PNEUMOCOCCAL CONJUGATE VACCINE

ADULT PROGRAM

Pre-Meeting Package
for
VRBPAC

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1.0 INTRODUCTION

Despite the use of the 23-valent pneumococcal polysaccharide vaccine in individuals ≥ 65 and high risk individuals, significant disease due to *S. pneumoniae* remains. Thus, there is a need for a vaccine that can address some of the limitations of the polysaccharide vaccine. Specifically, a vaccine that can provide protection over the entire period that the patient remains at high risk, would address an important public health need.

This briefing package will address the rationale for licensure of the pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease (IPD), on the basis of immunological responses compared with the 23-valent polysaccharide vaccine (23vPS). A mechanism of protection against encapsulated organisms in general, and *S. pneumoniae* specifically, is serum antibodies that target the capsular polysaccharides. Furthermore, efficacy of the 23vPS vaccine against IPD has been demonstrated, and, therefore, its antibody response can serve as a benchmark for licensure (using non-inferiority), similar to the pathway to licensure for the recently licensed 4-valent meningococcal conjugate vaccine, Menactra. Efficacy studies in the adult population are not feasible due to issues of trial design, ethics, and disease incidence - the very populations with a high enough incidence of disease to study are those in which a placebo-controlled trial would be unethical. This is discussed in **Appendix 1.**

The 13-valent pneumococcal conjugate (13vPnC) vaccine has fewer serotypes than the 23vPS vaccine and therefore the serotype coverage is less (56% of IPD for 13vPnC, vs 75% for PS). Thus, 13vPnC should have the potential for additional benefit, beyond non-inferiority of the serotypes included in the 13vPnC vaccine. This benefit is the duration of protection. Our preliminary data with 7vPnC vaccine, Prevnar®, suggest that the period of protection following conjugate vaccine immunization can be extended beyond that of PS vaccine, because, unlike the PS vaccine, the conjugate allows for re-immunization without blunting of the immune response. Thus, the 13vPnC has the potential to provide protection throughout the entire period of risk.

We therefore propose that 13vPnC should be licensed by demonstrating: (1) a functional antibody response that is non-inferior to 23vPS vaccine (2) no blunting of the immune response to subsequent vaccination, and, of course, (3) an acceptable safety profile.

2.0 BACKGROUND

2.1 Burden of disease

Invasive disease due to *S. pneumoniae* remains a major cause of morbidity and mortality in adults. Despite the use of the 23-valent pneumococcal polysaccharide vaccine (23vPS), with vaccine uptake estimates of about 60%, the incidence of invasive pneumococcal disease (IPD) in elderly adults (≥ 65 years) in 1995-1998 remained at 60 per 100,000, and was as high as 98.5/100,000 in individuals ≥ 80 years of age. Persons ≥ 65 years of age accounted for 51.4% of all deaths due to IPD in 1998, although they represented only about one-third of the IPD cases. Mortality rates ranged from 7.4/100,000 in ages 65-79 years to as high as 17.4/100,000 in those individuals ≥ 80 years, in whom the case-fatality rate was as high as 20.6% [1,2]. Since the licensure of Prevnar ®, some herd-immunity effect has been seen, with an 18% decrease in incidence of IPD observed in 2001- ranging from 49.5 - 60.1/100,000 [3], and a 35% decrease by 2004 – to 30.4/100,000 (preliminary data, personal communication, C. Whitney).

In 50-64 year olds, before the licensure of Prevnar, the overall IPD rate was 24/100,000, but the rate in blacks, estimated as high as 75/100,000, was substantially greater than the rates in whites. Smoking is another risk factor for IPD. When data are adjusted for other factors, persons 18-64 years of age with IPD were found to be 4.1 times more likely to be cigarette smokers compared to control subjects without IPD. In fact, 51% of the disease burden in immunocompetent adults 18-64 years of age was statistically attributable to smoking[4]. Since licensure of Prevnar, the overall IPD rate in the 50-64 year old age group has declined slightly to 20/100,000 (preliminary data, personal communication, C. Whitney)

Finally, current ACIP recommendations recognize various underlying medical conditions resulting in a high rate of IPD, including chronic cardiovascular, pulmonary, or liver diseases, renal diseases, diabetes mellitus, functional or anatomic asplenia, HIV infection or other immunosuppressive conditions, and CSF leaks [5]. Based on 1999-2000 data, the incidence of IPD in patients ≥ 18 years of age was 46.2/100,000 in persons with diabetes, 62.9/100,000 in persons with chronic lung disease, 93.7/100,000 in persons with chronic heart disease, 100.4/100,000 in alcohol abusers, and 300.4-503.1/100,000 in persons with immunocompromising conditions such as HIV/AIDs or cancer [6].

S. pneumoniae is the most common bacterial cause of community-acquired pneumonia (CAP). At least 500,000 cases of pneumococcal pneumonia are estimated to occur in the USA each year, although the precise rate is difficult to ascertain because routine diagnostic tests are neither sufficiently sensitive nor specific. For instance, *S. pneumoniae* may account for approximately 25-50% of cases of hospitalized community acquired pneumonia, but only about 10-25% of cases of pneumococcal pneumonia in adults are bacteremic [5].

2.2 Experience with Pneumococcal Polysaccharide Vaccine

2.2.1 Pneumococcal polysaccharide vaccine indication

The currently licensed 23vPS vaccine is indicated for vaccination against pneumococcal disease caused by those pneumococcal types included in the vaccine.

2.2.2 Efficacy / effectiveness

IPD

The efficacy of pneumococcal polysaccharide vaccines was demonstrated in controlled clinical trials in South Africa involving 12,000 young, adult, male gold miners. Six- and 13-valent PS vaccines were shown to be 82.3% effective in preventing pneumococcal bacteremia with the serotypes contained in the vaccine. Subsequently, 14- and then 23-valent PS vaccines were licensed on the basis of immunogenicity. Effectiveness against invasive pneumococcal disease in the population for which 23vPS vaccine is recommended in the United States (high risk patients including all subjects aged 65 years or older), as assessed in post-marketing studies, has generally ranged from 56-81%, although estimates are considerably lower in the immunocompromised [5,7,8,9.10].

In a case-control study of 1054 cases and 1054 matched controls ≥ 18 years of age (mean age 67.6 years), overall efficacy of the pneumococcal polysaccharide vaccine (14- or 23-valent) against serotypes present in the vaccine was 56% (95% CI 42, 67); for immunocompetent patients efficacy was 61% (95% CI 47, 72), and for immunocompromised patients it was 21% (95% CI –55, 60) [7]. Efficacy declined with length of time after vaccination, and the slope of this decline increased with increasing age at vaccination, being especially notable in the elderly [7].

Analysis of data from national surveillance for pneumococcal disease, using an indirect cohort analysis of 2837 persons aged 6 years and older (median age 57 years in vaccinated group and 50 years in unvaccinated group) demonstrated an overall efficacy against vaccine serotypes of 57% (95% CI 45, 66). Effectiveness in immunocompetent persons 65 years and older was 75% (95% CI 57, 85) [8].

Pneumonia

The efficacy of pneumococcal polysaccharide vaccine in prevention of pneumonia has recently been reviewed [10]. Although early studies in South African miners and in Papua New Guinea highlanders suggested efficacy against pneumonia, a metanalysis of subsequent, randomized trials in elderly or high-risk populations in developed countries shows no evidence of efficacy [10].

Observational methods have also failed to demonstrate efficacy/effectiveness against pneumonia in elderly subjects in the United States. In a retrospective cohort study within an HMO in Washington State of subjects 65 years of age or older, effectiveness was confirmed against pneumococcal bacteremia (immunized subjects multivariate adjusted hazard ratio 0.53, 95% CI 0.31-0.93). However, the hazard ratios were not significant for

any pneumonia category, community acquired pneumonia verified by medical record review 1.11 (95% CI 0.98, 1.26); outpatient pneumonia 1.02 (95% CI 0.94, 1.10); discharge diagnosis for pneumonia [ICD9 codes 480 through 487.0] 1.05 (95% CI 0.95, 1.15) [11].

2.2.3 Current Recommendations

Currently, the 23vPS vaccine is recommended for the prevention of pneumococcal disease in all persons ≥ 65 years of age, as well as high-risk individuals aged 2-64 years.

2.2.4 Limitations of 23vPS vaccine

Certain characteristics of the 23vPS vaccine limit its use in providing protection over the full duration of the period of risk of *S. pneumoniae* disease in healthy and high-risk persons.

As with other vaccines, there is evidence that antibody titers [5] and efficacy [7] wane over time after immunization with pneumococcal 23vPS vaccine. Nonetheless, because of the concerns noted below, a revaccination is not routinely recommended, except in certain high-risk populations, and even then, is limited to one additional dose [5]

The capsular PS is a T-independent antigen, which does not induce immunological memory, and therefore produces an immune response that does not provide an anamnestic response (i.e., is not boostable). In fact, some data suggest that immune response to a subsequent dose of 23vPS may be less vigorous than that measured after the initial dose of 23vPS, so-called "hyporesponsiveness" [12]. Our own data confirms this phenomenon (see **Section 6.2**). A possible mechanism for this effect is the depletion of PS-specific B-cell clones in the absence of establishment of memory cells.
There is also evidence that local reactogenicity of the 23vPS vaccine increases with revaccination, probably due to an Arthus reaction [13].

In addition, the efficacy of the 23vPS vaccine declines as the elderly age [7] and the functional antibody response to 23vPS vaccine, measured by opsonophagocytosis, is decreased in the very elderly as well [14].

