UNIT NO. 2

PNEUMOCOCCAL VACCINATION IN ADULTS

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ABSTRACT

Pneumonia is an important cause of mortality and morbidity worldwide including Singapore. It imposes heavy economic burdens on health care systems. *S. pneumoniae* is an important pathogen in community acquired pneumonia (CAP) in both developed and developing countries. Pneumococcal disease is importantly, vaccine preventable. The objectives of this review are to provide updates on: pneumococcal disease in adults; pneumococcal vaccines for adults; the need to increase uptake of pneumococcal vaccines; and recommendations on pneumococcal vaccinations in the current national adult immunization schedule. Pneumococcal disease in adults can be divided into invasive and non-invasive pneumococcal diseases. Two pneumococcal vaccines are currently available for adult vaccination in Singapore, namely, the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). The current recommended pneumococcal vaccine immunization strategy is to administer the PCV13 first followed by PPSV23 a year later in pneumococcal vaccine naïve patients. In patients given PPSV23 before, PCV13 is given to complete the protection. Cost effectiveness studies in Singapore have shown that pneumococcal conjugate vaccines may confer protection against pneumococcal disease both directly and indirectly through herd effects, and reduction of nasal carriage. Uptake of pneumococcal vaccines in Singapore is currently low. Characteristics associated with increased pneumococcal vaccination uptake were higher monthly income, higher educational level, having a regular doctor, and good self-rated health. A research-guided educational intervention may be an effective model to improve the knowledge and attitudes of patients towards pneumococcal vaccinations. We need to find ways to use vaccination and other strategies to reduce the mortality and morbidity associated with pneumococcal disease in Singapore.

Keywords: Pneumonia, community acquired pneumonia, non-invasive pneumococcal disease, invasive pneumococcal disease, vaccine preventable disease, NAIS.

SFP2018; 44(2) : 14-22

INTRODUCTION

Pneumonia is an important cause of mortality and morbidity worldwide. It imposes heavy economic burdens on health care systems. Pneumonia in Singapore moved up from being third to second-leading cause of death in Singapore in 2012[1, 2]. In Japan, where more than 21% of its population are aged 65 years or older, 95% of deaths from pneumonia occur in this age group[3] while in developing countries, almost two million children a year die from pneumonia[4]. *S. pneumoniae* is an important pathogen in community acquired pneumonia (CAP) in both older individuals in developed countries and in children in both developed and developing countries. Pneumococcal disease is importantly, vaccine preventable.

The objectives of this review are to provide updates on:
- Pneumococcal disease in adults;
- Pneumococcal vaccines for adults;
- The need to increase uptake of pneumococcal vaccines; and
- Recommendations on pneumococcal vaccinations in the current national adult immunization schedule.

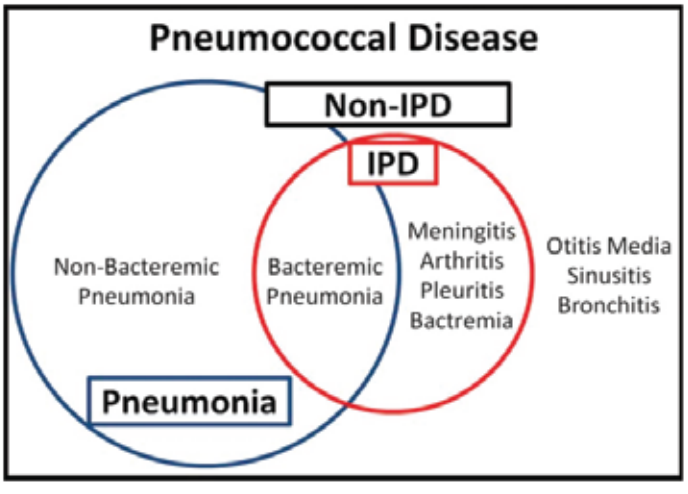
PNEUMOCOCCAL DISEASE IN ADULTS

S. pneumoniae causes morbidity and mortality in children and adults. A common colonizer of the upper respiratory tract, it can cause disease of the airways and also invade beyond the lower respiratory tract and occasionally cross the blood brain barrier. It causes a wide spectrum of diseases and is the most common cause of community acquired pneumonia (CAP)[1] as well as meningitis in adults globally.

