BRIEFING DOCUMENT

Pneumococcal Adult Vaccine

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List of Abbreviations

7-valent PCV or 7PCV	7-valent Pneumococcal Conjugate Vaccine
11-valent PCV	11-valent Pneumococcal Conjugate Vaccine
23-valent PPV	23-valent Pneumococcal Polysaccharide Vaccine
CAP	Community acquired pneumonia
Elderly	Adults aged 65 years or greater
ELISA	Enzyme-Linked Immunosorbant Assay
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
GSK Bio	GlaxoSmithKline Biologicals
IgG	Gamma class immunoglobulin
IPD	Invasive Pneumococcal Disease
OPA	Opsonophagocytic assay
PCV	Pneumococcal Conjugate Vaccine
PPV	Polysaccharide Pneumococcal Vaccine
PS	Polysaccharide

1. EXECUTIVE SUMMARY

1.1. Background

Pneumococcal polysaccharide vaccine (PPV) has been available for use in individuals 2 years of age and older for more than 20 years. The existing 23-valent PPV contains serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. The vaccine is indicated for vaccination against pneumococcal disease caused by serotypes included in the vaccine. In the United States (US), the 23-valent PPV is routinely recommended for all individuals 65 years of age and older and for persons 2-64 years of age with certain high risk underlying chronic illnesses.

The partial effectiveness of PPV against pneumococcal bacteremia has been well-documented, but despite immunization, *Streptococcus pneumoniae* remains a major cause of morbidity and mortality, especially in the older adult population where the infection presents itself as pneumonia with or without bacteremia. Nearly 60,000 cases of invasive pneumococcal disease (IPD) occur annually in the US; one third of cases and most deaths occur among the elderly 65 years of age and older (mostly related to pneumonic pneumococcal bacteremia).

Although the benefits of the 23-valent PPV are clear, the polysaccharide vaccine has a number of limitations. In young adults, PPV is effective in preventing pneumococcal pneumonia, evidence taken into account by FDA in 1977 during licensure of the first pneumococcal polysaccharide vaccine. However, prospective clinical trials evaluating the ability of PPV to prevent non-bacteremic pneumonia in older adults have shown that the vaccine is poorly effective in this age group. This may be due to 1) the difficulty in diagnosing non-bacteremic pneumococcal pneumonia and 2) lowered immune responses in the elderly. In older adults, it has also been observed that antibody levels to important serotypes decline to prevaccination levels within 3-7 years. This most likely contributes to the low level of clinical protection against several serotypes and the decline in overall protection observed during this same period. For those vaccinated at age 65 years or older, revaccination is not routinely recommended for several reasons, including lack of data on duration of protection from an initial dose. Moreover, there is evidence that a second dose is not as immunogenic as the first, demonstrating some level of reduced immune memory, i.e., hypo-responsiveness. In addition, data on effectiveness of a second dose are lacking. Although revaccination with PPV is safe and may prolong the duration of protection, many older individuals will remain incompletely protected.

Conjugation of polysaccharide antigens to carrier proteins improves the immune responses to polysaccharide antigens. A pneumococcal protein-polysaccharide vaccine (PCV) containing polysaccharides from the 7 most common serotypes that cause invasive disease in children <5 years of age in the US has been approved since 2000 and is recommended to be routinely administered to children. Randomized clinical trials of this vaccine (Prevnar®, PCV7) have demonstrated that PCV7 is highly protective against IPD (mostly non-pneumonic pneumococcal bacteremia), clearly reduces all-cause pneumonia, and is partially protective against acute otitis media in children <2 years of age. Routine use of PCV7 in young children has reduced the incidence of vaccine serotype and overall

IPD in children and adults. The most substantial decline in the rate of vaccine serotype disease has been in the target population of children aged <5 years. Recent data also demonstrate statistically significant reductions in the rates of both vaccine serotype IPD and total IPD for children aged 5 to 17 years, and in the total incidence of IPD in persons ≥65 years of age.

The effectiveness of PCV has not been extensively studied in adults, in part due to the existence of the polysaccharide vaccine. Given the need for a more effective pneumococcal vaccine, the development of PCVs should be pursued in older age groups. In older adults, PCVs have the potential to induce higher, more functional antibody levels that persist longer as compared to the currently licensed 23-valent PPV. If PCVs are effective against non-invasive pneumococcal disease in adults (such as non-bacteremic pneumonia) or if they confer longer protection, they likely will offer significant prevention in addition to or possibly as a replacement for the currently recommended polysaccharide vaccine. Another potential advantage of PCVs is that most of the serotypes contained in the 11-valent PCVs under development are those associated with increasing antimicrobial resistance in the older adults. A recent study comparing the hypothetical effects of the 23-valent PPV with that of new 7- or 11-valent PCVs on prevention of bacteremic and non-bacteremic pneumococcal (pneumonia) disease in persons >65 years of age has suggested that PCVs would improve overall disease prevention.

Recent studies with PCVs in older adults who received one dose of PCV have shown some increase in antibody concentrations to most serotypes tested as compared to control subjects who received one dose of PPV. Functional antibody response, such as opsonophagocytic activity (OPA), not the level of antibody concentration, appears to be better correlated with protection against pneumococcal disease. However, in the elderly, data available regarding the functional antibody response or induction of immunologic memory following vaccination with PPV and PCV remain limited.

