

## UNIT NO. 5

## PNEUMOCOCCAL VACCINATION IN ADULTS

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**ABSTRACT**

**Pneumococcus is the most common cause of community acquired pneumonia (CAP) accounting for 19-25% of all cases. The incidence of CAP increases with age and so does the morbidity and mortality. Hospitalization rates for CAP in the elderly (>65 years) have been reported to range from 31-78%. The increase in the elderly population globally and in Singapore makes intervention in reducing pneumococcal disease an important priority. At this time, pneumococcal disease is potentially the leading cause of vaccine preventable disease in man. Researchers focused on the improving the immunogenicity by using a protein conjugate to prime the immune system and to induce longer lasting memory.**

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**INTRODUCTION**

*Streptococcus pneumoniae* (pneumococcus) is an important cause of morbidity and mortality worldwide. The infection causes a wide spectrum of illness and disease burden is heaviest at the extremes of ages (those less than 5 years and those older than 65 years). Disease due to pneumococcus is divided into invasive and non-invasive forms. Pneumococcus often resides in the nasopharynx reservoir and can spread to the surrounding mucosal tissue causing acute otitis media, sinusitis and pneumonia. This is termed as "non-invasive" disease. When the infection spreads into the blood stream causing bacteraemia, meningitis and bacteraemic pneumonia; this is termed as invasive pneumococcal disease (IPD).

Pneumococcus is the most common cause of community acquired pneumonia (CAP) accounting for 19-25% of all cases. The incidence of CAP increases with age and so does the morbidity and mortality. Hospitalization rates for CAP in the elderly (>65 years) have been reported to range from 31-78%. The increase in the elderly population globally and in Singapore makes intervention in reducing pneumococcal disease an important priority.

In the past, we had focused primarily on treatment of the infection which in turn reduces the consequences of the illness and infection. However it is important to point out that treatment has little impact on the disease burden and prolific antibiotic usage has resulted in antibiotic resistance. Penicillin resistant pneumococcus has become a well recognized and well characterized global problem. In Singapore, reports of penicillin non-susceptibility in pneumococcus has been placed in the region of 30% and higher.

Preventive efforts have thus focused on vaccines. At this time, pneumococcal disease is potentially the leading cause of vaccine preventable disease in man. It is important to state from the outset that there are more than 90 serotypes that have been described that can cause disease in man. To further complicate vaccine development, these serotypes differ in chemical composition, immunogenicity and have differing epidemiological impact on different patient populations. A 14 valent pneumococcal polysaccharide vaccine was licensed in 1977 but this was soon superseded by the 23 valent vaccine which was licensed in 1983. This 23 valent pneumococcal polysaccharide vaccine (PPV 23) that is familiar to us for use in adults has been available more than 25 years globally. It was licensed for use in the elderly and high risk patients with underlying medical conditions like asplenia, alcoholism, chronic metabolic, heart and lung conditions. However, the benefits associated with PPV 23 use have been controversial. Further discussion on PPV will follow.

Researchers focused on the improving the immunogenicity by using a protein conjugate to prime the immune system and to induce longer lasting memory. The era of pneumococcal conjugate vaccine (PCV) started with the licensing of a 7 valent vaccine called Prevnar or PCV-7 by Wyeth in 2000. This was used in infants and young children less than 5 years. Surveillance of pneumococcal disease several years later revealed a marked reduction in IPD caused by the vaccine strains not only in the pediatric age group but also in other age groups. This will be described in greater detail below. 10 and 13 valent PCV have been licensed in several countries. The 10 valent PCV (Synflorix) was recently registered in Singapore and has become available for local prescription in April 2010. The PCV 13 Prevnar has been registered in the United States in March 2010 and will replace PCV7 in the childhood immunization schedule. PCV 13 is likely to be registered in Singapore after the third quarter of this year.

**USE OF PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV 23)**

PPV 23 contains 25ug of each of the 23 pneumococcal polysaccharide antigens (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). These 23 serotypes account for 85-90% of invasive pneumococcal infections in the US. In a recent review of IPD in a Singapore tertiary hospital, 82.8% of the pneumococcal isolates causing IPD would have been covered by the PPV23 serotypes.