1- Non-invasive pneumococcal disease (non-IPD), invasive pneumococcal disease (IPD), and pneumococcal pneumonia [1, 3]

Figure 1[3] shows the schematic spectrum of pneumococcal disease. It can be divided broadly into non-IPD and IPD.

Figure 1. Schematic spectrum of pneumococcal disease



Source: Namkoong et al, 2016 [3]
Footnotes: Non-IPD = Non-invasive Pneumococcal Disease; IPD = Invasive Pneumococcal Disease.
Note that pneumococcal pneumonia can be Non-invasive PD, or Invasive-PD

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Non-IPD. In most people, *S. pneumoniae* causes a non-IPD. Examples include otitis media, sinusitis, bronchitis, and non-bacteremic pneumonia. In a proportion of patients, the infection spreads into normally sterile areas, causing an IPD.

IPD. This is defined as the presence of *S pneumoniae* in sterile sites, namely, cerebrospinal fluid, pleural fluid, joint fluid, and blood. Non-bacteraemic pneumonia from *S pneumoniae* can progress to bacteraemic pneumonia or empyema in 10-30% of cases; this is the most commonly encountered IPD owing to the clinical frequency of pneumonia as a non-IPD. Risk factors for IPD include poor socioeconomic status, age, poor immune status, genetic background, and geographical location. In Singapore, IPD is legally notifiable under the Infectious Diseases Act since 2010. [1].

Pneumococcal pneumonia. This condition typically presents with malaise, chills, fever, productive cough, and dyspnea. Atypical presentations can occur in old, frail or immunocompromised patients. Pneumococcal pneumonia can progress to acute respiratory failure, septic shock, multi-organ failure, and death within a few days even with adequate antibiotic treatment. In adults, the risk factors implicated in the development of pneumococcal pneumonia are immunocompromised conditions such as asplenia, HIV disease, advancing age, chronic lung disease, chronic heart disease, smoking, alcohol consumption, and previous hospitalization for pneumonia [1].

2-Pneumococcal disease (PD) burden

The World Health Organisation estimates that every year, 1.6 million people die from PD. Two retrospective studies done in Singapore, give us some idea of PD rates in adults. Low et al (2007)[5] analyzed 4,275 records of patients hospitalized for PD from 1995-2004 and found that the mean annual hospitalization rate was 10.9 per 100,000 but the rates were considerably higher in children 4 years and younger (39 per 100,000) and in adults 75 years or older (95/100,000). Overall mortality rate of pneumococcal disease was 3.2%. However, with pneumococcal meningitis, the mortality rate rose to 23.3%. Hsu et al (2009)[6] in another retrospective Singapore study of 192 cases of IPD hospitalized from 2000-2007 reported an attributable mortality of 21.4%[1]. These data confirm the burden of pneumococcal disease on individuals and the Singapore health system.

3- S. pneumoniae antibiotic resistance

Antibiotic resistant *S. pneumoniae* infections add to healthcare costs. Antibiotic resistance has risen over the last 15-20 years, in both the paediatric and elderly populations in Singapore[2]. Marked increases of antimicrobial non-susceptibility in pneumococci carried by children in 2008, compared to 1997 for penicillin, erythromycin, clindamycin, tetracycline, and also multidrug resistance (defined as non-susceptibility to three or more classes of antibiotics) were observed[7]. With the increasing survivorship in our population this may be a problem. Increased penicillin and co-trimoxazole resistance were also observed in human immunodeficiency infected patients on long-term co-trimoxazole prophylaxis. More than 80% of penicillin-resistant *S. pneumoniae* is attributable to just six serotypes namely 6A, 6B, 9V, 14, 19F, 23F. These are covered by the 13 valent PCV vaccine. Pneumococcal vaccination may make a significant contribution to reducing the impact of *S. pneumoniae* antibiotic resistance.