2.2.5 Implications of limitations

As noted above, healthy individuals have an increasing risk of morbidity and mortality due to pneumococcal disease beginning at about 50 years of age. Recently, recommendations for influenza vaccine have been extended to healthy adults at age 50, and extension of the recommendation for pneumococcal vaccination down to that age group has been considered as well. Benefits of early immunization are that the immune system is likely to be more responsive, and substantial number of cases occurring in this age group could be prevented. However, concerns about waning immunity before entering the period of highest risk, as well as the potential for hyporesponsiveness, and reactogenicity have discouraged this approach to date, and age-based recommendations continue to begin at 65 year olds, except in high-risk individuals.

Due to these concerns, there has been no recommendation for routine revaccination after the initial dose at 65 years of age, even though disease risk increases steadily with age, and vaccine efficacy wanes.

3.0 POTENTIAL BENEFITS OF A PNEUMOCOCCAL CONJUGATE VACCINE

The use of an adult pneumococcal conjugate vaccine (PnC) could optimize protection against pneumococcal disease over the lifetime of the individual, by offering a solution to some of the limitations of the 23vPS vaccine. The PnC vaccine invokes T-dependent immune mechanisms, with the potential for more robust immunogenicity, including better functional antibody and lessened risk of hyporesponsiveness with subsequent dosing. Furthermore, the significantly reduced saccharide dose compared to the PS vaccine may result in more acceptable reactogenicity upon revaccination.

An adult pneumococcal conjugate vaccine could be administered early in the risk period. The PnC vaccine also could be given more than once to extend the age range of protection against pneumococcal disease, by being readministered at intervals, if needed.

An enhanced ability to induce functional antibody responses, especially in the elderly, would be a further benefit.

4.0 APPROACHES TO LICENSURE

There are two approaches to licensure of new vaccines, efficacy and immunogenicity.

Efficacy

In general, when no vaccine has been previously licensed for the same indication, and no well-accepted immunological surrogate of vaccine efficacy exists, an efficacy approach is used for licensure.

Immunogenicity

When a vaccine has already been licensed because it was demonstrated to be efficacious, immunogenicity has been the accepted approach to licensing a new vaccine for the same indication.

There are many examples that illustrate these two approaches.

The efficacy of Haemophilus influenzae type b polysaccharide vaccine was documented in an efficacy trial in Finnish toddlers. Subsequently, Hib conjugate vaccines were licensed in the same age group based on an immunogenicity approach. By contrast, Hib conjugate vaccine licensure in infants required an efficacy approach, as the polysaccharide vaccine could not be demonstrated to be effective in the infant population, and therefore could not be used as a benchmark for infants. Once efficacy was demonstrated for Hib conjugate vaccine in infants, subsequent licensure of a new Hib conjugate vaccine (for instance, PRP-T) required only non-inferiority to the previously licensed vaccine.

Meningococcus type C and type A (Men A/C) polysaccharide vaccines were demonstrated to be efficacious in field trials. The quadrivalent meningococcal A, C, Y, and W135 vaccine was licensed based on immunogenicity (serum bactericidal activity, SBA) comparable to Men A/C polysaccharide vaccine, plus similar responses for the new serotypes, which were inferred to be efficacious based on the same endpoints (four-fold rise in SBA titer). Consequently, the quadrivalent meningococcal conjugate vaccine, Menactra, was recently licensed based on demonstration of immune responses non-inferior to the licensed quadrivalent meningococcal polysaccharide vaccine.

A 7-valent pneumococcal conjugate vaccine has been licensed for use in infants on the basis of a large-scale efficacy study. It has been accepted that next generation pneumococcal conjugate vaccines with extended serotypes coverage may be licensed on the basis of acceptable immune response to those additional serotypes [15].

This approach is further supported by the well-known fact that protective immunity to encapsulated organisms (i.e., *Haemophilus influenzae type b*, meningococcus and pneumococcus), is mediated by antibodies. Data in animals and humans document that passive and active immunization with anticapsular antibody is protective [13,16]. It has long

been understood that the basis for this immune protection is functional antibody against the capsule. For the pneumococcus, this functional antibody, together with serum complement, is capable of promoting opsonophagocytosis of the organism. This can be measured in an OPA assay, where serum is added to polymorphonuclear leucocytes (PMNs) in the presence of complement, and killing of bacteria by the PMNs is measured.

5.0 APPROACHES TO LICENSURE OF PNEUMOCOCCAL CONJUGATE VACCINES IN ADULTS

The 23vPS vaccine is the currently licensed standard of practice in adults for prevention of pneumococcal disease, which includes both invasive pneumococcal disease (IPD), and pneumonia.

5.1 Pneumonia Indication

For pneumonia, efficacy of the polysaccharide vaccine was based on data in South African gold miners, with an endpoint of chest X ray confirmed clinical pneumonia. Subsequent post-marketing studies have, in general, failed to provide confirmation of efficacy in the target population for this vaccine. Thus, we believe that an efficacy approach is required for a pneumonia indication; an immunogenicity approach cannot be supported for this indication.

However, there are many barriers to the successful conduct of a pneumonia efficacy trial. The impact of a vaccine on all clinical pneumonia is not easily generalized across populations (i.e. different geographical areas, or outpatient vs. hospitalized), or across time periods (e.g. incidence may vary with fluctuations in influenza). The more appropriate assessment must therefore be the impact on pneumococcal pneumonia, with the ability to distinguish vaccine and non-vaccine serotypes. Unfortunately, diagnostic tests at present are not sufficiently sensitive or specific to support such a study.

For these reasons, we do not plan to seek licensure at this time for prevention of pneumococcal pneumonia.

5.2 IPD Indication

Efficacy for the pneumococcal polysaccharide vaccine has already been established for IPD, based on efficacy studies in young South African gold miners, and confirmed in adults and the elderly, where the vaccine has subsequently been demonstrated in post marketing studies, to be efficacious (see **Section 2.0**). The basis for this protection is induction of a functional antibody response.

Thus, for an IPD indication, the case for licensure of a new vaccine using an immunogenicity approach is clear, and it is entirely consistent with the historical approach described in **Section 4.0**.

6.0 LICENSING CRITERIA FOR 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN ADULTS

There are two important aspects of the licensing criteria for 13vPnC in adults. The first is non-inferiority of the immune response for 13vPnC, compared to PS vaccine, for each of the serotypes common to the two vaccines. However, because the 13vPnC vaccine has fewer serotypes than the 23vPS vaccine, 13vPnC must be demonstrated to have additional benefit beyond non-inferiority of the serotypes included in the 13vPnC vaccine. This additional benefit, lack of induction of hyporesponsiveness, allows for reimmunization without blunting of the immune response. Thus, unlike the PS vaccine, the 13vPnC has the potential to provide protection throughout the entire period of risk.

6.1 First Criterion: Non-Inferiority of a single dose of conjugate to polysaccharide vaccine

Licensure criteria for each of the serotypes that are common to both 13vPnC and 23vPS vaccines will be based upon serotype specific immune responses. A single administration of 13vPnC will be compared directly to a single administration of 23vPS to demonstrate non-inferiority.

6.1.1 Non-inferiority of functional antibody response

One of the key issues for vaccinating adults and the elderly with pneumococcal conjugate vaccine relates to whether immunogenicity is as good a surrogate of protection as it is in children. This issue arises because the elderly have significant levels of antibody to the pneumococcus as measured by ELISA pre-immunization, but are still very susceptible to pneumococcal disease. For this reason, we explored the functional antibody response, as measured by OPA, in two populations – the elderly and infants.

6.1.1.1 Reverse Cumulative Distribution Curves

The data in the elderly are from a study conducted in Germany. In this clinical trial, 217 elderly individuals ≥ 70 years of age who had never received any previous pneumococcal vaccination were randomized to receive 7vPnC vaccine (Prevnar®) or 23vPS vaccine. OPA titers shown were measured 1 month after immunization. The infant data are from a study conducted in the USA. Infants received Prevnar® at 2, 4, and 6 months of age, and OPA titers were measured one month after completion of the 3-dose primary series.

Figures 6.1.1-1 to 6.1.1-5 present Reverse Cumulative Distribution Curves (RCDC) of the OPA responses to the individual serotypes for both PnC and PS vaccines in adults. These are compared on the same axes to the RCDCs of the OPA response to Prevnar from the infant study, with antibodies measured one month after completion of the 3-dose primary series. The percent response rate corresponding to the serotype-specific efficacy in the infant population is indicated on each curve (specific for efficacy against that

serotype), and the response rate at the corresponding titer on the x-axis (referred to as "benchmark titer" hereafter) is used for the basis of comparison of OPAs between groups for that serotype.

The RCDCs for serotypes 6B, 9V, 18C, 19F and 23F are shown in **Figure 6.1.1-1 to 6.1.1-5** respectively. Serotype-specific efficacy in infants ranged from 81 to 98% (CDC case-control study, C.Whitney, personal communication), with 3 of the 5 serotypes showing a response in 96% or more subjects.

For each of the serotypes, the OPA values existing prior to immunization in naïve elderly are substantially lower than those achieved in immunized infants, and this may provide an explanation for the susceptibility of this population to IPD. Depending on serotype, only 25 to 55% of subjects achieved the benchmark titer.

Following immunization with 23vPS vaccine, the percentage of individuals with responses that were similar to the infant values was greater than at baseline for each serotype. Now 48 to 89% had responses above the benchmark titer, and for 4 of 5 serotypes, 75% or more of the subjects had responses above the benchmark for their serotype. Serotype 23F had the lowest response (48% above benchmark). Interestingly, this serotype was associated with the lowest point estimate of efficacy for the PS vaccine [8].

Following immunization with PnC vaccine, response rates, by contrast, ranged from 73 to 97%. Serotypes 9V and 18C achieved response rates as high as those seen in immunized infants. Serotypes 6B and 19F were more similar to the response to 23vPS vaccine, and the response to 23F was substantially improved over 23vPS.

