Protection of adults from invasive pneumococcal disease (IPD) by means of active immunization with currently licensed vaccine PNEUMOVAX 23™ (PPV23)

Introduction

In spite of many advances in the prevention and treatment of infectious diseases over the past 30 years, in particular the use of effective antibiotics, and the availability of preventive vaccine, invasive pneumococcal disease (IPD) remains an important cause of morbidity and mortality. This is especially true for the very young (two years of age or younger) and the elderly (65 years of age and older). In the younger population, sepsis without a known primary focus, and meningitis predominate; whereas, pneumonia with bacteremia remains the most important pneumococcal disease of the elderly. Furthermore, there is a substantial proportion of persons who are at higher risk of IPD than the general population, and who fall in between these age extremes.

1. Capsular polysaccharide vaccines

Vaccines against *Streptococcus pneumoniae* have been studied since before WWI. Two 6-valent vaccines available after WWII did not find sufficient use to keep them on the market. Thirty years later, the license to manufacture and the approval to market such a vaccine were based on a clinical efficacy study of healthy, young gold miners with a high incidence of bacteremic pneumococcal pneumonia and in whom a 6-valent vaccine was shown to be protective. Subsequently, antibody responses were shown to 8 additional capsular serotypes and the first modern pneumococcal vaccines were licensed in the US in 1977, as a 14-valent formulation, and then in 1983, as a 23-valent formulation. In order to fully appreciate the difficulties of providing vaccines against IPD, it is essential to remember that each polysaccharide serotype must be independently validated, scaled-up, and manufactured. Furthermore, some serotypes are easily produced on a large scale, and others are much more difficult. Thus a 23-valent vaccine (PPV23) is really a formulation of 23 independent polysaccharide vaccines. Each multivalent conjugate must be made with 7, 9 or 11 different isolated polysaccharides, and the same number of conjugations must be performed before final formulation.

PPV23, containing 25 µg of each capsular polysaccharide from 23 different serotypes, is T-cell independent, and, therefore, not thought to induce memory. The antibody produced allows polymorphonuclear leukocytes and macrophages to phagocytose and kill pneumococcal organisms carrying the particular capsular type to which the antibody is directed. Antibodies against individual polysaccharides may be measured by a non-functional test such as EIA (enzyme-linked immunoassay), or by functional tests of opsonizing and killing ability known as the opsonophagocytosis (OPK) assay. Peak immunogenicity of PPV23 occurs from 4-6 weeks after immunization [Artz 2003]. An important point is that the level of antibody to prevent IPD is not known, in contrast to the case for *Haemophilus* type b protection from induced antibody, [Long 2005].

One 23-valent formulation is available as PNEUMOVAX-23 (PPV23). This is approved for use in persons over 50 years of age, but also recommended for persons down to the

age of 2 years who might have particular problems with resisting infection or disease caused by encapsulated organisms. The ACIP had recommended routine use of a single dose of PPV23 in all persons 65 years of age or older.

A strong rationale exists for the use of PPV23 from age 50. PPV23 is generally well tolerated; most reactions are local, self-limited and require no treatment. In patients who are given PPV23, it has an aggregate effectiveness rate from 80%-50% for the prevention of IPD in the elderly [Fedson 1999]. However, the proportion of the elderly who actually take this vaccine is disappointing, in the range of 64% [Fedson 1999], and improved utilization would impact disease incidence.

Furthermore, the subpopulation in the US at higher risk for IPD (i.e., smokers, African Americans, Native Americans, Alaskan Americans, and patients with chronic pulmonary disease) is significant. An age based approach at 50 years would prevent more cases in these populations as compared with the ≥65 year age time point. Also, given the current recommendations for administration of influenza vaccine at 50 years, PPV23 vaccination at 50 years would be logistically feasible [Fedson 1999].

Following a favorable cost-benefit analysis of PPV23 vaccination in persons 65 years of age and older [Sisk 1999] , a similar analysis of the use of PPV23 in persons from 50 -64 years supported the use of PPV23 in the 50 year age group as well [Sisk 2003]. Finally, the recognition that many strains of pneumococci have acquired resistance to available antibiotics makes presumptive or definitive treatment of IPD more difficult and the outcomes less predictable [Whitney 2000] and supports a broader use of prevention.