PPV 23 induces antibody to the capsular polysaccharides but does not produce a T cell mediated or memory response. The former is measured by geometric mean titer (GMT) and the latter by opsonophagocytic activity (OPA). The vaccine is given intramuscularly or subcutaneously as a single 0.5ml dose to the

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deltoid region. Adverse reactions to PPV 23 are predominantly local. Up to 30-30% of recipients experience local pain, swelling and erythema that usually lasts for less than 48 hours. Systemic reactions such as fever or myalgia occur in fewer than 1% of PPV 23 recipients. There are two PPV23 registered in Singapore; Pneumo 23™ by Sanofi Pasteur and Pneumovax 23™ by MSD (see below).

**CONTROVERSIES ON THE 23 VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV)**

The PPV23 is currently recommended for high risk patients and the general elderly population. PPV23 offers high serotype coverage but is poorly immunogenic in some individuals. Whilst PPV has the potential to prevent disease and death, the degree of protection afforded against various clinical endpoints and within different populations is uncertain. Various “analyses” have been conducted to shed light on this but the results have been far from conclusive and continue to be debated in the medical literature. In fact, the number of reviews, systematic reviews, meta-analyses and reviews of meta-analyses of pneumococcal vaccination may soon exceed the number of relevant studies themselves. In essence, most of the observational studies found that PPV23 was beneficial, although the estimates of its efficacy vary widely. On the flip side, the clinical trials as a group have been inconclusive in demonstrating a significant benefit of PPV23 in the elderly. These clinical trials have been criticized as lacking sufficient power to demonstrate moderate but clinically relevant protective effects against pneumonia and IPD. However, it would be appropriate to mention that most experts agree that the benefits of PPV23 against “all cause pneumonia” and “all cause mortality” are unclear. Recent studies indicate significant protective effects in reducing the risk and severity of IPD in vaccinated elderly patients. It is estimated to provide approximately 60% protection against invasive disease in the general elderly population. This protective benefit against IPD has made PPV23 “cost-effective” when used in persons >65 years of age and in high risk groups.

Hsu et al reviewed pneumococcal isolates causing IPD in 192 adult patients at Singapore General Hospital from 2000-2007. The median age group of this study population was 64 years with age ranging from 14-96. 82.8% of the isolates causing IPD in

this study were covered by PPV23 and none of the patients had received prior PPV23. The authors suggest that appropriate use of PPV23 may result in a decrease in deaths caused by pneumococci in Singapore adults.

**IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE IN CHILDREN AND ADULTS**

Pneumovax (7 valent) pneumococcal conjugate vaccine (PCV7) was first licensed in the United States of America in 2000 and was incorporated into the routine childhood immunization schedule. This 7 valent vaccine was conjugated with CRM 197, a nontoxic cross reacting mutant of diphtheria toxin. PCV7 was licensed in Singapore in 2002 but only became available for routine use from 2005 onwards. A 10 valent PCV using recombinant Non-typeable Hemophilus influenza Protein D as the conjugate has been registered in Singapore in April 2010. This section will focus on the impact of the pneumococcal conjugate vaccine on disease burden only.

Since the incorporation of the 7 valent pneumococcal conjugate vaccine (PCV7) in 2000, the incidence of IPD in the United States due to Streptococcus pneumoniae vaccine serotypes (4,6B, 9V, 14, 18C, 19F and 23F) has markedly decreased both among children and adults. In children < 5 years, IPD had decreased by 76%. After PCV7 was introduced in the US, rates of IPD caused by the 7 serotypes also decreased substantially among unvaccinated children and adults. In persons > 50 years in the US, the incidence of IPD caused by the vaccine serotypes decreased by 55% but disease caused by the 16 serotypes covered by PPV23 and not PCV7 did not change in incidence. This indirect (or herd) effect resulted from reduced nasopharyngeal carriage of pneumococcus in PCV7 vaccinated children and reduced transmission from children to unvaccinated children and adults. Thus, the most recent and important advance in prevention of pneumococcal disease in adults, was the result of introduction of routine PCV7 in infants and children < 2 years of age! Hsu et al did not detect any reduction in these serotypes causing IPD in adults following the routine use of PCV7 in Singapore in 2005 but the authors cautioned that it may be too early to make any definitive conclusions.