After 23vPS vaccine, the elderly, in general, are not able to achieve functional antibody titer values that are as large as those seen with 7vPnC immunization in children. This may well be the reason that the polysaccharide vaccine in the elderly has not been as effective as the conjugate vaccine in children.

Nonetheless, it is well documented that the pneumococcal conjugate vaccine does confer around 60% efficacy overall [7]. The ability of conjugate vaccine to achieve similar or higher titers than polysaccharide vaccine should result in equal or greater efficacy in this population for each serotype where this is true, and this comparison can be the basis for an immunological approach to licensure.

Figure 6.1.1-1: Infant vs. Adult OPA RCDC for Serotype 6B

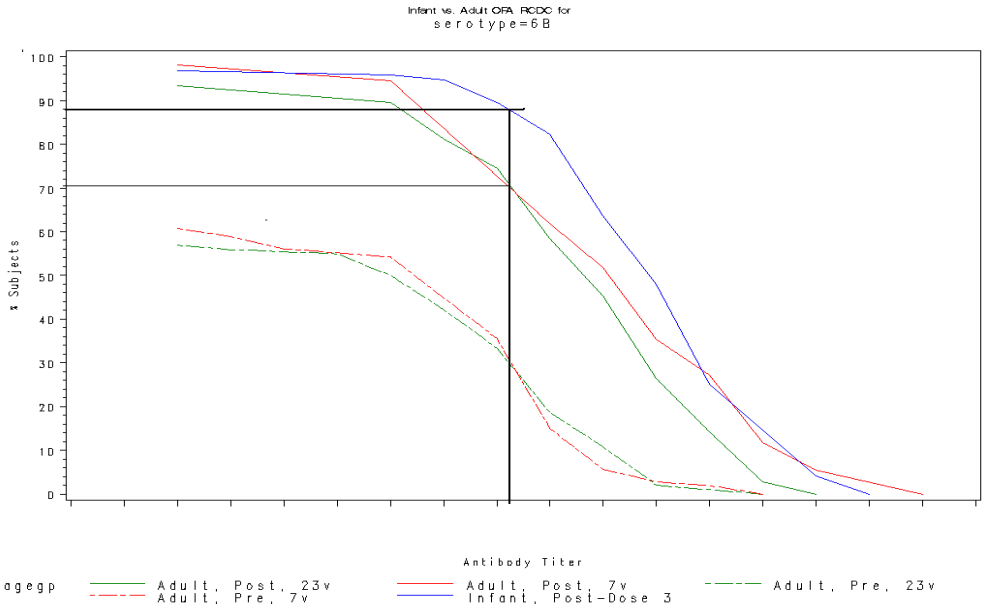


Figure 6.1.1-2: Infant vs. Adult OPA RCDC for Serotype 9V

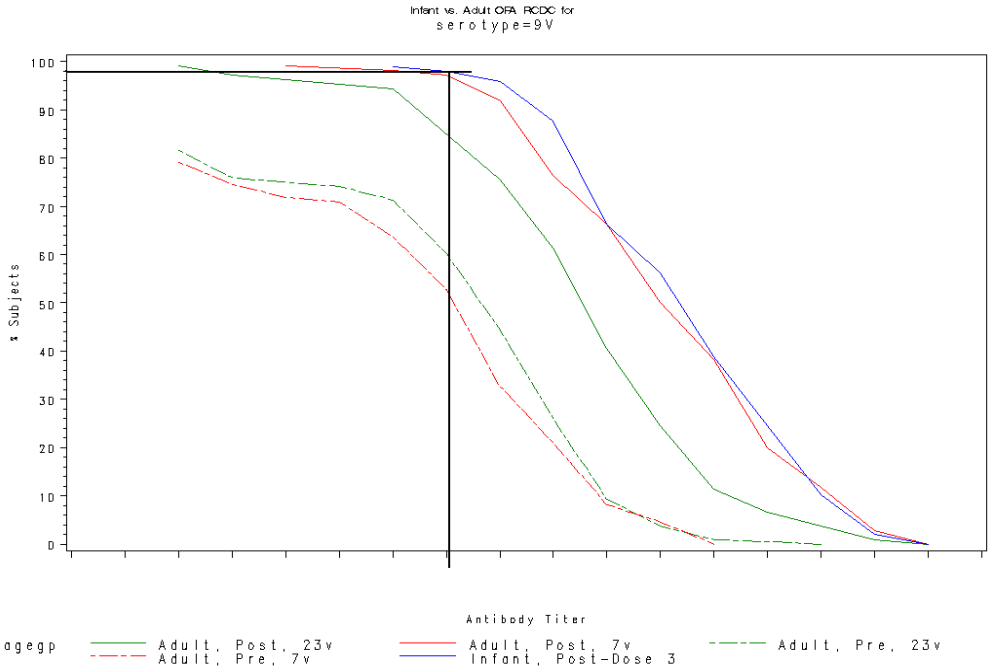


Figure 6.1.1-3: Infant vs. Adult OPA RCDC for Serotype 18C

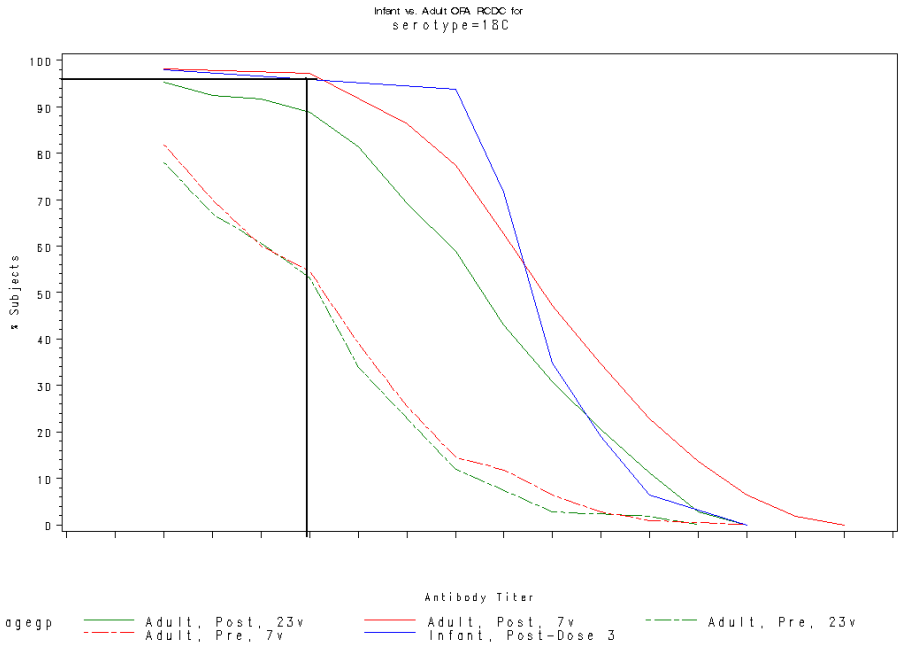


Figure 6.1.1-4: Infant vs. Adult OPA RCDC for Serotype 19F

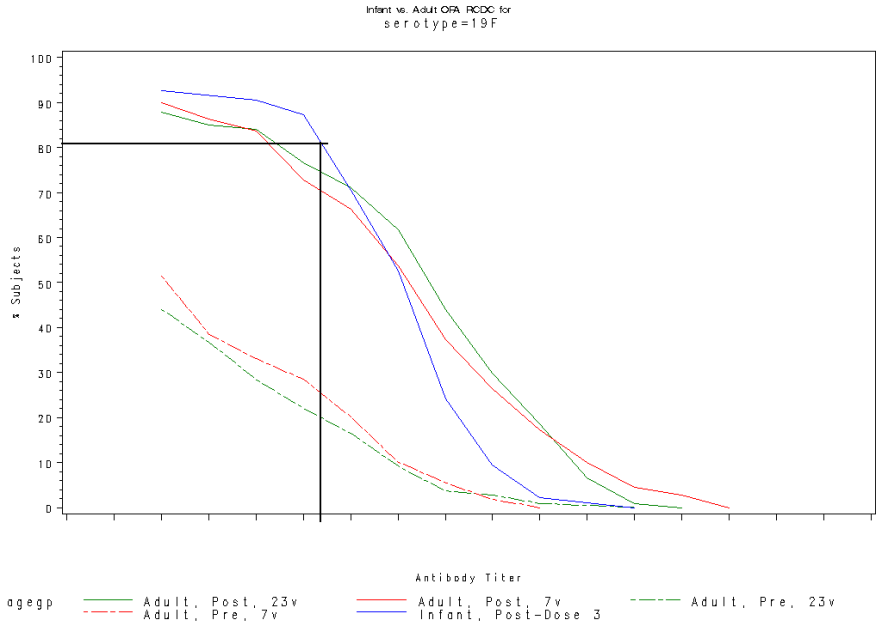
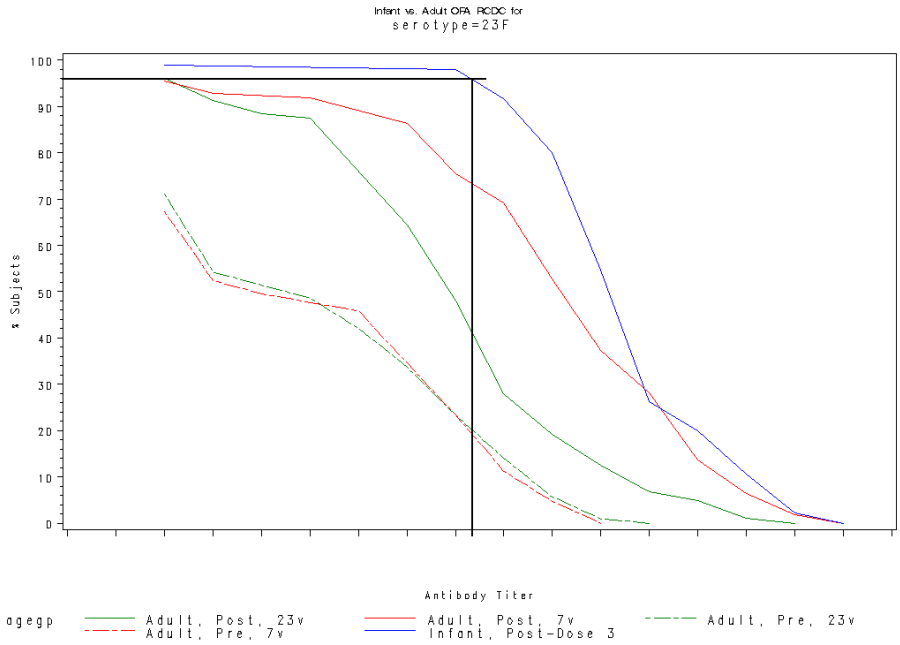