1.1 Effects of PPV23 on epidemiology of nasopharyngeal carriage

Studies have not demonstrated changes in the nasopharyngeal carriage of resident serotypes of pneumococcus in children after the use of the 14-valent formulation [Herva 1980]. The expectation is that this would hold true for the 23 valent formulation.

1.2 Duration of protection- Need for revaccination

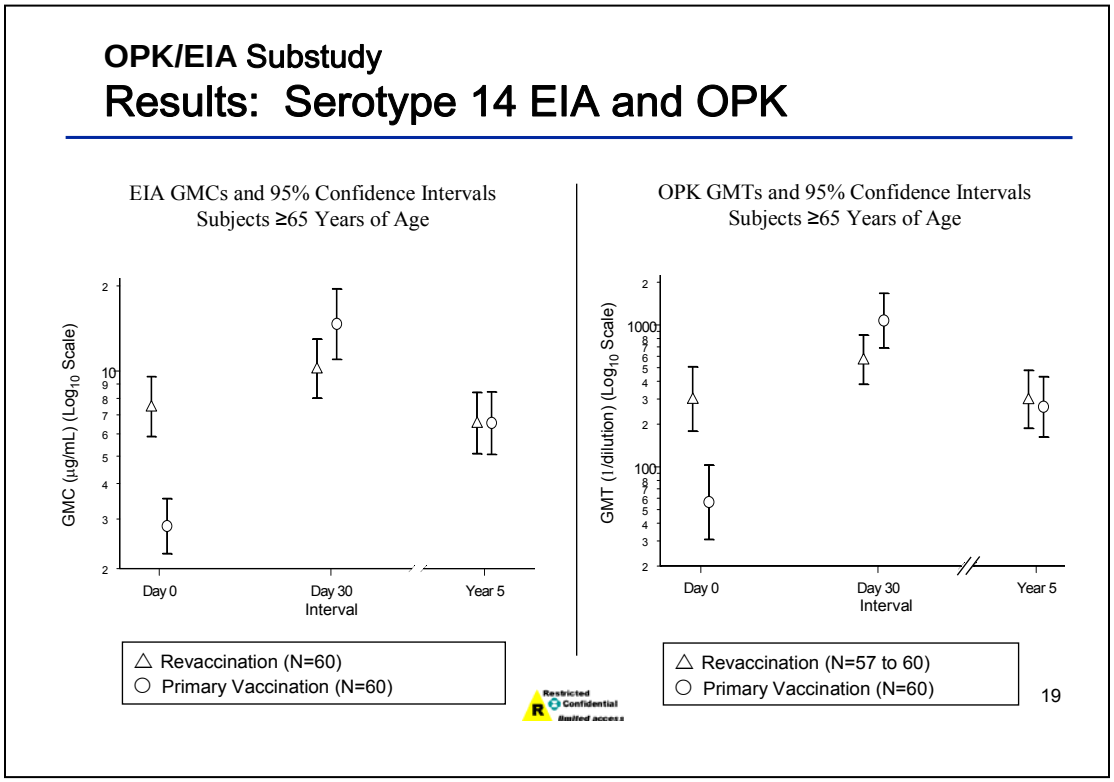
Levels of protective antibody are expected to wane. Estimates vary from study to study. Antibody levels are predicted to fall to pre-vaccination levels in 3 to 8 years [Artz 2003].

1.3 Revaccination

With the gradual fall of antibody levels, a concern exists that protective efficacy will also fall. This raises the question of the potential need for revaccination [Whitney 2001]. Merck Research Labs, therefore, undertook a study of revaccination with PPV23, referred to as Study 007.

This was a randomized, double-blind, crossover study of the safety and immunogenicity of PPV23 comparing the responses of first-time vaccinees to those of revaccinees, and compared by age groups 65 and older vs. those 50-64 years of age. Overall rates of local and systemic reactions were similar for vaccinated [first time] and revaccinated persons. [Musher 2000]. A planned substudy compared antibodies to selected capsular serotypes by EIA and OPK assay.

Because there is no proven laboratory surrogate marker for clinical effectiveness, efforts have focused on measuring the functional humoral immune response. The OPK assay may be a better marker than others as a measure of potential protection because it measures antibody that binds and triggers phagocytosis [Artz 2003]. The following section gives the immunogenicity results from one serotype to illustrate that:
[1] there is general concordance of the responses of the EIA and OPK test
[2] the baseline level of antibodies was higher in revaccinees,
[3] both first time and revaccinees had good responses to PPV23, and
[4] by year 5, the levels of both antibodies in the first time vaccinees and re-vaccinees had returned to or near baseline. [data on file at MRL].