1.2. GSK Proposal

GSK recently generated data with the 23-valent PPV (Pneumovax®) in young adults 18-45 years and in elderly subjects aged 65 and above. By applying a sensitive ELISA assay (including pre-adsorption of non-polysaccharide specific antibodies), as well as an opsonophagocytic assay (OPA), noteworthy differences were found between the elderly and young adult groups, particularly significantly lower opsonic antibody titers were found in the elderly as compared to young adults. These differences may explain the 23-valent PPV's lack of protection against pneumonia in the elderly, while such protection has been observed in younger adults. GSK believes that an improved PCV that induces opsonic antibody levels in elderly subjects comparable to the levels induced by 23-valent PPV in young adults would provide protection against pneumococcal pneumonia in older adults. Additionally, as a compliment to the current recommendation of routine immunization with a single dose PPV in adults 65 years and older, priming with PCV and then boosting with PPV, or an initial dose of PPV and then boosting with PCV, may provide opportunities to improve prevention of bacteremic and non-bacteremic pneumococcal pneumonia in adults. Once licensed for use in adults, recommendations on

the use of a new conjugate pneumococcal vaccine in relation to PPV would need to be driven by data on immunogenicity, safety, duration of immunity and boostability.

GSK has developed an 11-valent pneumococcal conjugate vaccine, comprising serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and is planning to assess the immunogenicity and safety of this vaccine in clinical trials in older adults (≥ 50 years of age).

2. PNEUMOCOCCAL POLYSACCHARIDE AS COMPARED TO PNEUMOCOCCAL CONJUGATE VACCINES IN THE ELDERLY

2.1. Background: Burden of disease

Streptococcus pneumoniae remains a major cause of morbidity and mortality, especially in the elderly population where most of the infections present themselves as pneumonia and/or bacteremia. Nearly 60,000 cases of invasive pneumococcal disease occur annually in the US; one-third of cases and most deaths occur in persons 65 years and older.

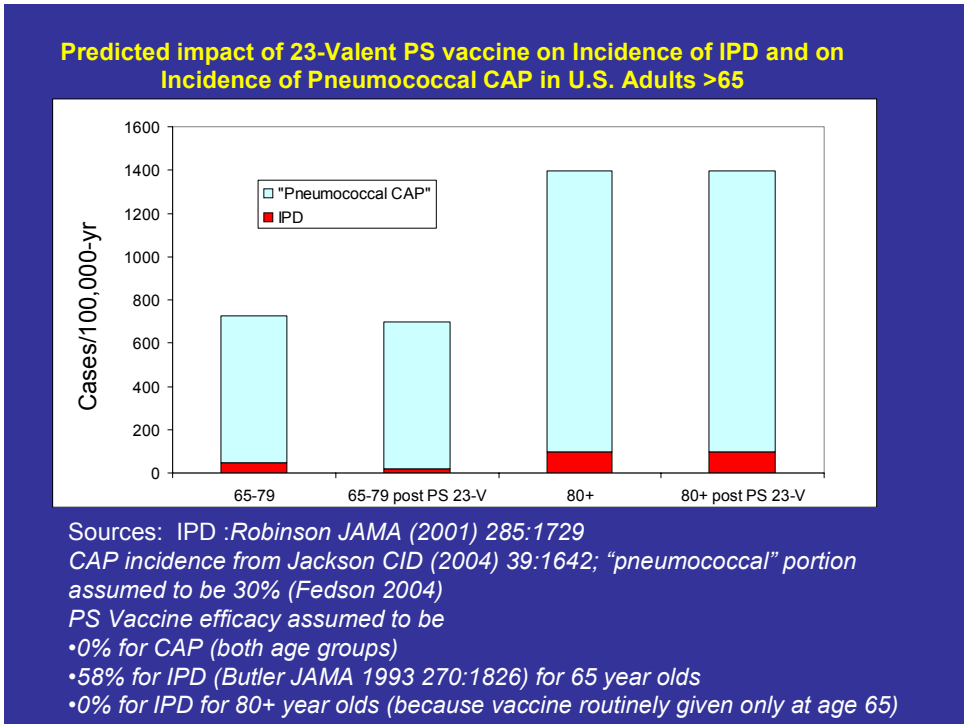
Community-acquired pneumonia (CAP) is one of the leading causes of death in adults ≥ 65 years of age. Annual rates of hospitalization due to pneumonia have been reported to be 1.1/100 for ≥65 year olds [Jackson,2003; Marston,1997] with rates of outpatient CAP 2-3 fold higher in this age group (Jackson L et al CID 2004 **39** 1642). A large number of studies have established *S. pneumoniae* as a major pneumonia pathogen, although estimates of the incidence of pneumococcal pneumonia vary widely [Marston,1997; Koivula,1997; Almirall,2000; Jokinen,2001]. CAP can be caused by different bacterial and viral pathogens and a pathogen is not identified in 50% or more cases. Regardless of the setting or the study, *S. pneumoniae* is the pathogen most commonly identified in patients with CAP [Fedson, 2004b]. For those cases without a defined etiology, there is evidence that pneumococcus plays an important role. It is generally assumed that 30 to 50% of hospitalized CAP cases are caused by *S. pneumoniae* [Fedson, 2004a]. Development of laboratory techniques, with sufficient sensitivity and specificity to reliably identify the etiologic bacterial agents causing CAP, remain a highly desirable objective.

Bacteremia is the most common representation of IPD in the elderly, 90% of which are from pneumonia cases [Fedson, 2004b]. The reported annual incidence of IPD in elderly adults 65 years of age and older is in the range of 25-75 cases/100,000 per year [Fedson, 2004b; Robinson, 2001; Kyaw, 2003]. These rates rise steeply with age: in elderly ≥75 years IPD rates are 2-3 times higher.