PNEUMOCOCCAL VACCINES FOR ADULTS

In adults, the first pneumococcal vaccine to be widely used was the PPSV23. In children, the PCVs have been used more recently. Currently, there are two leading vaccines targeted against *S. pneumoniae*: the polysaccharide vaccine (PPSV23) and the 13 valent conjugate vaccine (PCV13)[1,8,9,11]. In addition, the PHiD10 and PCV7 are also approved in Singapore.

1-Comparison of the two pneumococcal vaccines

Each pneumococcus is contained in a polysaccharide capsule which protects it from destruction by the host and the environment. Antigenic variations reside in the polysaccharide capsules. Over 90 distinct capsular serotypes have been identified. PPSV23 contains antigens from 23 common serotypes and PCV13 contains antigens from 13 serotypes. There is substantial overlap in the antigens in the two vaccines. Twelve of the 13 serotypes included in PCV13 are also covered by PPSV23. See Table 1 [1].

Table 1. Serotypes included in pneumococcal vaccines

Vaccine	Serotypes included
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F
PCV7	4, 6B, 9V, 14, 18C, 19F, and 23F
PCV10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F
PCV13	1,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Source: Eng et al, 2016 [1]

Footnotes: Abbreviations: PCV7 = 7-valent pneumococcal conjugate vaccine. PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine. PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

PPSV23 vaccine contains purified capsular polysaccharides alone whereas PCV7, PhiD10, and PCV13 vaccines contain the purified polysaccharides conjugated to carrier proteins. The conjugate protein in PCV7 and PCV13 is a nontoxic variant of diphtheria toxin known as CRM197[1]; in PhiD10, the conjugate protein is a *Hemophilus influenza* protein-D[12].

The pneumococcal conjugate vaccines are able to induce T-cell dependent immunity and this provides long-term protection. PPSV23 vaccine on the other hand induces a T-cell independent immunity, with its protection waning over time. Revaccination is recommended but the actual booster effect is not clear[3]. Comparisons of the structure, strengths and weaknesses of the two types of pneumococcal vaccines are shown in Table 2.

Table 2. Comparison between PPSV23 and PCV13		
Characteristic	PPSV23	PCV13
Structure	Inactive vaccine made of capsular polysaccharide.	Inactive vaccine made of capsular polysaccharide combined with diphtheria toxoid.
Strengths	Wider coverage of serotypes. Long history of experience.	T-cell dependent immunity. Memory immunity is evoked.
Limitations	T-cell independent immunity. Lack of memory immunity.	Narrower coverage of serotypes. Less evidence of cost effectiveness.
Source: Namkoong et al, 2016 (slightly adapted) [3] Footnotes: PPSV23 = 23-valent pneumococcal polysaccharide vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine		

2-Pneumococcal polysaccharide vaccine (PPSV23)

PPDV23 was first approved for adult use in Singapore by the Health Sciences Authority in 1988. This vaccine contains 25ug of each of the 23 pneumococcal polysaccharide antigens. Vaccine effectiveness of PPSV23 in preventing IPD in older adults ranged from 43 – 81%[1].

PPSV23 is a safe vaccine with minimal side effects, even in pregnancy. The Advisory Committee on Immunization Practices (ACIP) of the United States recommended that pneumococcal vaccine may be administered at the same time as an influenza vaccine (separate injection on the other arm) without decreased antibody response to either vaccine, or an increase in adverse effects[1]. Unlike the pneumococcal conjugate vaccines, PPSV23 has not been shown to interrupt carriage, Hence, PPSV23 may not have the potential for herd effects. Nevertheless, it could be argued that by reducing disease it may reduce spread of colonization. Hence, PPSV23 is still useful. Due to concerns about immunogenicity, older and high risk (immunocompromised) individuals may be less likely to benefit from PPSV23. Nonetheless, PPSV23 has a broader range of strains covered and hence is still considered a cost-effective intervention for adult pneumococcal disease[1].