OPK/EIA Substudy
Results Summary:
<u>For all 4 serotypes, by EIA:</u>
[1] Results of subset are similar to the results of full study population
[2] Revaccination subjects had higher Day 0 GMCs than primary vaccination subjects
[3] GMCs increased following revaccination and primary vaccination
[4] Day 30 GMCs were similar for the two study groups, and slightly lower following revaccination for 2 serotypes

<u>For all 3 serotypes, by OPK</u>
[1] Revaccination subjects had higher Day 0 GMCs than primary vaccination subjects

[2] GMCs increased following both revaccination and primary vaccination
[3] Day 30 GMCs were slightly lower following revaccination than primary vaccination, but this was not statistically significant

Overall Immunogenicity and Safety Conclusions

In adults 50 years of age or older who received a single injection of PNEUMOVAX™ 23 either as a revaccination after receiving a previous dose of 23-valent pneumococcal polysaccharide vaccination at least 3 to 5 years prior to this study, or as a primary vaccination, the following conclusions can be made:

Immunogenicity:

1. Revaccination with PPV23 in adults ≥65 years of age who had been vaccinated 3 to 5 years previously with a 23-valent pneumococcal polysaccharide vaccine is immunogenic.
2. Revaccination with PPV23 in adults 50 to 64 years of age who had been vaccinated at least 3 years previously with a 23-valent pneumococcal polysaccharide vaccine is immunogenic.
3. As expected, the immunogenicity of vaccination (both primary and revaccination) with PPV23 is generally more robust in subjects with lower preexisting antibody levels than in subjects with higher preexisting antibody levels.
4. The overall kinetic profiles of revaccination vs. primary groups are comparable, indicating that revaccination should provide effectiveness that is similar to that from primary vaccination.

Safety:

1. Adults ≥65 years of age have a higher incidence of injection-site moderate pain, severe pain, and/or large induration following revaccination with PPV23 than following primary vaccination with PPV23.
2. The rate of overall local adverse experiences PPV23 was higher among revaccination subjects ≥65 years of age than among primary vaccination subjects ≥65 years of age.
3. Following a dose of PPV23, the rate of overall systemic adverse experiences was similar among revaccination subjects ≥65 than among primary vaccination subjects ≥65
4. Adults 50-64 years of age have a higher incidence of injection-site moderate pain, severe pain, and/or large induration following revaccination with PPV23 than following primary vaccination with PPV23.
5. The rate of overall local and systemic systemic adverse experiences PPV23 was similar among revaccination subjects 50-64 years of age and primary vaccination subjects 50-64 years of age.

Others studies have demonstrated the safety of revaccination with PPV23 [Jackson 1999, Jackson 2005, Walker 2005] and commented on the need for more information on the effectiveness of a PPV23 when given as a second dose [Whitney 2005].

1.4. Summary: PPV23 Vaccination and Revaccination

Studies have demonstrated the effectiveness, safety, and immunogenicity of vaccination with PPV23, as well as the potential need and utility of revaccination with PPV23. Because the mechanism of protection from IPD is related to the ability to mount a response of functional anticapsular antibody, the correspondence between EIA levels and OPK levels support the use of EIA to evaluate serotype-specific protection. Public Health officials have argued convincingly for the broad use of PPV23, as well as for revaccination. PPV23 is not recommended in persons under two years old, and may not induce antibody responses in persons with immune deficiency such as HIV-AIDS, or post splenectomy.

2. PCV7 in adults

2.1 Known effects of PCV7 in children

Both direct [i.e., in vaccinees] and indirect [in nonvaccinees] effects were demonstrated:
[1] There has been a dramatic decrease in the incidence of IPD caused by vaccine types in the pediatric population [Anon. 2005, Black 2000].
[2] There was an increase in the number of cases of IPD in non-vaccinees calculated to have been prevented after the use of PCV7, most of that benefit occurring in the populations under 5 years and 65 years or older. This has been attributed to herd immunity [Whitney 2003; O'Brien 2003].
[3] A similar effect was recorded in the incidence of IPD due to vaccine-type pneumococci in the unvaccinated population who associate with vaccinees [Whitney 2003; O'Brien 2003].