Surveillance data has revealed that the incidence of non-vaccine pneumococcal serotypes has increased in some instances

The standard recommendations for PPV23 use are as follows:

<b>Groups for which vaccination is recommended</b>	<b>Re-vaccination</b>
Immunocompetent age > 65 years	Second dose if patient received vaccine > 5years earlier and younger than 65 years at time of vaccination
Age 2-64 years with chronic cardiovascular disease, chronic respiratory disease, diabetes mellitus	Not routinely recommended
Age 2-64 years with alcoholism, chronic liver disease or CSF leaks	Not routinely recommended
Age 2-64 years with functional or anatomical asplenia	If age >10 years, re-vaccination > 5 years after previous dose
	If age < 10 years, revaccinate 3 years after previous dose
Immunocompromised patient > 2 years including those with HIV, leukemia, lymphoma, multiple myeloma, chronic renal disease, those receiving immunosuppressive treatment and those who received organ or bone marrow transplant	Re-vaccination 5 years after previous dose.
	If age <5 years, consider re-vaccinating 3 years after previous dose

and this has been termed as “serotype replacement”. The increase in IPD caused by serotypes other than PCV7 has offset some of the gains from PCV7. In particular, surveillance data has demonstrated that serotype 19A has increased both in nasal carriage and as a cause of IPD in all age groups. There is also data to suggest that incidence of IPD in the United States appears to have “stagnated” in the past 5 years.

In a recent analysis of an estimated 4,600 cases of IPD in 2007 in the United States, approximately 70 cases were caused by serotypes contained in PCV7. The vast majority of recent cases of IPD were caused by serotypes other than those covered in PCV7. However, 2,900 cases were caused by serotypes covered under the new PCV 13 that has just been registered in March 2010 in the US. With the impending replacement of PCV7 with PCV 13, surveillance data will be important to determine if a further reduction of IPD will be achieved.

### PCV IN ADULTS

Numerous studies have reported the use of pneumococcal conjugate vaccine (PCV 7 and PCV13) in the elderly. Suffice to say that for every serotype studied, the use of PCV showed similar or higher antibody titers compared with vaccination using PPV. However the number of serotypes covered is smaller when compared with PCV23 and this is an important shortcoming. There is a Phase III trial of PCV13 (CAPITA) that will involve 84,000 elderly patients to determine the direct impact of this vaccine in reducing community acquired pneumonia. The study results are likely to be available only in several years.

The indirect herd effects of widespread childhood PCV immunization in the adult population has been described above.

### FUTURE

Pneumococcal infection causes a large disease burden worldwide and is probably the leading cause of vaccine preventable disease. An efficacious vaccine will therefore be highly desirable. The latest meta-analysis provides evidence which support the recommendation for the use of PPV23 to reduce IPD in the

elderly. However, the current PPV23 provides incomplete protection and clearly needs to be improved. It may be replaced by “increased valent” PCV formulations in future. In numerous countries where PCV has been incorporated in the childhood immunization programmes since the early 2000s, PCV has demonstrated superior efficacy in reducing IPD in children and also had a significant “herd effect” in reducing IPD in other age groups. It is likely that such benefits will extend to the Singapore population with the widespread incorporation of PCV. The use of PCV in elderly patients is now in Phase III studies and their “direct” effects in the older age group are awaited.

### SUGGESTED READINGS

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### LEARNING POINTS

- **Pneumococcus is the most common cause of community acquired pneumonia (CAP) accounting for 19-25% of all cases.**
  - **PPV 23 induces antibody to the capsular polysaccharides but does not produce a T cell mediated or memory response.**
  - **Whilst PPV has the potential to prevent disease and death, the degree of protection afforded against various clinical endpoints and within different populations is uncertain.**
  - **For every serotype studied, the use of PCV showed similar or higher antibody titers compared with vaccination using PPV.**
  - **The latest meta-analysis provides evidence which support the recommendation for the use of PPV23 to reduce IPD in the elderly. However, the current PPV23 provides incomplete protection and clearly needs to be improved.**
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