Vaccination against *S. pneumoniae* has the potential to offer an effective means to reduce the morbidity and mortality of pneumococcal disease in adults. However, if one assumes that 30% of non-invasive CAP is pneumococcal in origin, a vaccine effective only against IPD can, by necessity, only make a small impact on the total disease burden due to the pneumococcus. According to this model, administering one dose of 23-valent PPV to adults 65-79 years old is estimated to prevent only 50% of invasive pneumococcal

disease cases for approximately 5 years. Thus, this intervention has a marginal impact on the total burden of pneumococcal disease (Jackson L et al CID 2004 **39** 1642). Figure 1 illustrates the predicted impact of the current standard of care.

Figure 1 Predicted Impact of 23-Valent PS Vaccine given once at 65 years of age on Incidence of IPD and Pneumococcal CAP



2.2. Pneumococcal polysaccharide vaccines

The existing 23-valent PPV contains serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. The vaccine is indicated for vaccination against pneumococcal diseases caused by the serotypes included in the vaccine.

The 23-valent PPV is recommended by the Advisory Committee on Immunization Practices for the Centers for Disease Control and Prevention for routine vaccination of persons 65 years of age or older, and for persons ≥2 years with chronic illnesses that place them at moderate to high risk for pneumococcal disease or complications of pneumococcal disease (chronic cardiovascular disease, chronic pulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid leaks, cochlear implants, or functional or anatomic asplenia, persons living in special environments or social situations), as well as immunocompromised persons ≥2 years.

Most adults receive the PPV only once. However, a second dose is recommended for those who are at highest risk of serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibodies, provided at least 5 years have elapsed since receipt of the first dose of PPV. In addition, individuals >65 should be

administered a second dose if they received the vaccine ≥ 5 years earlier and were < 65 years old at the time.

The 23-valent PPV vaccine is beneficial and provides at least partial protection against pneumococcal disease. However, the 23-valent PPV vaccine has limitations, some of which (partial effectiveness against IPD in older adults; limited antibody persistence) have been summarized by Fedson *et al.* (2000) as shown in Table 1.

Table 1 Limitations of pneumococcal polysaccharide vaccine in older individuals

Serotype	Antibody persistence (years)	Vaccine effectiveness against IPD age >50 years % (95% CI)
1	--	77 (50,90)
3	--	42 (5,65)
4	4.5	76 (6,58)
5	--	---
6B	3	46 (-4,72)
7	--	53 (8,76)
9V	5	52 (12,74)
14	7.7	62 (44,75)
18C	--	36 (-20,66)
19F	3.8	27 (-50,65)
23F	4.7	15 (-24,41)

-- = no data or not mentioned

Purified pneumococcal capsular polysaccharides have been shown to prevent pneumococcal pneumonia and bacteremia in healthy young adults (see Table 2). Initially, polysaccharide vaccines were found to prevent pneumococcal pneumonia in military recruits (18-32 years of age for >95% of the study population) [MacLeod, 1945]. Later studies in adult South-African young adult novice miners and New Guinea highlanders confirmed this very high level of protection; [Smit, 1977; Austrian, 1976; Riley, 1977].

These results supported the licensure of PPV with the indication of prevention of pneumococcal infection including pneumonia. However, post-licensure, efficacy trials conducted in the elderly demonstrated rather low or even absent protection rates against non-bacteremic pneumococcal pneumonia (see Table 2). The efficacy of PPV against pneumonia in elderly patients appears to be low [Jackson,2003; Honkanen,1999], although some impact on all-cause pneumonia could be demonstrated in cohort studies in the elderly with chronic lung disease or patients in extended stay geriatric hospitals [Nichol,1999; Wagner,2003]. The impact on pneumococcal bacteremia in patients ≥65 years old was found to be approximately 50% [Shapiro,1991 The difference of approximately 50% efficacy against (mostly pneumonic) pneumococcal bacteremia and no demonstrable efficacy against non-bacteremic pneumococcal pneumonia can be explained by 1) bacteremia is the more serious form of adult pneumococcal pneumonia and easier to prevent and/or by 2) the pneumonia efficacy trials were underpowered to be able to demonstrate efficacies between 0-50% against non-bacteremic pneumococcal pneumonia (Fedson,2004b).

Table 2 PPV Efficacy against Pneumococcal Pneumonia (Lower Respiratory Infection) in Clinical Trials*

Study, publication year	Population studied	Vaccine Efficacy % (95% CI)
Pre-licensure trials		
MacLeod, 1945	Military recruits (18-32 years)	84% (54%, 94%)
Austrian, 1976	South African young adult gold miners	79% (65%, 88%)
Smit, 1977	South African young adult novice gold miners	92% (49%, 100%)
Riley, 1977	Papua New Guinea subjects, aged >10 years	86% (<0%, 99%)
Post-licensure trials		
Simberkoff, 1986	Veterans, >55 years	<0% (<0%, 45%)
Koivula, 1997†	Elderly in community, >60 years	15% (<0%, 50%)
Örtqvist, 1998	Elderly in community, 50-85 years	<0% (<0%, 34%)
Honkanen, 1999 †	Elderly in community, >65 years	<0% (<0%, 20%)