3-Pneumococcal conjugate vaccines

To improve the immunogenicity of pneumococcal vaccines, the pneumococcal conjugate vaccines (PCVs) were developed. These vaccines are also inactivated vaccines but unlike PPSV23, the polysaccharide antigens are connected to carrier proteins and they have been found to be effective in developing an immune response and in reducing nasopharyngeal carriage of vaccine type pneumococci. The PCVs were initially used in childhood immunization against pneumococcal infections. Several PCVs have been developed over time, three are licensed in Singapore – PCV7, PhiD10, and PCV13[12].

PCV7. This was developed in the US in 2000. It induces sufficient immune responses even in infants who have immature immune systems. PCV7 was licensed in 2002 for childhood immunization in Singapore and in Oct 2009 it became part of the National Childhood Immunisation Program (NCIP) [1].

Indirect herd effect of PCV7. It was noted that after PCV7 was introduced in the US, rates of IPD caused by the 7 serotypes decreased substantially, not only in those vaccinated, but also among the unvaccinated population. This indirect benefits of vaccination, or herd effect, likely resulted from reduced nasopharyngeal carriage of pneumococcus in PCV7-vaccinated children and this reduced transmission from children to unvaccinated children and adults. Surveillance data in many geographic locations also showed reduction in IPD, pneumonia, and acute otitis media in young children where PCV7 was introduced[1]. The concern however was with increases in non-vaccine serotypes namely, serotype replacement; this is being monitored closely in both the United States and Singapore as well as in other countries which use the PCV7 vaccine.

Protective effect in patients at increased risk of pneumococcal disease. PCV7 was also shown to be protective compared to placebo in a RCT study of Human Immunodeficiency Virus (HIV) infected patients in Malawi published in 2010. Also when compared with PPSV23, PCV7 was shown in a paper published in 2009 to induce a superior immune response in patients with chronic obstructive pulmonary disease[1].

PhiD10 vaccine. To provide improvements in serotype coverage and also to potentially reduce remaining IPD burden, two other pneumococcal conjugate vaccines were subsequently released in Singapore – the PhiD10 vaccine and PCV13 vaccine [1, 7]. PhiD10 vaccine is a 10-valent pneumococcal vaccine conjugated to *Hemophilus influenza* protein-D and approved for use in Europe in 2009 and in Singapore in 2010[12]. The pneumococcal serotypes covered are shown in Table 1[1].

PCV13 vaccine. PCV13 was introduced in the paediatric population in 2010 as a replacement for PCV7 due to the concern about serotype replacement. The conjugate vaccines have proven to be successful at reducing the burden of pneumococcal disease due to vaccine serotypes in the pediatric population.

4- Is PCV-13 vaccine combined with PPSV23 vaccine superior to PPSV23 alone for reducing incidence or severity of pneumonia in older adults?

This was the title of a paper by Hayward, Thompson, and McEachern. They described two studies that provided useful information comparing the effect of PPPSV23 and PCV13[9]:

The first study of relevance was a 2013 study which examined the safety and effectiveness of PCV13 in elderly adults who had previously received vaccination with PPSV23. In this study, measured anti-pneumococcal opsonophgagocytic (OPA) titres were used to evaluate vaccine efficacy although this is more a measure of immunogenicity. The study was a randomized trial of 936 adults aged 70 years or older who had been previously vaccinated with PPSV23 at least 5 years prior to the trial. Study participants were divided into 2 groups. One group received a second dose of PPSV23, and the other received PCV13. Both groups received a dose of PCV13 one year later. OPA titres were measured prior to, 1 month following each vaccine administration[9] .