Figure 6.1.1-5: Infant vs. Adult OPA RCDC for Serotype 23F

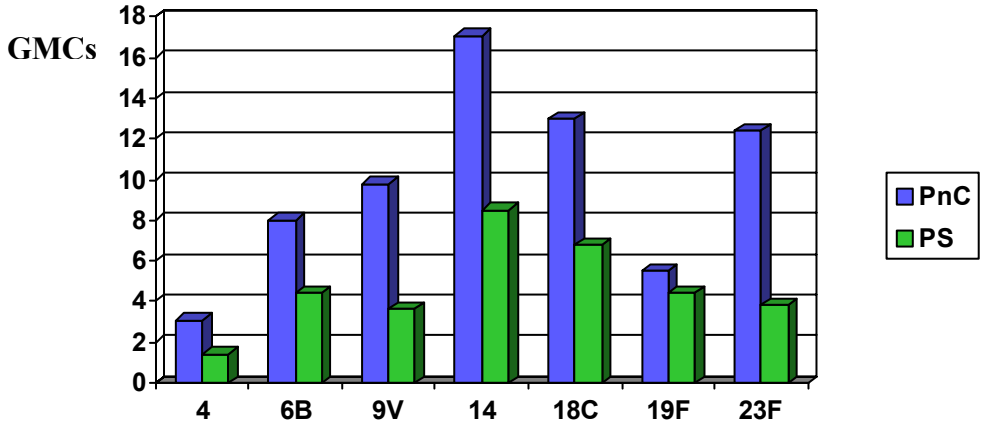


The OPA/ELISA ratio, that is, the functional activity of antibody per ELISA unit, in general, appears to be higher for children and young adults, compared to the elderly. Thus, the ELISA levels that have been established for evaluation of pediatric vaccines are not likely to be appropriate for evaluation of vaccines in the elderly. Until the correlation between ELISA and functional antibody in elderly adults is more completely elucidated, the OPA titer will be the primary assessment variable for demonstration of non-inferiority between the conjugate and polysaccharide vaccines.

6.1.1.2 Geometric Means

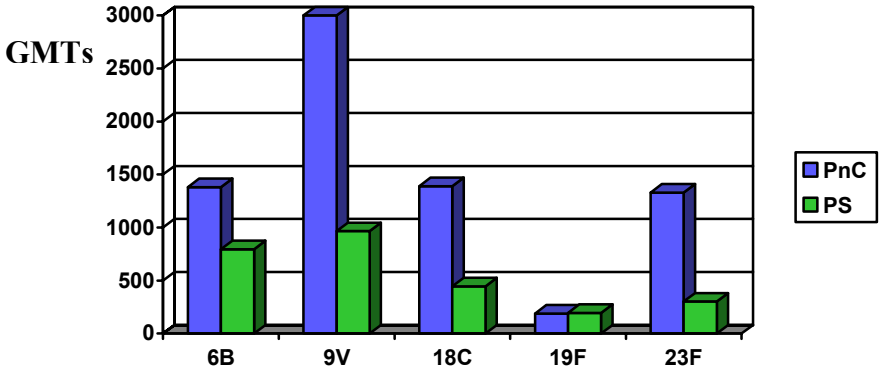
The geometric mean concentrations (GMCs) by ELISA, and geometric mean titers (GMTs) by OPA from the German trial described above are compared in **Figures 6.1.1-6** and **6.1.1-7**. GMCs 1 month after immunization were statistically superior in 7vPnC recipients, compared to 23vPS recipients for all serotypes, except for 19F, which was statistically non-inferior. A similar pattern was seen in the geometric mean titers (GMTs) of opsonophagocytic (OPA) antibody titers 1 month after immunization. . The GMTs measured for 3 of the 5 serotypes (i.e. 9V, 18C, 23F) were statistically significantly higher among recipients of 7vPnC compared to 23vPS.

Figure 6.1.1-6 Year 1: Naïve elderly PnC compared to PS (IgG)



N = 110 PnC, 107 PS
Statistically significant, except 19F (non-inferior)

Figure 6.1.1-7: Year 1: Naïve elderly PnC compared to PS (OPA)



N = 109 PnC, 105-8 PS
Statistically significant: 9V, 18C, 23F

6.2 Second criterion: Lack of hyporesponsiveness, allowing for reimmunization without blunting of the immune response

A second dose of 13vPnC will be compared directly to a first administration of 23vPS to demonstrate, by testing for non-inferiority of the serotypes in common between the two vaccines, that a repeat dose of 13vPnC is as immunogenic as a single dose of 23vPS.

6.2.1 Rationale

Recall that one of the limitations of the polysaccharide vaccine is that it blunts the immune response to subsequent doses, resulting in immune responses that are lower than the response to the first dose of vaccine. This has limited recommendations for use of repeat doses of PS vaccine in practice. Data from Prevnar® studies demonstrate that if 23vPS is given first it blunts the response to a subsequent dose of conjugate vaccine compared to a single dose of conjugate **(Section 6.2.2.1)**. However, when conjugate vaccine is given first, no such blunting is seen; the subsequent dose of 23vPS produces an immune response which is at least as good as a single dose of 23vPS.

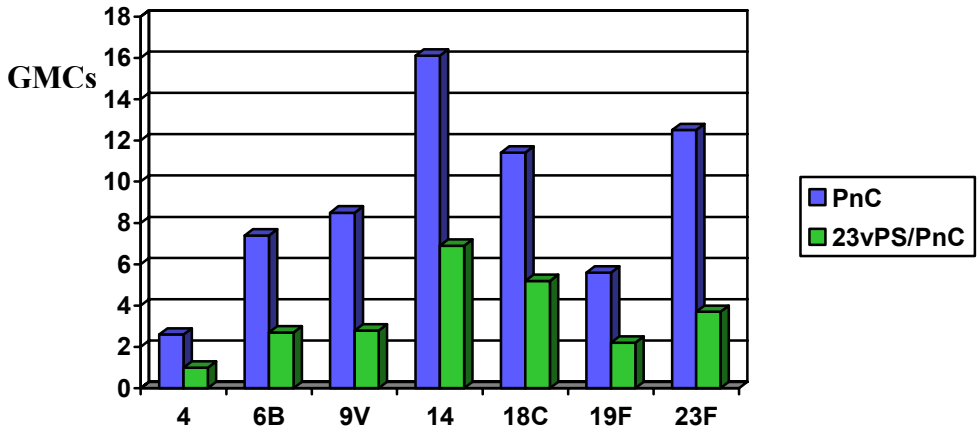
6.2.2 Data from Prevnar® studies

In the previously described German study, subjects who had received 7vPnC were re-randomized one year later, to receive a second dose of either 7vPnC (PnC/PnC group) or 23vPS (PnC/PS group). All subjects who received 23vPS vaccine in the first year received 7vPnC for their second dose (PS/PnC group).

6.2.2.1 Prior PS vaccine suppresses the response to PnC vaccine

Subjects who subsequently received 7vPnC vaccine one year after their 23vPS dose (PS/PnC group) were compared to subjects receiving 23vPS vaccine for the first time. GMCs measured one month after 7vPnC vaccine were significantly lower in subjects who had received 23vPS vaccine 1 year before 7vPnC, compared to those who were naïve to 23vPS at the time of their PnC immunization (**Figure 6.2.2-1)**

Figure 6.2.2-1: Compare 23vPS/PnC to initial dose of PnC (IgG)



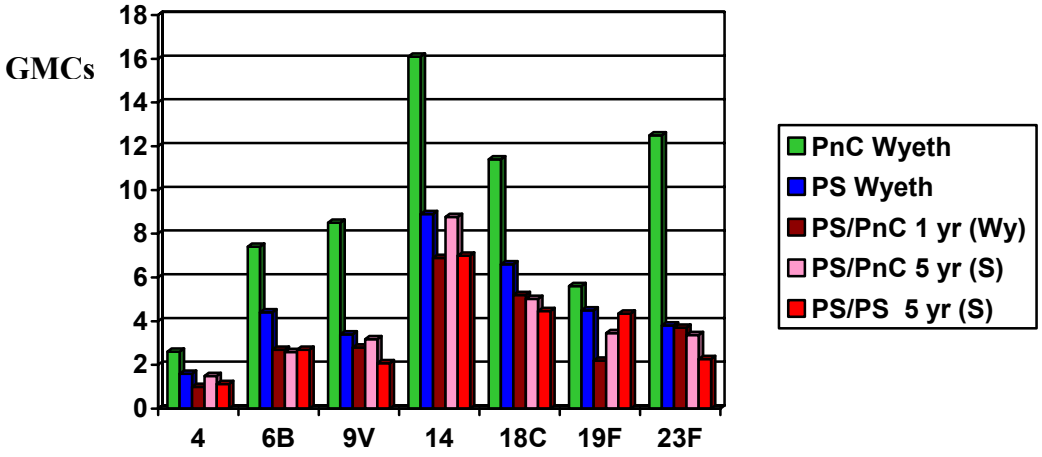
n= 61 PnC; 62 23vPS/PnC
All statistically significant (except type 14)