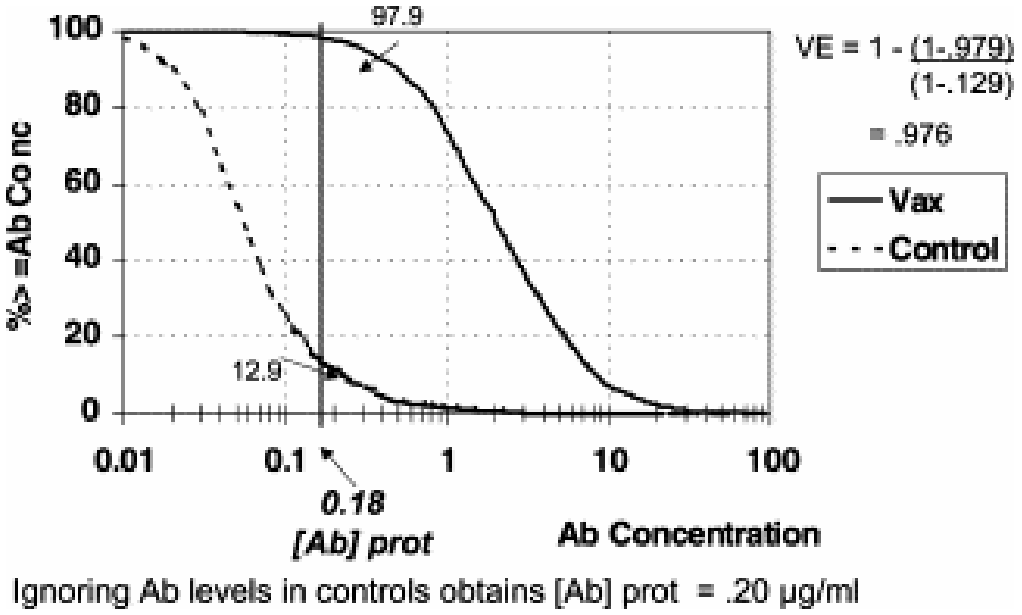
*Studies utilizing ≤60 µg of each capsular polysaccharide and >200 participants
†PPV plus influenza vaccine compared with influenza vaccine alone

The protective mechanisms induced by PPV are most likely antibody mediated, and in particular, antibodies that mediate opsonophagocytosis [Poolman, 2004]. Recently, ELISA assays that include adsorption of non-polysaccharide specific antibodies (inhibition with cell wall polysaccharide and 22F-polysaccharide) have been developed allowing specific and sensitive antibody measurements against pneumococcal capsular polysaccharides [Concepcion, 2001]. As measured by ELISA, relatively minor differences have been noted in antibody concentrations against pneumococcal capsular polysaccharides when comparing young adults to the elderly [Musher, 2003; Ruben, 1985; Sankilampi, 1996]. These findings do not explain the differences with respect to protection from pneumonia between young adults and the elderly. However, one publication [Romero-Steiner, 1999] demonstrated noteworthy differences with respect to the detectable levels of opsonic antibodies between adults and the elderly after vaccination with PPV. This finding may provide an explanation for differences in efficacy against pneumonia in younger and older adults.

2.3. Correlates of Protection

The anti-polysaccharide antibody levels that are associated with the observed protection against (non-pneumonic) pneumococcal invasive diseases after pediatric immunization with the licensed 7-valent conjugate vaccine are in the range of 0.2 µg/ml by ELISA (Jodar, 2003). (See Figure 2)

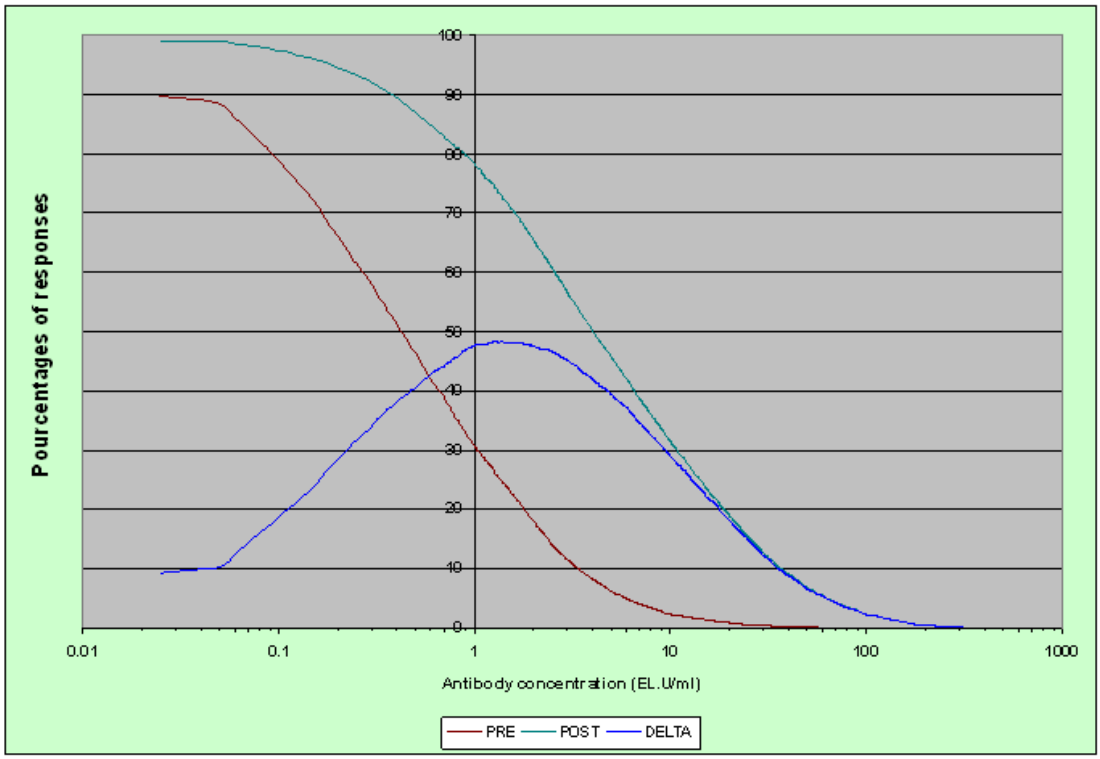
Figure 2 Geometric Mean Concentrations Post-Dose 3 (ELISA) in Infants Vaccinated with PCV 7



Using a similar approach to deduce an antibody threshold after PPV immunization in the elderly, assuming approximately 50% protection against (mostly pneumonic) pneumococcal bacteremia, GSK has calculated antibody thresholds of approximately 1-5 µg/ml when evaluating the responses measured via a specific anti-polysaccharide ELISA (using CPS and 22F inhibition,Henckaerts,ISPPD,Helsinki,2004).