The results of this study showed that significantly greater OPA response for 10 of the 12 common serotypes resulted following vaccination with PCV13 compared to re-vaccination with

PPSV23. The study then evaluated immune response following PCV13 in both groups 1 year following the initial PCV13 or PPSV23 vaccine. OPA titre responses were significantly higher for 11 common serotypes in the group who received PCV13 at enrollment and at 1 year compared to the group who received PPSV23 initially. This study suggests that there may be benefits for using the combination of the two vaccines in terms of immunogenicity[9].

The second study of relevance was the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). This was conducted to find out the clinical efficacy and safety of PCV13 in the adult population in the Netherlands, where routine pneumococcal vaccination was not that common as in Singapore. The study, funded by Pfizer, the vaccine manufacturer, included 84,496 pneumococcal naïve adults 65 years or older in a randomized, double-blinded, placebo-controlled trial. Participants were randomly divided into 2 groups in a 1:1 ratio, either receiving PCV13 or placebo injection. Study participants were followed for an average of approximately 4 years [9].

The primary objective of this study was to demonstrate prevention of first episode vaccine-type community-acquired pneumonia (CAP). Secondary objectives were the prevention of first episode non-bacteremic and non-invasive vaccine type CAP (negative cultures of sterile sites), and prevention of vaccine-type invasive pneumococcal disease (*S. pneumoniae* present in sterile site). Table 3 shows the trial results [9].

Table 3. PCV13 – Efficacy in first episode vaccine type pneumococcal disease

	PCV13 (n = 42,200)	Placebo (n = 42,256)	% Vaccine Efficacy	P value
First episode vaccine-type CAP	49	90	45.6%	<0.001
First episode vaccine non-bacteremic, non-invasive CAP	33	60	45.0%	0.007
First episode vaccine-type invasive pneumococcal disease	7	28	75.0%	<0.001

Source: Hayward, Thompson, McEachern, 2016 [9]
Footnote: CAP = community acquired pneumonia

The conclusions are CAPiTA trial was successful in demonstrating efficacy and safety for PCV13 in older adults for prevention of vaccine-type pneumococcal disease. The limitation of the trial was Dutch patients were PPSV23 vaccine naïve. Hence, while this study showed effectiveness of PCV13, it does not address the question of PPSV23 in combination with PCV13 compared to PPSV23 alone and as the benefit was confined to the vaccine serotypes, the ACIP recommendation is the two vaccine strategy [9].

Table 4. Comparisons of pneumococcal OPA geometric mean titres (GMTs) for the 12 common serotypes and serotype 6A 1 month after vaccination

	Vaccine Group			
Serotype	PCV13	PPSV23	Comparison	
	GMT, n = 350 - 366	GMT, n = 350 - 366	Ratio	(95% CI)
1	103	78	1.3	(0.99 - 1.75)
3	44	61	0.7	(0.59 - 0.89)
4	1016	392	2.6	(1.96 - 3.44)
5	347	118	2.9	(2.22 - 3.86)
6A	2122	676	3.1	(2.38 - 4.14)
6B	1995	1440	1.4	(1.10 - 1.75)
7F	1901	1361	1.4	(1.12 - 1.74)
9V	858	379	2.3	(1.59 - 3.24)
14	1028	1059	1.0	(0.77 - 1.23)
18C	2015	938	2.1	(1.61 - 2.86)
19A	985	429	2.3	(1.81 - 2.92)
19F	773	388	2.0	(1.42 - 2.79)
23F	456	180	2.5	(1.84 - 3.49)

Source Shiramoto et al, 2015[10]

A Japanese study by Shiramoto et al, 2015[10] further confirmed the immunogenicity of PCV13 compared to PPSV23. This was a randomized, modified double-blind trial comparing the opsonophagocytic activity (OPA) titres of PCV13 against corresponding serotype OPA titres of PPSV23. This study did not have clinical endpoints.