A study from a large health care system identified all cases of pneumococcal IPD in children from 1996 -2003, and then identified the serogroups causing IPD in the affiliated children's hospital center from the early post-vaccine [PCV7] use period, 2001-2003 [Byington 2005]. They found significant decreases in the proportion of cases caused both by serogroups represented in the vaccine, as well as by antibiotic-resistant serogroups. At the same time, there was an increase in the proportion of cases of severe IPD and empyema, caused by non-vaccine serogroups. In the same study, the children who did develop IPD with the non-vaccine-type serotypes had more severe disease than those with vaccine-type disease [Whitney 2003; O'Brien 2003].

2.2 Known effects of PCV7 in adults

A preliminary report, [Kuhnke 2004] indicates that adults 70 years of age or older appear to have responded to the 2 μg dose of PCV7. The OPA responses after that vaccine for 3 serotypes tested were higher than for the PPV23; similarly, the responses measured by enzyme linked immunoassay were greater for PCV7 than they were for PPV23.

[1] There has been a decline in hospitalizations for IPD in the US elderly [McBean 2005] temporally related to the increase in the use of PCV7.
[2] The incidence of IPD caused by the 16 serotypes in PPV23, but not in the PCV7 vaccine in persons 5 years of age and older rose 11% between 1998-99 and 2003 [Anon 2005].

[3] The incidence of IPD caused by all the serotypes not in the PCV7 among children 5 or younger and 40 or older rose significantly in the same time period [Anon. 2005].

2.3 Special considerations for use of a conjugate vaccine in adults

[1] Changes in nasopharyngeal carriage have been documented in animal models [Lipsitch 2000]; such changes have also been shown in humans both with respect to antibiotic resistance and to patterns of serotype resistance that have occurred since the introduction of PCV7 to the pediatric population [Huang 2005]. If our understanding of the mechanism of herd immunity is correct, then we may expect changes in nasopharyngeal carriage in the contacts of these vaccinated children (both children and adults).

[2] Increase in IPD due to non-vaccine serotypes has already been described [Anon. 2005]. Studies monitoring for changes in nasopharyngeal flora and the incidence of IPD by serotype are essential to understand this issue more fully.

2.4 Conclusions

[1] Although the putative mechanism for protection from infection and disease caused by encapsulated bacteria has been understood since the 1930's, if not before, and a vaccine effective in the elderly has been available since 1983, there has been inadequate use of the vaccine, and IPD continues to be an important cause of morbidity and mortality in the very young and the elderly.

[2] Public Health measures to increase higher uptake of adult vaccines need to be developed.

[3] Revaccination with PPV23 has been demonstrated to be safe and to stimulate antibodies to the vaccine serotypes included.

[4] Enormous progress in the prevention of pediatric IPD caused by the most common pediatric serotypes has been made with the widespread use of the conjugate vaccine.

[5] There have been substantial indirect benefits in terms of less vaccine-type disease in people who associate with PCV7 vaccinees. Unpredicted, unfavorable changes in disease patterns due to non-vaccine types have occurred; the cause of which is undefined. One possibility would be an increased attack rate from children to adults by non-PCV7 serotypes.

[6] Pneumococci in the normal flora are a mixed blessing: they appear to be the stimulus for the formation of protective antibody, and also the source of IPD for most patients.

[7] There is poor understanding of what factors control the rates of carriage of PN serotypes, of what strains tend to dominate and why, and what will be the long-term consequences of changing the nasopharyngeal flora by vaccination with conjugated PN vaccines.

[8] Antibiotic resistant pneumococci are increasing in prevalence in some areas and this should stimulate more use of available vaccines.

[9] The major question needing to be addressed at this time is "What can we do to assure that adults and children receive/continue to receive optimum protection against IPD?"

The complicated nature of the interaction of humans and pneumococci is not well understood; the optimal approach to adult vaccination will depend on answers to the following:

[1] What is the cause of the increased rate of non-PCV7 serotypes found in adults in recent years?
[2] Can the conjugate vaccines add to the current means to provide protective efficacy against IPD in adults?
[3] What is the level of specific antibody that correlates with protection?
[4] Is there general agreement on which test is the best surrogate marker for protective efficacy?

Glossary of abbreviations used:

PN	Pneumococcus
PCV7	Pneumococcal conjugate vaccine
PPV23, [Pneumovax 23], PPV23	23 valent capsular polysaccharide vaccine
IPD	Invasive pneumococcal disease
NP	Nasopharyngeal
OPA	Opsonophagocytic activity
OPK	Opsonophagocytic killing

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