This value is obtained when analyzing the anti-polysaccharide levels at approximately 50% protection or similarly when evaluating the antibody levels at which the difference between vaccinees and controls is highest (Figure 3). Both approaches lead to the calculation of similar thresholds of approximately 1-5 µg/ml. Several factors may explain why this antibody threshold is higher than that calculated for IPD in children. First, most IPD in children is not pneumonia, whereas in adults it is pneumonia and more antibody may be needed to protect against pneumonia. Secondly, the antibody thresholds required for protection after a conjugate vaccine may be lower than those needed after a polysaccharide vaccine. Finally, the quality of the anti-polysaccharide antibodies (opsonophagocytic activity) could be impaired in the elderly, or there may be other immune impairments in the elderly that necessitate higher levels of antibodies to achieve the same level of protection.

Figure 3 **23-valent PPV responses in elderly: Reverse cumulative curve for aggregated responses (11 polysaccharides pooled) (unpublished GSK data using 22F-ELISA after PPV in individuals ≥ 65 yrs of age)**



2.4. GSK Biologicals data comparing 23-valent pneumococcal polysaccharide vaccine responses in young versus elderly adults

Table 3 and Table 4 show the results of two recent GSK studies conducted in parallel in Belgium and for which data were generated using the same assays. In both studies, participants received the 23-valent PPV (Pneumovax®) and the results illustrate the difference between responses to this vaccine in adults aged 18-45 years as compared to elderly subjects aged 65 years and above.

In these studies, a single dose of 23-valent PPV (Pneumovax®) was administered to both young adults and elderly subjects (N=25/group), who were not previously vaccinated against *Streptococcus pneumoniae*. Blood samples were collected 1 month post-vaccination and anti-polysaccharide total IgG concentrations (ELISA), as well as oposonophagocytic activity titers (OPA assay), for 11 serotypes were measured.

The ELISA results show that the antibody levels are significantly lower in the elderly group for 4 (1, 3, 4 and 14) out of 11 serotypes, when compared to the young adult group. The OPA assay shows that the opsonophagocytic activity titers are significantly lower for 7 (1, 4, 6B, 7F, 9V, 14, 18C) out of 11 serotypes for the elderly group when compared to the young adult group. Rank orders differ between ELISA and OPA results, which are in

line with the observation that depending on serotype, different levels of ELISA antibodies are needed for effective opsonophagocytic activity.

For some serotypes (1, 4, 9V) OPA Geometric Mean Titers were found to be approximately 10-fold lower in the elderly as compared to young adults.

In conclusion, these results indicate that upon vaccination with 23-valent PPV, both the quantity and the quality of anti-polysaccharide antibodies are decreased in the elderly as compared to young adults.

Table 3 Geometric Mean Concentrations (GMCs [µg/ml]) post-dose 1 (ELISA) in young adults and elderly subjects vaccinated with 23-valent PPV

	young adults (18-45years)			elderly adults (≥ 65years)			
Serotypes	**GMC (1 Mo Post vaccination)**			**GMC (1 Mo Post vaccination)**			**p-value***
		95%CI			**95%CI**		
	Value	**LL**	**UL**	**Value**	**LL**	**UL**	
1	7.6	4.4	13.1	2.7	1.5	4.6	**0.0067**
3	3.6	2.2	5.9	1.1	0.6	1.9	**0.0031**
4	4.7	2.4	9.1	1.5	0.9	2.8	**0.0244**
5	4.9	2.2	10.7	5.3	2.2	12.4	NS
6B	3.7	1.7	8.0	2.6	1.2	5.3	NS
7F	9.8	5.7	16.9	4.2	2.2	8.0	NS
9V	5.6	3.5	8.9	4.4	2.8	7.1	NS
14	30.9	16.3	58.4	10.7	6.3	18.2	**0.0040**
18C	5.5	2.7	11.1	4.1	2.3	7.3	NS
19F	12.7	6.9	23.3	7.9	3.9	16.2	NS
23F	3.1	1.2	8.2	2.4	1.2	4.7	NS

p-value: Comparisons between young adults and elderly using the Wilcoxon test (Non-parametric test). P-values less than 0.05 (highlighted in bold) were considered as significant. NS: non-significant; 95%CI: LL,UL = 95% Confidence interval: LL: lower limit; UL: upper limits