6.2.2.2 Blunting of the immune response by PS vaccine lasts at least 5 years

In a CDC sponsored study (Seattle study) 88 elderly individuals ≥ 70 years of age who had received PS vaccine at least 5 years previously, were randomized to receive 7vPnC or 23vPS vaccine. Immune responses were measured just before and 1 month after each immunization. (Personnel communications with L. Jackson)

7vPnC vaccine produces higher GMCs in naïve individuals (German study) compared to subjects who had previously received 23vPS vaccine (German study, and Seattle study). The lower response to 7vPnC when given after 23vPS is similar whether the interval after pneumococcal polysaccharide administered was at 1 year (German study) or 5 years (Seattle study). Although data compared across studies must always be interpreted cautiously, these studies were similar with respect to age of subjects; antibody titers between the two laboratories (German study/Wyeth lab; Seattle study/Moon Nahm lab) have previously been shown to correlate well.

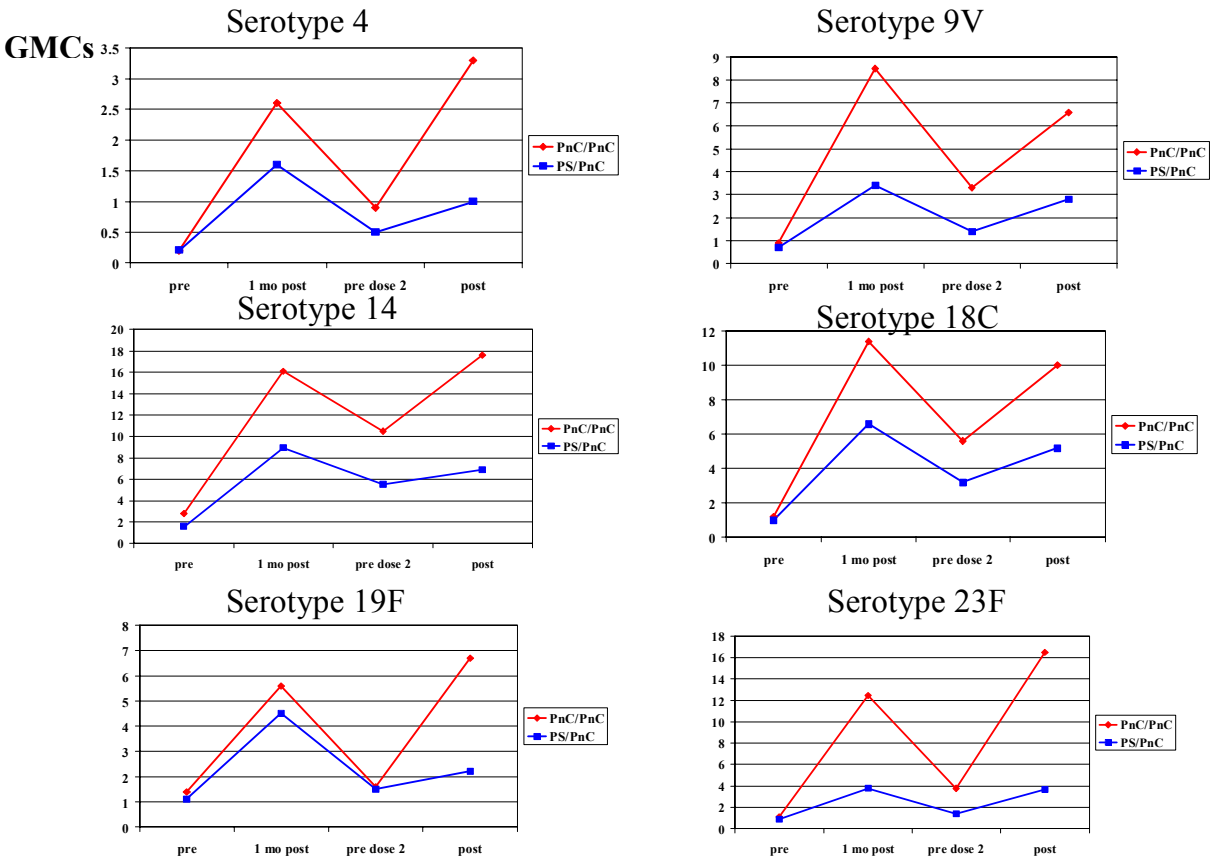
Figure 6.2.2-2: Wyeth and Seattle studies: effect of PS on subsequent PnC or PS dose (IgG)



6.2.2.3 PnC vaccine does not induce hyporesponsiveness (blunting) of the immune response

Subjects who received 7vPnC were given a second dose of PnC one year later (PnC/PnC). GMCs measured one month after the second dose of pneumococcal conjugate vaccine were at least as good, or better than those achieved after the first dose, and significantly higher than antibody levels achieved in subjects who had initially received 23vPS (PS/PnC). Thus, initial administration of a pneumococcal conjugate vaccine allows for reimmunization, if needed.

Figure 6.2.2-3: Comparison of two dosing regimens – PnC following PnC (PnC/PnC) and PnC following PS (PS/PnC)



Note: Ranges on the Y axis varies

7.0 PUBLIC HEATH IMPACT

The 13vPnC vaccine covers fewer serotypes than the 23vPS vaccine, but potentially has the additional benefits of a conjugate vaccine (e.g. lessened risk of induction of hyporesponsiveness with subsequent dosing, and the ability to boost the response with subsequent vaccination). Data from clinical trials with 7vPnC (Prevnar), described in **Section 6.0**, suggest that a conjugate vaccine will, in fact, provide these benefits.

In order to develop an understanding of the public health potential of a conjugate vaccine, Fry and his colleagues at the CDC, developed a model to look at the relative potential public health impact of various conjugate formulations as compared to the currently available 23vPS vaccine in adults >65 years of age [17]. The model, based on IPD cases observed in 1998, incorporates estimates of PS vaccine usage, vaccine efficacy values and duration, and serotype coverage to estimate disease prevented by the 23vPS as currently used. They then estimated the potential impact of lesser valent conjugate vaccines. The authors found a significant benefit of the conjugate vaccines based on the potential for more durable immunity and perhaps higher efficacy.

With input from the CDC, we updated the model using IPD cases observed in 2004 (which have been significantly reduced since 1998). We also expanded the analysis to include the 50 to 64 year old age cohort. We assumed that a 13v conjugate vaccine had the same level of efficacy for the serotypes in the vaccine as the currently available 23vPS vaccine but a longer duration of immunity that could be sustained either through the induction of memory or through re-immunization. In addition, we assumed that an uptake level of 60% vaccination in the population would be achieved, which is comparable to the current estimates for 23vPS coverage in >65 year olds.

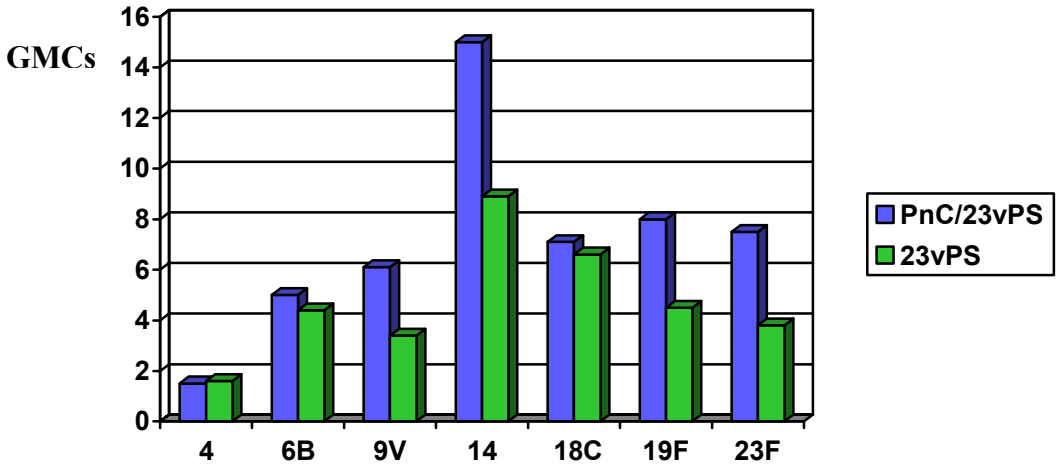
Similar to the original Fry et al estimates, the model predicts that more cases of IPD could be prevented with the 13vPnC vaccine compared to the cases currently prevented with the 23vPS vaccine (5544 vs. 2979). This is due in part to the ability to expand the age of initial vaccination down to 50 years of age without the risk of diminished immune responsiveness later in life and in part due to the ability to maintain immunity as suggested by Fry et al. A more detailed review of the model can be seen in **Appendix 2**.

8.0 POTENTIAL FOR USING POLYSACCHARIDE AFTER CONJUGATE

Although we will be seeking licensure of the 13vPnC vaccine as a stand-alone vaccine, it need not completely replace the use of the 23vPS vaccine. Recommending bodies and physicians may wish to use both vaccines in order to leverage both the benefits of conjugate vaccine and the additional serotype coverage of the 23vPS vaccine, in some or all of their patient populations.

