. However, demonstration of efficacy for pneumonia endpoint in an elderly population would be a stringent test of effectiveness, and, based on observational studies, would likely not be met by the licensed polysaccharide vaccine in a randomized controlled study.

Another design for that might be considered involves delaying the polysaccharide vaccine from a group for whom it is recommended for sufficient time to allow ascertainment of efficacy of the new vaccine in that population. For example, informed subjects older than age 65 years could elect to defer immunization with the 23-valent polysaccharide for a period of 2 to 3 years while they participate in a well-monitored clinical study. It is not clear how such a study would be viewed by IRBs or potential trial participants. However, since the polysaccharide vaccine is administered only once for persons over age 65 years, duration of immunity is uncertain, and questions have been raised about vaccine induced hypo-responsiveness to pneumococcal polysaccharide antigens, a reasonable decision to defer immunization might be made. Such trials could be placebo-controlled and conducted in a high-risk group, thus allowing for more feasible study designs in a highly relevant population.

Indirect effects of vaccination with PCV7 are thought to be due to prevention of colonization and carriage of pneumococcus in the nasopharynx of infant vaccine recipients, with a resulting reduction in transmission to older adults in the household. Clinical studies designed to evaluate prevention of pneumococcal colonization would provide some clinical data on which to base a licensure decision. However, prevention of colonization or carriage has not previously been used as clinical endpoint in vaccine efficacy trials to support licensure. Since colonization and carriage are asymptomatic conditions, their prevention offers no direct benefit to the vaccine recipient. Nevertheless, studies demonstrating prevention of colonization and carriage might be considered as part of a body of data demonstrating a vaccine effect.

An assessment of benefit of a new conjugate vaccine comprised of fewer serotypes than are covered by the 23-valent polysaccharide vaccine is complicated by the loss of protection afforded by the additional serotypes in the polysaccharide vaccine. Persons vaccinated with the new conjugate would remain susceptible to serotypes not included in the vaccine. Also, a vaccine providing coverage for young children may not provide optimal serotype coverage for prevention of pneumococcal disease in older adults, particularly as the epidemiology changes as a result of indirect effects of universal immunization of infants with PCV7. Thus, serotypes not represented in the conjugate vaccine used in childhood may assume greater prominence as a cause of pneumococcal disease in adults.

Other considerations regarding the relative merits of clinical endpoint studies for licensure include:

- The quantitative effect of a vaccine on disease outcomes generally provides better information for public health decision-making than an evaluation of immunologic outcomes. A study of immunologic outcomes would be far less precise in the estimated benefits of vaccination.

- If a vaccine is approved based on immunologic criteria, the opportunity to study the vaccine post-licensure for clinical endpoints in a randomized, controlled study could be lost if randomization to placebo is viewed as unacceptable to informed subjects or to Institutional Review Boards.

- The biologic and immunologic factors underlying the lack of vaccine efficacy of the polysaccharide vaccine in certain high-risk groups, and apparent lack of protection for the outcome of non-bacteremic pneumonia, have not been well-defined. A vaccine development plan for a conjugate vaccine, or other new vaccine, that bridges to efficacy of the polysaccharide vaccine based on immunologic criteria would also bridge to some of the uncertainties about the effectiveness of polysaccharide vaccine in high-risk persons.

- Essential components of the OPA assay include a source of complement (rabbit) and phagocytic cells (cultured HL60 cells). Studies have not yet confirmed that phagocytic cells of the elderly and other high-risk populations behave similarly to cultured cells in vitro, and the correlation of OPA with preventive efficacy has not been

confirmed in prospectively designed clinical endpoint studies in adult populations.

- Historically, clinical studies designed to evaluate vaccine efficacy have required large numbers of participants (several thousands). Thus, efficacy studies have also provided the largest component of the safety database at licensure for many vaccines. For example, in the large safety and efficacy study for 7-valent pneumococcal conjugate vaccine conducted at Northern California Kaiser Permanente health care system (NCKP), approximately 38,000 infants were enrolled to demonstrate efficacy for the primary endpoint, invasive disease. The safety evaluation, making use of the large automated safety database at NCKP, provided substantial assurance about the safety of the new vaccine in an infant population. The opportunity to evaluate serious adverse events that occur at rates similar to the disease studied in an efficacy trial allow for meaningful risk/benefit assessments. If licensure were to be based on immunologic critera, relatively smaller sample sizes may be sufficient to evaluate the immunologic outcomes. Unless a safety signal were observed in early phase studies necessitating additional safety studies, it is unlikely that a large safety database would be available at the time of licensure.