Table 4 Geometric Mean Titers (GMTs [µg/ml]) post- dose 1 (OPA) in young adults and elderly subjects vaccinated with 23-valent PPV

	young adults (18-45years)			elderly adults (≥ 65years)			
ST	GMT (1 Mo Post vaccination)			GMT (1 Mo Post vaccination)			p-value*
		95%CI			95%CI		
	Value	LL	UL	Value	LL	UL	
1	1300.8	686.1	2466.1	64.8	27.8	151.1	**<.0001**
3	112.5	71.0	178.4	75.2	41.4	136.4	NS
4	5639.5	4054.1	7844.9	558.2	235.2	1324.4	**<.0001**
5	177.8	81.1	389.9	95.0	36.0	250.4	NS
6B	3257.0	2237.1	4741.9	1173.8	575.3	2395.0	**0.0090**
7F	6183.1	3585.4	10663.1	1547.5	700.5	3419.0	**0.0045**
9V	7698.9	4805.9	12333.3	965.3	568.6	1638.9	**<.0001**
14	2893.4	1607.5	5207.8	936.1	566.4	1547.2	**0.0053**
18C	377.8	251.4	567.8	75.2	44.1	128.4	**<.0001**
19F	368.8	160.6	847.0	238.7	109.8	519.2	NS
23F	2091.5	1318.2	3318.4	906.3	419.8	1956.7	NS

p-value: Comparisons between young adults and elderly using the Wilcoxon test (Non-parametric test). P-values less than 0.05 (highlighted in bold) were considered as significant. NS: non-significant; 95%CI: LL,UL = 95% Confidence interval: LL: lower limit; UL: upper limits.

2.5. Pneumococcal conjugate vaccines in adults

In older adults, PCVs have the potential to induce higher, more functional antibody levels that persist longer as compared to the currently licensed 23-valent PPV. If PCVs are effective against non-invasive pneumococcal disease in adults (such as non-bacteremic pneumonia) or if they confer longer protection, they likely will offer significant prevention in addition to or possibly as a replacement for the currently recommended polysaccharide vaccine. Another potential advantage for PCVs is that most of the serotypes contained in the 11-valent PCVs under development are those associated with increasing antimicrobial resistance in the older adults. A study comparing the hypothetical effects of the 23-valent PPV with that of new 7- or 11-valent PCVs on prevention of invasive and non-invasive disease in persons >65 years of age has suggested that PCVs would improve overall disease prevention [Fry, 2002].

In renal transplant patients, who normally have a poor response to 23-valent PPV, responses to the PCV7 were found to be significantly more immunogenic than 23-valent PPV [Kumar, 2003]. Use of PCV7 in children with recurrent infections who were unresponsive to the 23-valent PPV resulted in induction of an IgG response [Sorensen, 1998]. In a study with children non-responsive to 23-valent PPV, the PCV7 elicited superior antibody levels than those elicited by the 23-valent PPV [Zielen, 2000]. Healthy adults who failed to produce IgG to 5 or more polysaccharides after having received 23-valent PPV were shown to respond to most polysaccharides after receiving a series of PCVs [Musher, 1998]. The immunogenicity of a series of PCVs, including PCV7, compared to 23-valent PPV was demonstrated to be superior to 23-valent PPV in elderly subjects aged ≥70 years without prior pneumococcal immunization [Kuhnke, 2004].

Since the elderly have been found to demonstrate clearly lowered opsonophagocytic antibody activity post-PPV as compared to young adults (Romero-Steiner, 1999) there is room for improvement by way of PCV immunization. In this context, it should be noted that polysaccharide vaccine non-responders have been found to respond to PCV [Abraham-Van Parijs, 2004; Musher, 1998].

In addition to improving functional antibody levels, vaccination with PCV may prevent the hypo-responsiveness that can occur following re-immunization with PPV. Recently, new data with PCV7 given before or after 23-valent PPV were presented by de Roux *et al*. (2005) and are summarized in Table 5. In pneumococcal vaccine-naïve individuals aged ≥70 years, PCV7 induced superior ELISA responses compared to 23-valent PPV for 6 of 7 serotypes and appeared to increase antibody responses to subsequent doses of 23-valent PPV as compared to an initial dose of PPV. However, initial dosing with 23-valent PPV appeared to induce hypo-responsiveness as measured by decreased antibody responses to subsequent doses of PCV7. It may be most beneficial to give PCV before PPV [de Roux 2005]. A vaccination strategy of priming with PCV at age 50-60 years followed by PPV vaccination in patients ≥65 years may provide an improvement over the existing strategy of vaccinating patients 65 years of age and older with a single dose of PPV. Since this strategy may leave people unprotected at approximately 70 years of age, studies would be needed to determine if priming with PCV followed by boosting with PPV and then re-boosting with PPV or PCV would offer a solution for the hypo-responsiveness that may be induced by initial vaccination with PPV.

Although revaccination with polysaccharide may lead to lower antibody levels, no general recommendation for revaccination has been implemented [Artz, 2003; Torling, 2003].

Table 5 Pneumococcal antibody concentration [µg/ml] to the 7 serotypes in PCV7 (Prevnar®) 30 days post-vaccination in adults >70 years (deRoux, 2005)

Results presented as GMCs (95% confidence interval)

Vaccines Administered	N	4	6B	9V	14	18C	19F	23F
7vPnC	110	3.1 (2.2 – 4.3)	8.0 (6.0 – 10.8)	9.8 (7.5 – 12.8)	17.1 (12.3 – 24.0)	13.0 (10.1 – 16.7)	5.5 (4.1 – 7.4)	12.4 (9.0 – 17.0)
7vPnC 23vPS	36	2.0 (1.2 – 3.5)	5.4 (3.3 – 9.0)	5.7 (3.6 – 8.9)	14.5 (8.8 – 23.9)	7.6 (5.2 – 11.1)	8.4 (5.3 – 13.1)	7.4 (4.0 – 13.6)
23vPS	107	1.4 (1.1 – 2.0)	4.4 (3.4 – 5.8)	3.6 (2.8 – 4.6)	8.5 (6.0 – 12.1)	6.8 (5.2 – 8.9)	4.4 (3.4 – 5.8)	3.8 (2.9 – 5.0)
23vPS 7vPnC	78	0.9 (0.6 – 1.3)	2.2 (1.5 – 3.2)	3.0 (2.2 – 4.0)	6.7 (4.5 – 9.9)	5.1 (3.7 – 6.8)	2.1 (1.5 – 3.0)	3.8 (1.9 – 4.8)