Results from the German study showed that subjects who were initially immunized with 7vPnC and then received 23vPS vaccine one year later, achieved GMCs one month after immunization that were as good as, or in most cases better than, those achieved after 23vPS alone.

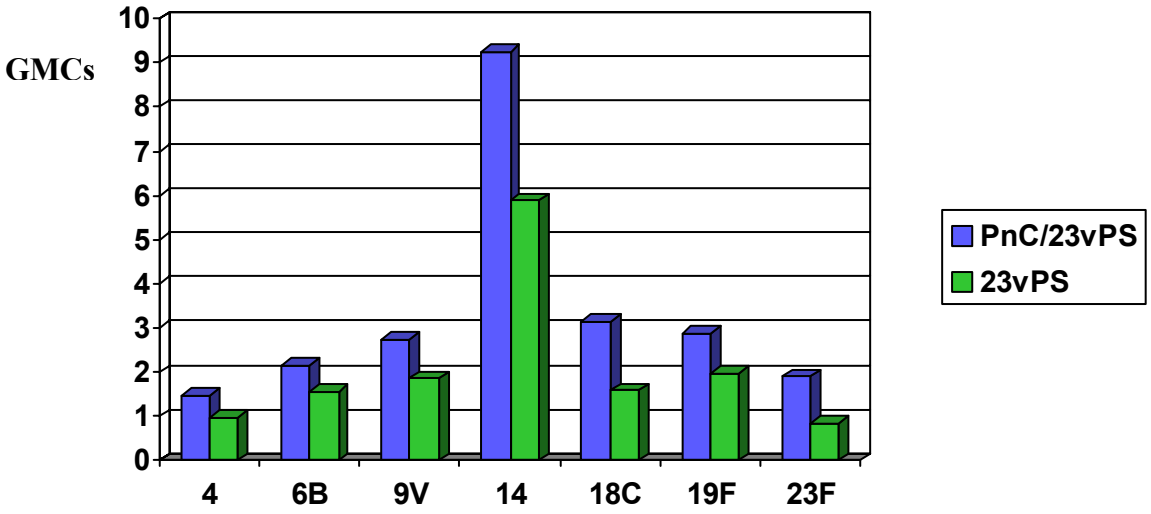
Figure 8.0-1: Healthy Elderly (Wyeth study): 23vPS following PnC (PnC/23vPS) compared to 23vPS alone (IgG)



n=62 PS; 30 PnC/PS
95% CI's all overlap

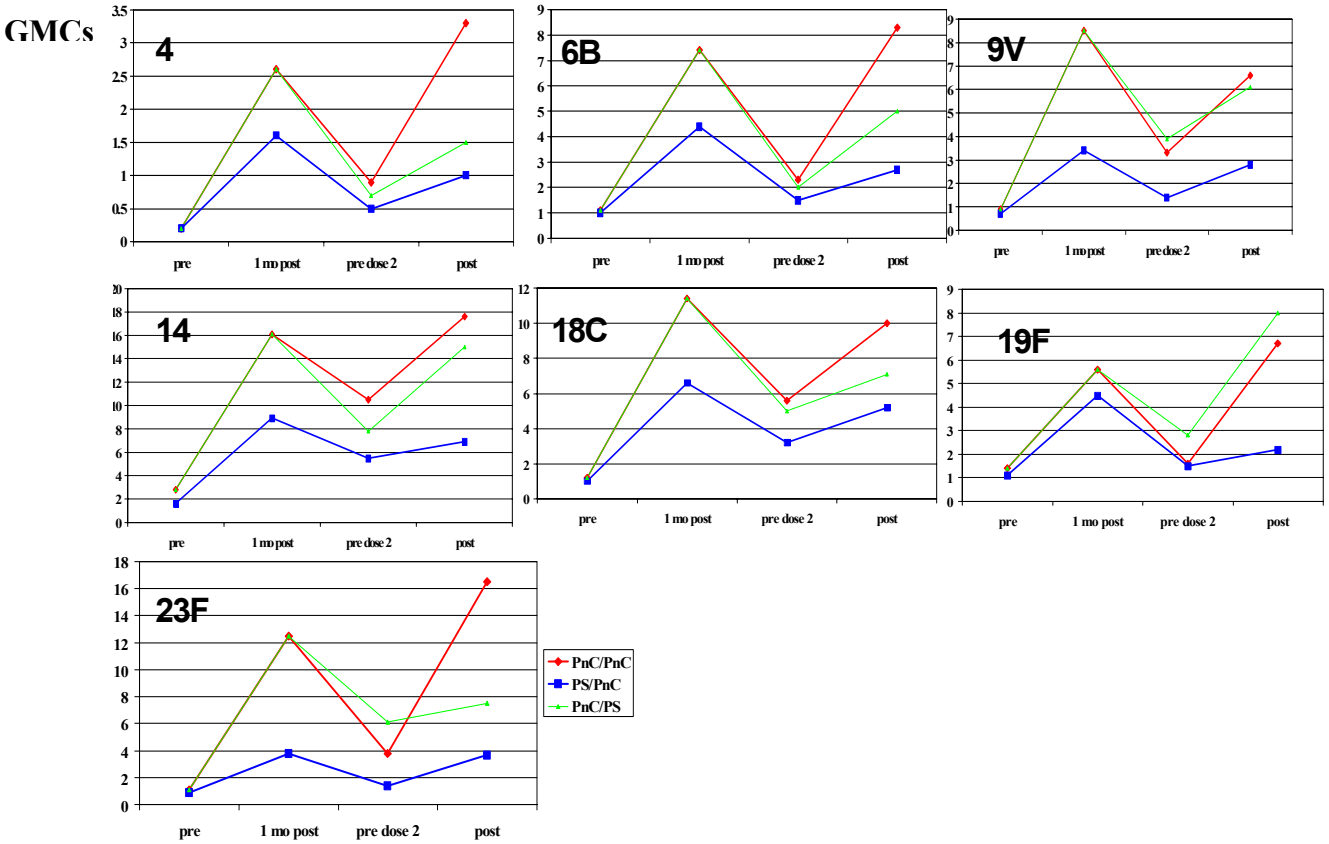
In a ANRS sponsored study, HIV+ individuals ≥ 18 years of age, with no history of 23vPS vaccine within 5 years of study start, were randomized to receive either 23vPS or a regimen of 7vPnC followed by PS 1 month later. Immune responses were measured just before each dose and 1 month after the completion of each regimen. Results from this study showed that subjects immunized with 7vPnC, followed by 23vPS one month later, achieved better antibody GMCs compared to subjects who received only 23vPS.

Figure 8.0-2: HIV+ Study: PnC/23vPS compared to 23vPS alone (IgG)



When both PnC and PS vaccines are to be given, PnC should be given first, to avoid hyporesponsiveness. This was clearly demonstrated in the German study in >70 year olds, shown in **Figure 8.0-3** where previous vaccination with the PS vaccine clearly inhibited the response to a subsequent dose of conjugate vaccine. Hyporesponsiveness, which has been previously noted after multiple doses of polysaccharide, was not seen when the conjugate is given as the priming vaccine dose.

Figure 8.0-3: Comparison of three dosing regimens - PnC following PnC (PnC/PnC), PnC following PS (PS/PnC) and PS following PnC (PnC/PS)



Note: Ranges on the Y axis varies

9.0 CONCLUSIONS

Comparison of immune response to a licensed vaccine is a well-accepted strategy for licensure of a new vaccine for the same indication. The PS vaccine is the standard of practice for protection of elderly and high-risk adults against invasive disease by *Streptococcus pneumoniae.* Thus, licensure of a conjugate vaccine in adults should be based on non-inferiority of the immune response to the licensed polysaccharide vaccine for the serotypes in the conjugate vaccine

The13vPnC has fewer serotypes than the 23vPS vaccine. Therefore, additional benefit beyond non-inferiority of the serotypes included in the 13vPnC should be demonstrated. The most important potential benefit is the duration of protection. The demonstration that re-immunization is possible, without blunting of the immune response, would allow protection to be extended throughout the period of risk, even if the immune response to the first dose is shown to wane over time.

Data with Prevnar® in elderly adults demonstrate that immunization with PnC results in an antibody response that is superior to that produced by PS for most serotypes, and that is non-inferior for the rest. Furthermore, the PnC does not blunt the response to subsequent re-immunization. If the 13vPnC vaccine can be demonstrated to have these attributes, it has the potential to provide a significant public health impact on morbidity and mortality of invasive disease due to *Streptococcus pneumoniae* in the elderly and other high-risk adults.

Thus, we proposed that 13vPnC should be licensed by demonstrating: (1) a functional antibody response that is non-inferior to 23vPS vaccine (2) no blunting of the immune response to subsequent vaccination, and (3) an acceptable safety profile.

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APPENDIX 1 - SAMPLE SIZE CALCULATIONS

1.0 CONSIDERATIONS IN PERFORMING A PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY TRIAL

1.1 The trial must be placebo controlled

The only trial design that can conclusively demonstrate the efficacy of pneumococcal conjugate vaccine in adults is a placebo-controlled trial in which the 23vPS vaccine is not given to either group. Whereas healthy individuals 50-64 year old may be enrolled in a placebo controlled trial, the lower incidence of disease in this age group significantly increases the sample size. Furthermore, efficacy demonstrated in healthy 50-64 year olds may not be applicable to high risk groups.

However use of a placebo is not possible in high risk adults such as individuals greater than 65 years of age and those under 65 years with high risk conditions who are recommended to receive 23vPS.

Current recommendations include Native American adults among the high-risk groups and we have verified that this recommendation is being followed on the Navajo and Apache reservations.