- If it is proposed that the appropriate use of a new vaccine is in combination with the currently licensed polysaccharide vaccine, a number of complex regulatory issues would need to be addressed. For example, it is

not clear what the regulatory status of the new vaccine would be if the polysaccharide vaccine were to become unavailable at some point in the future. There are no examples of vaccine combinations comprised of vaccines licensed for the same indication and made by different manufacturers. As noted above, evaluation of a vaccine combination using immunologic criteria in a non-inferiority design would not be meaningful for a combination regimen (i.e., response after PCV + PPS is no worse than PPS alone). Evaluation of superiority of immune response would be a novel approach for vaccines, as it is not clear that higher Geometric Mean Concentration of serum antibodies, or greater response rates at higher threshold levels, correspond with greater protection from disease.

- OPA activity could be described as an outcome that is reasonably likely to predict clinical benefit, and as such, would meet the requirements of a surrogate for efficacy under the accelerated approval regulations (21 CFR 601.41). These regulations provide for licensure of a biologic product based on a surrogate endpoint for severe or life-threatening conditions, where adequate alternative therapies are not available. A necessary condition of an accelerated approval is that data from clinical endpoint studies confirming clinical benefit must be provided post-licensure. Of note, it may be difficult to enroll subjects to a placebo group post-licensure once the new product is available on the market. Therefore, if this regulatory pathway is pursued, confirmatory studies should be well underway at the time of an accelerated approval.

A recent example of a vaccine approved under the accelerated approval regulations was Fluarix™, trivalent inactivated influenza vaccine, which was approved based on immunogenicity data (hemagglutination inhibition antibody); a condition of the approval was that a confirmatory clinical endpoint study evaluating influenza disease would be conducted. A similar path might be considered for new a pneumococcal vaccine.

Immunologic predictors of efficacy

In certain situations, the effectiveness of a vaccine may also be established through an immunological endpoint, in particular in cases where there is an accepted immune correlate of protection. A correlate of protection is a laboratory parameter that has been shown to be associated with protection from clinical disease. An immunological correlate of protection is most useful if it measures a known biological function associated with protection. For example, quantitation of capsule specific antibody by ELISA has been used to assess the adequacy immune responses for some bacterial pathogens. In the case of *Haemophilus influenzae*, protective antibody levels were established based on antibody levels to polyribosylribitol phosphate (PRP) capsular antigen observed in individuals not developing clinical disease (Robbins *et al.*, 1973).

On March 8, 2001, the VRBPAC was convened to consider alternate approaches for licensure of 2nd and 3rd generation

pneumococcal conjugate vaccines indicated for children less than 2 years of age. VRBPAC recommended the following:

a. Non-inferiority immunogenicity studies conducted in the US comparing a pneumococcal conjugate candidate vaccine to Prevnar™ based on an antibody response quantified by ELISA would be an acceptable approach for inferring efficacy against invasive disease for the candidate vaccine. Of note, the committee did not provide clear advice about whether non-inferiority would have to be demonstrated for all 7 serotypes contained in Prevnar™, or whether specific serotypes should be weighed more heavily based on the disease impact of those serotypes.

b. For additional serotypes not contained in Prevnar, immunological parameters may be used to infer efficacy of the additional serotypes.

c. Data from invasive disease efficacy study(ies) performed in non U.S. population(s) with a new pneumococcal conjugate vaccine could support licensure of the vaccine in the U.S. provided that adequate bridging studies of safety and immunogenicity are conducted that would include Prevnar as a control arm to establish comparability of the new product.