7vPnC : 7-valent pneumococcal conjugate vaccine (Prevnar™)
23vPS : 23-valent pneumococcal polysaccharide vaccine (Pneumovax™)
7vPnC 23vPS : 7-valent pneumococcal conjugate vaccine followed 1 year later by 23-valent pneumococcal polysaccharide vaccine
23vPS 7vPnC : 23-valent pneumococcal polysaccharide vaccine followed 1 year later by 7-valent pneumococcal conjugate vaccine

2.6. Conclusions

Although the benefits of the 23-valent PPV are clear, the polysaccharide vaccine has a number of limitations. In young adults, PPV is effective in preventing pneumococcal pneumonia, evidence taken into account by FDA allowing licensure of the 14-valent and later 23-valent polysaccharide vaccines. However, prospective clinical trials evaluating the ability of PPV to prevent non-bacteremic pneumonia in the elderly have shown that the vaccine is not very effective. In the elderly it has been observed that antibody levels to important serotypes decline to pre-vaccination levels within 3-7 years. This is likely responsible for the decline in overall protection observed during the years following vaccination. For those vaccinated at age 65 years or older, revaccination is not routinely recommended for several reasons, including evidence that a second dose is not as immunogenic as compared to the first. This reduction of existing polysaccharide-specific B-cell memory (and the absence of renewed memory) appears a major shortcoming of PPV. Without revaccination, the elderly become unprotected approximately 5 years post-PPV.

In older adults, PCVs have the potential to induce stronger and more functional immune responses of longer duration than the currently licensed 23-valent PPV. Pneumococcal conjugate vaccines may provide an improved option for the immunization schedule of older adults. Recent studies conducted with PVC7 have demonstrated improvement of the immune response in elderly, particularly in terms of functional antibody response. A functional assay that detects opsonophagocytic activity is generally believed to produce a more reliable indicator for the induction of immunity. This is supported by the recent data generated by GSK Biologicals comparing the immune response to the 23-valent PPV in young adults to elderly (Section 2.4). Lower opsonophagocytic antibody titers were found in the elderly as compared to the young adult group. These lower opsonophagocytic antibody titers may explain the difference observed with respect to protection against pneumonia between young adults and the elderly.

Significantly improved antibody responses (ELISA and OPA) with PCV in elderly adults (≥65 years) as compared to PPV such that non-inferiority to PPV responses in young adults can be demonstrated, are supportive as a pathway for licensure with an indication of pneumococcal pneumonia in older adults.

GSK Biologicals is currently assessing pneumococcal conjugate vaccine formulations vis-à-vis the 23-valent PPV in older adults. In addition, studies are planned to investigate the hypo-responsiveness phenomenon observed with the 23-valent PPV and to examine how a PCV would best fit into the immunization schedule if used to complement the existing polysaccharide vaccine.

3. REFERENCES

Abraham-Van Parijs B. Review of pneumococcal conjugate vaccine in adults: implications on clinical development. *Vaccine* 2004;22:1362-71.

Almirall J, Bolibar I, Vidal J, Sauca G, Coll P, Niklasson B, Bartolome M, Balanzo X. Epidemiology of community-acquired pneumonia in adults: a population-based study. *Eur Respir J*. 2000 15: 757-63

Artz AS, Ershler WB, Longo DL. Pneumococcal vaccination and revaccination of older adults. *Clin.Microbiol.Rev*. 2003;16:308-18.

Austrian R, Douglas RM, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. *Trans.Assoc.Am.Physicians* 1976;89:184-94.

Concepcion NF, Frasch CE. Pneumococcal type 22F polysaccharide absorption improves the specificity of a pneumococcal-polysaccharide enzyme-linked immunosorbent assay. *Clin.Diagn.Lab Immunol*. 2001;8:266-72.

de Roux A., Schmoele-Thoma B., Ahlers N., Gruber W., Siber G., Sikkema D., Welte4, H. Lode T. Different immune response after sequential use of pneumococcal polysaccharide and pneumococcal conjugate vaccine. The Eight Annual Conference on Vaccine Research, Baltimore-USA, 2005.

Fedson DS, Musher DM. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4rth edition. PhiladelphiaWB Saunders Co, 2004a: 529-588

Fedson DS, Liss C. Precise answers to the wrong question: prospective clinical trials and the meta-analysis of pneumococcal vaccine in elderly and high-risk adults. *Vaccine*.2004b;22: 927-46.

Fedson DS. Pneumococcal conjugate vaccination for adults: why it's important for children. Pediatr Infect Dis J. 2000 Mar;19(3):183-6.

Fry AM, Zell ER, Schuchat A, Butler JC, Whitney CG. Comparing potential benefits of new pneumococcal vaccines with the current polysaccharide vaccine in the elderly. Vaccine. 2002 Dec 13;21(3-4):303-11.

Henckaerts I, De Grave D, Ashton L Goldblatt D, Poolman J. Critical difference between pneumococcal polysaccharide ELISAs with or without 22F inhibition at antibody levels <1µg/ml in pedicatric post-conjugate immunization sera. Fourth International Symposium on Pneumococci and Pneumococcal Diseases. PSV-24. 2004.

Honkanen PO, Keistinen T, Miettinen L, Herva E, Sankilampi U, Leinonen M, Kivela SL, Makela PH. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine*, 1999; 17:2493-2500.

Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, Hanson CA, Mahoney LD, Shay DK, Thompson WW; Vaccine Safety Datalink. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med*. 2003;348:1747-55

Jackson ML, Neuzil KM, Thompson WW, Shay DK, Yu O, Hanson CA, Jackson LA. The burden of community-acquired pneumonia in seniors: results of a population-based study. Clin Infect Dis. 2004 Dec 1;39(11):1642-50.

Jodar L, Butler J, Carlone G, Dagan R, Goldblatt D, Kayhty H, Klugman K, Plikaytis B, Siber G, Kohberger R, Chang I, Cherian T. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. Vaccine. 2003 Jul 4;21(23):3265-72.

Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Kleemola M, Koskela M, Leinonen M, Ronnberg PR, Saikku P, Sten M, Tarkiainen A, Tukiainen H, Pyorala K and Makela PH. Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. *Clin Infect Dis*. 2001; 32: 1141-54.

Koivula I, Sten M, Leinonen M, Makela PH. Clinical efficacy of pneumococcal vacine in the elderly: a randomized, single-blind population-based trial. *Am J Med*, 1997; 103: 281-90.

Kuhnke A, Lode H, De Roux A, Ahlers N, Thoma B, Madore D, Welte T. Comparison of immunogenicity of pneumococcal conjugate (PnC) and 23-valent polysaccharide vaccine (23vPS) in elderly patients. *ICAAC* 2004; G-1675-2004

Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized double blind controlled trial of pneumococcal vaccination in renal transplant recipients. J Infect Dis 2003;187:1639-45.

Kyaw MH, Christie P, Clarke SC, Mooney JD, Ahmed S, Jones IG, Campbell H. Invasive pneumococcal disease in Scotland, 1999-2001: use of record linkage to explore associations between patients and disease in relation to future vaccination policy. *Clin Infect Dis*. 2003;37:1283-91.

MacLeod M., Hodges R.G., and Heidelberg M. BWG. Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J.Exp.Med*. 1945; 82 445-465.

Marston BJ, Plouffe JF, File TM, Jr., Hackman BA, Salstrom SJ, Lipman HB, Kolczak MS and Breiman RF. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. The Community-Based Pneumonia Incidence Study Group 1997; 157:1709-1718

Musher DM, Groover JE, Watson DA, Rodriguez-Barradas MC, Baughn RE. IgG responses to protein-conjugated pneumococcal capsular polysaccharides in persons who are genetically incapable of responding to unconjugated polysaccharides. *Clin.Infect.Dis*. 1998;27:1487-90.

Musher DM, Watson DA, Baughn RE. Genetic control of the immunologic response to pneumococcal capsular polysaccharides.Vaccine. 2000 Nov 8;19(6):623-7.

Musher DM. How contagious are common respiratory tract infections? N Engl J Med. 2003;348:1256-66.

Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch.Intern.Med. 1999;159(20):2437-42.

Ortqvist A, Hedlund J, Burman LA, Elbel E, Hofer M, Leinonen M, Lindblad I, Sundelof B, Kalin M. Randomized trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *The Lancet*, 1998; 351: 399- 403.

Poolman JT. Pneumococcal vaccine development. Expert.Rev.*Vaccines*. 2004;3(5):597-604.

Riley ID, Tarr PI, Andrews M, et al. Immunisation with a polyvalent pneumococcal vaccine. Reduction of adult respiratory mortality in a New Guinea Highlands community. *Lancet* 1977;1:1338-41.

Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, Damaske B, Stefonek K, Barnes B, Patterson J, Zell ER, Schuchat A, Whitney CG; Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era *JAMA*. 2001 ;285:1729-35.

Romero-Steiner S, Musher DM, Cetron MS, et al. Reduction in functional antibody activity against Streptococcus pneumoniae in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. *Clin.Infect.Dis*. 1999;29:281-8.

Ruben FL, Uhrin M. Specific immunoglobulin-class antibody responses in the elderly before and after 14-valent pneumococcal vaccine. *J.Infect.Dis*. 1985;151:845-9.

Sankilampi U, Honkanen PO, Bloigu A, Herva E, Leinonen M. Antibody response to pneumococcal capsular polysaccharide vaccine in the elderly. *J.Infect.Dis*. 1996;173:387-93.

Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N.Engl.J.Med*. 1991;325(21):1453-60.

Simberkoff MS, Cross AP, Al-Ibrahim M, Baltch AL, Geiseler PJ, Nadler J, Richmond AS, Schiffman G, Shepard DS. Efficacy of pneumococcal vaccine in high risk patients. Results of a Veterans Administration Cooperative Study. *N.Engl.J.Med* 1986; 315: 1318-1327.

Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ, Hilleman MR. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 1977;238(24):2613-6.

Sorensen RU, Leiva LE, Giangrosso PA, Butler B, Javier FC, Sacerdote D, Bradford N, Moore C. Response to a heptavalent conjugate Streptococcus pneumoniae vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. *The Pediatric Infectious Disease Journal* 1998; 17: 685-691

Torling J, Hedlund J, Konradsen HB, Ortqvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. *Vaccine* 2003;22:96-103.

Wagner C, Popp W, Posch M, Vlasich C, Rosenberger-Spitzy A. Impact of pneumococcal vaccination on morbidity and mortality of geriatric patients: a case-controlled study. *Gerontology* 2003;49:246-50.

Zielen S, Buhring I, Strnad N, Reichenbach J, Hofmann D. Immunogenicity and tolerance of a 7-valent pneumococcal conjugate vaccine in nonresponders to the 23-valent pneumococcal vaccine. *Infect.Immun*. 2000;68:1435-40.