The subjects were PPSV23 naïve adults aged 65 years or older. A total of 764 Japanese adults were randomized to receive PCV13 (n = 382) or PPSV23 (n = 382). The study results showed that for 9 out of the 12 common serotypes in common with both vaccines, and for serotype 6A, unique to PCV13, significantly greater OPA geometric mean titres (GMTs) were elicited one month after vaccination in the PCV13 group compared to the PPSV23 group. There were no serious treatment-related adverse events in either group [10].

The results of this Japanese study supports the perspective that PCV13 has the potential for improved clinical efficacy against the substantial burden of IPD and pneumonia caused by PCV13-associated serotypes in Japan compared to PPSV23[10], again providing a rationale for a two vaccine strategy. Each vaccine has its own set of benefits and limitations. See Table 2 [3, 4]. What is now known is the current pneumococcal vaccination strategy with PPSV23 alone has not been as successful as desired in the adult population. The potential of adding PCV13 to the adult immunization programme has been suggested by these immunogenicity studies and the CAPiTA study although clearly more work with clinical endpoints needs to be done perhaps in real world large scale observational studies.

5-PCV13 vaccine for adult use

In 2012, ACIP in the US recommended that adults older than 19 years with immunocompromising conditions, functional or anatomical asplenia, cerebrospinal leaks, or cochlear implants receive PCV13 although there were no clinical trials in these populations most likely because of logistic and ethical considerations. In 2013, ACIP added guidance for the first time on the timing of administration of PCV13 relative to the PPSV23 in adults[1].

When both PCV13 and PPSV23 are indicated in adults, the ACIP recommendation was a dose of PCV13 should be given first. For patients who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and 5 or more years since the most recent dose of PPSV23[1].

RECOMMENDATIONS FOR PNEUMOCOCCAL VACCINES IN ADULTS

1-Current ACIP recommendations for pneumococcal vaccines in adults

Current ACIP recommendations for pneumococcal vaccines for adults (released in 2014) are now recommended internationally including in Singapore. These are described by Hayward, Thompson, and McEachern in their paper and

reproduced in Figure 2[9].

Figure 2. Current ACIP Recommendations Regarding Pneumococcal Vaccination, 2014

Pneumococcal vaccine naïve persons aged ≥ 65 years		
Give PCV13 at age ≥ 65 years	≥ 1 year	Give PPSV23
Previously received PPSV23 at age ≥ 65 years		
Give PCV13 at age ≥ 65 years	≥ 1 year	Give PCV13

.

Previously received PPSV23 before age ≥ 65 years and are now aged ≥ 65 years				
PPSV23 received age <65 years	≥ 1 year	Give PCV13 at age ≥ 65 years	≥ 1 year	PPSV23 booster #

Sources: Hayward et al, 2016 [9] ; Kobayashi et al, Advisory Committee on Immunisation Practices, MMWR.
Footnote: # = Recommend ≥ 5 years between PPSV23 and PPSV23 booster

2-National Adult Immunisation Schedule – Singapore, 2017

The Ministry of Health (MOH) Singapore has established the National Adult Immunisation Schedule (NAIS) in 2017 to provide guidance on vaccinations that persons aged 18 and older should adopt to protect themselves against vaccine-preventable diseases. Also, from 1 Nov 2017, Medisave can be used to pay for recommended vaccinations for the specific target adult population groups under the NAIS [14].

Currently, the National Childhood Immunisation Programme (NCIP) aims to achieve herd immunity among children in the population and reduce the risk of disease outbreaks and the morbidity and mortality associated with common childhood illnesses including pneumonia.

The current pneumococcal vaccine immunization strategy recommended by ACIP in the US and by our local vaccine experts including the College of Family Physicians[8] is to continue with the use of PPSV23 and add to this PCV13 to enhance the vaccine protection. With regards to the NAIS, adults who have not been previously vaccinated or who are at risk and their doctors will be able to make more informed choices on vaccination. Pneumococcal (PCV13/PPSV23) vaccines are among of the 7 types of vaccines in the NAIS. That for pneumcoccal disease is shown in Figure 3[11]. Read Figure 3 together with Figure 2[9].