The situation is somewhat different in South Africa, where the 23vPS vaccine, though available, is not generally recommended for adults, because of the concern that inadvertent immunization of HIV (+) adults could be deleterious. A placebo-controlled study may thus be ethically feasible in South Africa.

1.2 The trial must enroll individuals naïve to 23vPS

We have shown that the response to pneumococcal conjugate is 2 to 3 fold lower in individuals who have received 23vPS a year before when compared to naïve individuals. Even if the vaccine had a benefit in previously immunized individuals, this benefit is likely to be lower and therefore more difficult to demonstrate directly. This excludes previously immunized individuals from participating in the trial.

1.3 The trial results must be applicable to the general population

Since we are seeking an indication for relatively immunologically intact individuals, studies in immunocompromised groups such as HIV (+) patients where the immune response is likely to be lower are not pivotal to the indication.

1.4 Sample size calculations

In spite of these constraints we have performed sample size calculations for IPD, which are described below.

2.0 GENERAL POPULATION

The sample size calculation was based on the following assumptions:

- Incidence rate of vaccine type IPD is 25 per 100,000 (high) or 15 per 100,000 (low)
- Note: Most recent CDC estimates (2003) are 18.8/ 100,000, including high risk groups. Northern California Kaiser Permanente (NCKP) incidence is 10.2/ 100,000
- 56% of IPD covered by 13vPnC
- V_E of 70%, 80% or 90% for vaccine type IPD
- 90% power
- Lower 95% confidence interval of >30%
- Trial length of 3 yrs: 1 yr enrollment, 2 yrs mean follow-up

Table 2.0-1: Required Number of Cases

VE	LCI_{95}>	# cases	split	power
90	30	18	15/3	93
80	30	37	28/9	92
70	30	69	49/20	90

Table 2.0-2: Required Number of Subjects Per Group– 2 year Follow Up

		Event Rates (per 100,000)	
		15	25
VE	LCI_{95}>	Subjects per group	
90	30	50,007	30,007
80	30	**93,347**	56,041
70	30	**163,357**	98,024

With incidence rates of 15 and 25 cases per 100,000, 80% vaccine efficacy and a lower confidence interval > 30%, 93,000 and 56,000 individuals, respectively would have to be enrolled to collect 37 cases of IPD with a 28/9 split. If vaccine efficacy is 70% the sample size would even have to be doubled.

This sample size calculation reveals that an efficacy study in the *general population* requires an impractically high number of individuals. Therefore we assessed whether a

trial in a population with a higher incidence of disease would lower the sample size required.

Summarized below, is information provided by Katherine O'Brien and Mathu Santosham (Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD) and Keith Klugman (Rollins School of Public Health, Emory University, Atlanta, GA) on the possibility of running an IPD efficacy study *in high risk populations* such as the Navajo/White Mountain Apache (WMA) population and in Soweto (South Africa). Additionally, Wyeth assessed the option of doing an efficacy trial in the Veterans Administration population.

3.0 NAVAJO/WHITE MOUNTAIN APACHE

3.1 Background

The Navajo Nation consists of about 200,000 members and the WMA tribe consists of about 14,000 enrolled members. Navajo and WMA adults are known to be at high risk of invasive pneumococcal disease and are recommended to receive polysaccharide vaccine before they reach 65 years of age. Active population and laboratory based surveillance for invasive pneumococcal disease has been ongoing in this population since 1988. A community randomized efficacy trial of a 7-valent conjugate pneumococcal vaccine (7vPnC) among children less than 2 years of age was conducted between April 1997 and October 2000. Since October 2000, open label Prevnar has been in routine use among children less than 5 years of age.

3.2 Rate of IPD

The Navajo population has nearly 4 times the rate of pneumococcal disease compared to the general US population. In 40 to 65 year olds the annual rate of IPD is approximately 75/100,000 with about 50% caused by the 13 serotypes in the 13vPnC vaccine. In the over 65 year olds the incidence is about double at 159/100,000 (**Figures 3.2-1, 3.2-2 and Table 3.2-1**). The introduction of Prevnar in infants appears to have had an indirect effect on vaccine type disease in adults, reducing the rate of Prevnar type IPD.

Figure 3.2-1: Rate of all serotype IPD, Navajo adults, 1995-2004

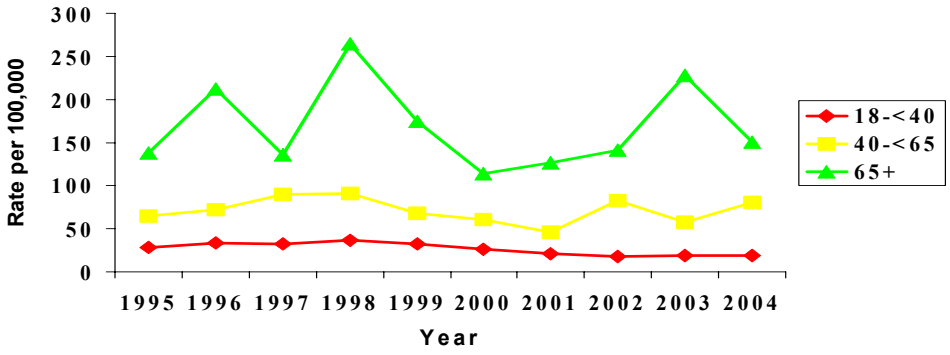

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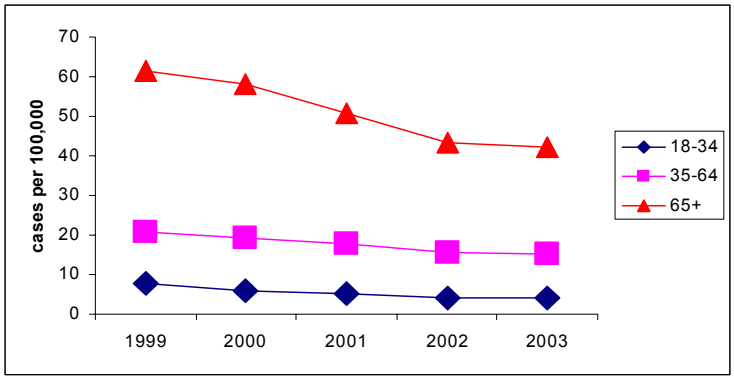
Figure 3.2-2: U.S. Incidence of IPD, by Year and Age Group



Source: CDC, ABCs 15

Table 3.2-1: Rate of disease and case counts by vaccine formulation, Navajo/WMA, 2001-2004

		2001-2004		2004 Only
Age Group	**N Vaccine Type**	**Annual Rate per 100,000***	**Total Cases* (All 4 yrs)**	**Total Cases**
50-<65 y	All	74	81	24
	7	11	13*	1
	13	32	35*	6
65+ y	All	159	103	25
	7	17	11*	1
	13	91	59*	12

* Accounting for the % serotyped

Risk factors

A substantial proportion (20 – 30%) of patient cases have an underlying medical risk factor for IPD (in addition to being Native American). In the 50 – 65 year old age group the most frequent medical risk factor is diabetes mellitus (33%) followed by alcoholism (31%) and renal failure (21%). About 56% of individuals with underlying conditions in this age group are routinely vaccinated with 23vPS, in addition to 70% in the age group >65 years.

3.3 Sample Size Calculations

Wyeth prepared the sample size calculations outlined in **Table 3.4-1** based on the information we received from Katherine O'Brien. The sample size calculations are based on the same assumptions (outlined below) that were used for the sample size calculations in the general population above and include the total population available. The total population in the 50-64 year old age group is between 24,064 and 26,568 (**See Figure 3.4-1**). Sample size calculations for vaccine efficacy of either 70 or 80% exceed the population available.

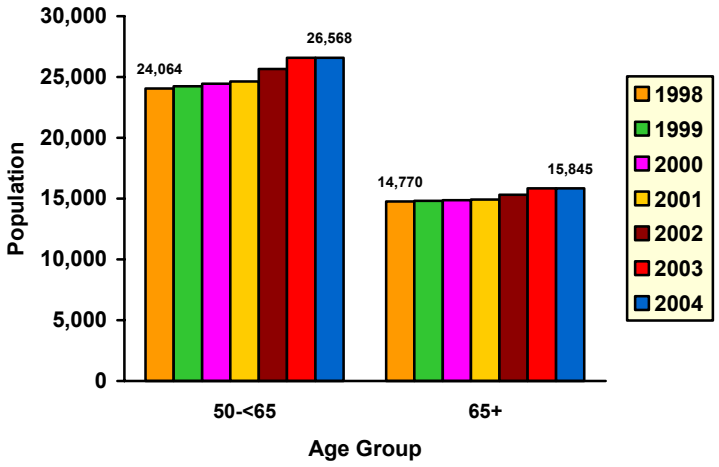
3.3.1 Assumptions for sample size calculations

- Incidence rate of vaccine type IPD is 32 per 100,000 (50-64 years old) or 91 per 100,000 (65+ years old)
- 56% of IPD covered by 13vPnC
- V_E of 70%, 80% or 90% for vaccine type IPD
- 90% power
- Lower 95% confidence interval of $\geq$30%
- Trial length of 3 yrs: 1 yr enrollment, 2 yrs mean follow-up

Table 3.4-1: Required Number of Subjects Per Group

		Event Rates (per 100,000)	
		32 *(50-65y)*	**91 *(65+y)***
VE	**LCI $_{95}$>**	**Subjects per group**	
90	30	20,008	7,040
80	30	36,264	12,761
70	30	61,274	21,562

Figure 3.4-1: Total Population in the 50-64 and 65+ year old age group



3.4 Summary of Navajo Population

- Although the incidence rate for IPD in 50-65 year olds is 3 to 4 times higher than in the general US population, a substantial proportion (20-30%) of the patients have underlying medical risk factors for IPD such as diabetes mellitus, alcoholism or renal failure and are recommended to receive 23vPS vaccine. For ethical reasons these subjects would not be appropriate to be included in a placebo controlled efficacy trial. Indeed, Native American adults without medical risk factors are considered to be at high risk and are all recommended to receive 23vPs vaccine.
- Due to the high use of polysaccharide vaccine in >50 year olds, the number of individuals available to be included in a placebo controlled study is only about half of the total population.
- In this high-risk population, vaccination with a conjugate vaccine would require administration of polysaccharide vaccine as a complement shortly afterwards to broaden serotype coverage. The complementary use of conjugate and polysaccharide vaccine would not allow the efficacy of the conjugate alone to be assessed.
- As a consequence the Navajo population is not large enough to gain a sufficient number of individuals/cases for an efficacy study and, in any event, is not feasible for ethical reasons.