Of note, the VRBPAC recommendation in 2001, namely to demonstrate efficacy of future pneumococcal conjugate vaccine based on non-inferiority immunogenicity studies, specifically pertained to inferring efficacy in prevention of IPD in an infant target population, since a clinical endpoint efficacy

study had been conducted. However, such efficacy data are not available for adults.

At present no correlates of protection after vaccination with pneumococcal vaccine have been established. The established efficacy of Prevnar™ in term of preventing invasive disease in infants and toddlers provided an opportunity to determine serologic parameters associated with protection in that setting. A threshold antibody level of 0.35 ug/mL in a 2nd generation standard ELISA assay was agreed upon in WHO consensus meetings to be an appropriate threshold for assessing new conjugate vaccines for use in infants. This antibody level was based on pooled efficacy estimates from three clinical efficacy trials: the Northern California Kaiser Permanente (NCKP) trial (VE 97.4% (84.8%, 99.9%)), the American Indian (VE 76.8% (-9.4%, 95.1%)) study and a South Africa (VE 90.0% (29.7%, 99.8%)) trial which studied a 9-valent conjugate vaccine. The model used in the analysis was a step-function where the risk of disease is high and constant below a certain level and low and constant above this level. Antibody threshold estimates derived from the three efficacy trials are (appr. 95% CI) as follows: Northern California, 0.20 ug/mL (0.03, 0.67); American Indian, 1.00 ug/mL (0.25, > 50.00); South Africa, 0.68 ug/mL (0.03, 6.00). The antibody threshold estimate pooled over the three efficacy trials is 0.35 ug/mL (0.09, 0.89). Additional analyses showed that an ELISA antibody level of 0.21 to 0.35 correlates with an opsonophagocytic antibody titer (OPA) of 1:8 (Chang I *et al.*, 2003). Data from a case-control study conducted by CDC yielded an estimate of protective efficacy similar to the pooled estimate noted above, thus providing additional support for the corresponding ELISA antibody threshold level.

However, it is unclear whether serologic parameters currently considered as "protective" threshold levels for infants can be used as a benchmark to define protective antibody titers in adults. Antibody levels that correlate with protection in the adult population have not been defined, adults may have already high pre-titers, and protective antibody levels may differ by disease, e.g., invasive disease versus community acquired pneumonia. Furthermore, the ability to extrapolate from younger populations to older populations is problematic because of current gaps in understanding immune senescence with increasing age. Since the adult population is composed of diverse risk groups, with differing levels of immunocompetence, a new pneumococcal conjugate vaccine may need to be studied in several adult subpopulations.

When considering licensure pathways for pneumococcal vaccines in adults that are based on an immunological endpoint, measures of functional antibody are probably more relevant than ELISA antibody levels. Use of antibody thresholds based upon antibody measurements in infant sera are problematic when used for adults, because most unimmunized adults have antibody levels above the 0.35 ug/mL threshold proposed for infants. In infants nearly all of the anti-pneumococcal polysaccharide antibodies measured post immunization are directed to known pneumococcal serotype polysaccharides, whereas adults may have substantial amounts of non-pneumococcal cross-reactive antibody that binds to the different pneumococcal serotype polysaccharides. Furthermore, for adults there is often a poor correlation between antibodies quantitated by ELISA and opsonic titers.

The capsular polysaccharide is the principal virulence factor enabling the pneumococcus to cause invasive disease. Type specific antibody is considered protective, whereby protection is thought to be mediated through antibody binding to the bacterial surface leading to complement mediated uptake into phagocytic cells (opsonophagocytosis). Thus, functional antibody likely plays a central role in protection against pneumococcal disease. Therefore, opsonic antibodies measured in vitro (OPA) provides evidence for in vivo protection, and in most assays the usual minimum detectable opsonic titer is 1:8. By analogy, detection of direct bactericidal effect in a serum is evidence for protection against invasive meningococcal disease (Goldschnider I *et al.*, 1969).

Considerable progress has been made towards developing standardized and automated assays to assess the opsonophagocytic activity of anti-pneumococcal antibodies (Romero-Steiner *et al.*, 1997, Fleck *et al.*, 2005). However, the quantitative relationship of OPA titers (as measured by existing assays) to clinical efficacy in the adult population has not been established.

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