4.0 SOWETO POPULATION

4.1 Background information

The total population in Soweto in 2001 greater than 45 years old was 156,658 with 120,206 in the 45-64 year age group and 36,452 in the > 65 year age group. There is no significant use of 23vPS vaccine in these age groups. Although, there are no exact data on numbers of HIV+ individuals in the population in Soweto, it is estimated at between 1-5%. **Table 4.1-1** shows the number of individuals with bacteremia in 2003/2004 that were HIV+. In 45-64 years olds, 55% of pneumococcal bacteremia occurred in the HIV (+) subgroup.

Table 4.1-1: Number of individuals with bacteremia that were HIV+

Age	Year	Bacteremia #	HIV + #
45 – 64y	2003	69	40
	2004	56	29
>65y	2003	14	0
	2004	12	2

Based on Keith Klugman's information the number of cases of IPD in Soweto in 2004 were 520. The total number of cases covered by 13vPnC serotypes is outlined in **Table 4.1-2**.

Table 4.1-2: Total number of IPD cases covered by 13vPnC

Age Group	Amount Serotyped	# Covered by 13vPnC (%)
45-64	42	38 (90%)
>64	6	4 (67%)

4.2 Sample Size Calculations

Wyeth performed sample size calculations for an IPD efficacy study in healthy 45-64 year olds and >64 year olds based on the information outlined in **Tables 4.1-1, 4.1-2**, (see **Table 4.2.1).** The exact calculations used to determine the incidence rates for each population is outlined below. The sample size calculations are based on the same assumptions outlined above for the Navajo population.
Note that the HIV+ population is only 1-5% of the entire population, so the denominator can be the entire population when estimating incidence rate.

Incidence Rate / 100,000 = 100,000 * (%Coverage)*(Average # healthy bacteremia) / (total population), where %Coverage = (#IPD cases covered by 13vPnC / # IPD cases serotyped)

For 45-64,
Incidence Rate = 100,000*{(38/42)*[(69-40 + 56-29)/2]} / (120,206)
100,000*{(.9047)*[28] / (120,206) = 21.07493

For 65 and older,
Incidence Rate = 100,000*{(4/6)*[(14+12-2)/2]} / (36452)
100,000*{(.667)*[12] / (36452) = 21.9466

Using these incidence rates, 21.1 and 21.9, respectively for 45-64 year olds and 65+ the following sample sizes per group are required:

Table 4.2-1: Required Number of Subjects Per Group

		Event Rates (per 100,000)	
		21.1 *(45-64y)*	**21.9 *(65+y)***
VE	**LCI $_{95}$>**	**Subjects per group**	
90	30	30,339	29,231
80	30	54,990	52,982
70	30	92,915	89,522

4.3 Summary of Soweto Population

Although the Soweto population has a high rate of IPD in the 45 -64 year olds, approximately ½ occurs in HIV+ patients. Wyeth cannot support a trial in immunocompromised groups such as HIV (+) patients, as the results are not relevant to the population we want to study. When the rates of IPD in the HIV+ population are removed from the calculations, the disease rates are similar to those in a healthy US population. Thus the sample size is similar to that presented previously for the general US population and too large to be feasible.

5.0 VETERANS ADMINISTRATION POPULATION

The Veterans Health Administration is the largest integrated health system in the US. A sample size calculation was done to assess whether an efficacy study in naïve, 50-64 year old smokers without other high-risk conditions would be feasible in the VA population. This population would be at high risk for IPD, but would fall outside the current recommendations for PS vaccine, so that a placebo-controlled trial could be considered.

The incidence rate of IPD in healthy individuals aged 50-64 years (before Prevnar launch in infants) is estimated to be 9.9/100,000 [6]. The incidence rate of IPD due to serotypes in 13vPnC would be 5.5/100,000 (multiply by 56%, 13vPnC serotype coverage). The risk of IPD in smokers is approximately 4 fold higher [4], which calculates to an estimated incidence rate of 22.2/100,000. With this incidence rate the sample size required is in the same range as described for the previous populations.

Table 5.0-1: Required Number of Subjects Per Group

		Event Rate (per 100,00)
		22.2
VE	**LCI $_{95}$>**	**Subjects per group**
90	30	54,126
80	30	101,038
70	30	176,816

The rate information in Kyaw et al [6] is not adjusted for smoking. So to the extent that there were smokers among the healthy individuals, multiplying by 4 should give a value that is an overestimate of incidence. In addition, the incidence doesn't take into account herd immunity post introduction of Prevnar into the pediatric schedule. For both these reasons, the true incidence rate is likely to be less than estimated here, requiring an even higher sample size.

APPENDIX 2 - PUBLIC HEALTH MODEL: A COMPARISON OF 13VPNC AND 23VPS VACCINES

In order to develop an understanding of the public health potential of a conjugate vaccine, we have modeled this information for our 13vPnC vaccine and for the 23vPS vaccine, using methodology described by the CDC[17].
The first step in this analysis is to estimate the "base case", that is, the number of cases of IPD that would have been observed in the absence of either vaccine. Fry et al used a model based on IPD cases observed in 1998, and incorporating estimates of PS vaccine usage, efficacy amount and duration, and serotype coverage to arrive at this estimate[17].
We used the base case figures provided by Fry, with the following changes:

1. Figures were adjusted downwards by the % decrease in observed IPD incidence between 1998 and 2004 to account for the decline in adult IPD with the licensure of Prevnar in children. (Cases in 65-79 year age group were adjusted downward by 35%, those in 80+ years olds by 39%). (ABC surveillance, 1998-2004)
2. Data on 50-64 year olds were not available from Fry. The total number of cases in this age group was calculated using 2004 incidence and population figures for this age group (ABC surveillance, 2004www.cdc.gov/abcs; US census population figures, 2004).
    a) The % of cases of IPD occurring in immunocompromised, immunocompetent high-risk and healthy individuals was estimated to be 27%, 56%, 17%, respectively (2004 data, personal communication, C. Whitney)
    b) To calculate the number of cases expected in the absence of PS use we applied the Fry methodology, using the following assumptions:
        - 42.6% vaccine usage in immuncompetent high risk [18]
        - 0% vaccine usage in immunocompetent healthy
        - 88% efficacy in immunocompetent high-risk
        - 0% efficacy in immunocompromised
        - Efficacy declines from 88% to 75% to 62% over 15 year period [7]
        - 75% serotype coverage (ABC surveillance, 2003)

Base Case 2004 (no vaccination)

Age	Immunocomp	High-risk	Healthy	Total
50-54	607	1751	382	2740
55-59	607	1656	382	2645
60-64	607	1570	382	2559
65-69	540	3060	-	3600
70-74	413	2343	-	2756
75-79	535	3031	-	3566
80+	740	4193	-	4933

Using the amended base case figures, we applied the following assumptions to allow a direct comparison of 13vPnC with 23vPS:

Table Assumptions

Parameter	**PnC**	**PS**	**Reference**
Vaccine usage	60%	60% (age65 +) 42.6% (age 50-64, high risk) 0% (age 50-64, healthy)	NHIS 2004 MMWR 2004[18]
Vaccine efficacy (immunocompetent)	88%	88%	Shapiro (NEJM, 1991) [7]
Efficacy over time	Efficacy maintained At 88%	50-64: 88% to 75% to 62% each 5 year period. 65+ loses half of efficacy each 5 year period 1-5 y 80% (65-69) 6-10 y 40% (70-74) 11-15 y 20% (75-79) >15 y 0% (80+)	PnC: efficacy is maintained, reimmunization is necessary PS: Fry[17], Shapiro[7]
Vaccine efficacy (immunosuppressed)	none	none	per Fry[17]
Vaccine serotype coverage	56%	75%	CDC data 2003

Applying these assumptions to the base case (i.e. estimated IPD cases in 2004 without use of PS vaccine) gives the following numbers of cases prevented in each age group.

Subjects per group

Age	**No of Cases (Base)**	**Cases Prevented (PS)**	**Cases Prevented (PnC)**	**Deaths Prevented (PS)**	**Deaths Prevented (PnC)**
50-64 high risk healthy total	7944	1183 0 1183	1472 339 1811	204 0 204	253 27 280
65-69	3600	1102	905	175	144
70-74	2756	422	693	67	110
75-79	3566	273	896	43	142
80+	4933	0	1239	0	218
Subtotal 65+	***14,855***	***1797***	***3733***	***285***	***614***
Total	**22,799**	**2979**	**5544**	**489**	**895**

For all age groups but one, a PnC regimen has a clear advantage in cases of IPD and deaths averted, compared to the polysaccharide vaccine. The increased serotype coverage of the 23vPS vaccine provides an advantage in the 65-69 year old age group only. Overall, 13vPnC has the potential for prevention of substantially more cases and deaths compared to 23vPS.