Figure 3. National Adult Immunisation Schedule – Singapore, 2017

Recommended groups	Schedule
Persons aged 65 years or older	1 dose each
Persons aged 18 year and older with chronic illnesses such as chronic lung, heart, kidney, or liver diseases and diabetes mellitus	1 or 2 doses (a)
Persons who are immunocompromised or with other medical conditions (c).	1 or 2 doses (b)

Source: Ministry of Health, Singapore , 2017[11]
Footnotes:
(a) One dose each of PCV13 and PPSV23 is recommended for persons aged 65 years and above
(b) The number of doses and vaccine type depend on medical condition and age.
(c) Other medical conditions include:
- Persons with cochlear implants or cerebrospinal fluid leaks;
- Persons with anatomic or functional asplenia (including conditions such as homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction).

The NAIS and NCIP together provide comprehensive vaccination recommendations for Singaporeans and Singapore residents of all ages [11].

COST EFFECTIVENESS OF PNEUMOCOCCAL VACCINES

The costs associated with the treatment of CAP is likely to be high but difficult to determine accurately. Nevertheless, some studies have been done. A study conducted in a large urban hospital in the US and published in 2006 showed that median hospital costs were US $8,654 and US $9,441 for CAP mediated by penicillin-susceptible and penicillin non-susceptible S. pneumoniae respectively, showing antibiotic resistance to be a small additional cost factor[1].

In the Singapore setting, a study by Tyo et al on the cost-effectiveness of pneumococcal conjugate vaccines used in Singapore namely, the 7-valent (PCV7), 10-valent (PhiD10), and 13-valent (PCV13) vaccines in its National Childhood Immunisation Programme was published in 2011[12]. The data showed that for PCV13, the baseline cost-effectiveness thresholds were $37,644 Sing dollars. Herd effects of vaccination (40% direct cost) was $18,566. If herd effects of vaccination were not considered, the cost-effectiveness would be $204,535 which is very cost-effective. Hence, it can be interpreted that herd effect of pneumococcal vaccinations contributes tremendously to the cost-effective results. This has also been the experience on cost effective studies on pneumococcal studies in Hong Kong, Korea, and Netherlands[1].

The study by Tyo et al has several interesting points of note[12]:
- This was the first estimate for cost effectiveness of pneumococcal vaccination in Singapore and the first analysis of cost-effectiveness of newer vaccines (PhiD10 and PCV13) in an Asian population.
- The study made extensive use of Singapore-specific morbidity and mortality data and the MOH of Singapore's claims data for hospitalized cost analyses.
- The use of a Singapore Delphi panel was a novel component that improved the "real world" validity of estimates for ambulatory costs and quality losses.
- In the absence of country specific data, assumptions had to be made from data in the medical literature as were done in this study.

UPTAKE OF PNEUMOCOCCAL VACCINES FOR ADULTS

Pneumococcal vaccination is recommended for the elderly (i.e., those aged 65 years or older) and in people with chronic medical conditions. The current reality is that adult vaccines were underused as Eng et al have observed, both in Singapore and in many countries worldwide, and much needs to be done.

Two published studies on the uptake of pneumococcal vaccines in Singapore, namely, a study by Ang et al in 2013[13], and a study by Ho et al in 2017[14], both provide useful information on factors associated with poor uptake of pneumococcal vaccines,

and what can be done to improve things.

1-National Health Surveillance Survey (NHSS), 2013

The NHSS 2013 was the third in a series conducted every 6 years since 2001 commissioned by the MOH Singapore. The primary aim of the series is to assess the health status of community-dwelling Singaporeans as part of the MOH's nationwide surveillance of non-communicable diseases and to identify behavioral risk factors to improve the health of Singaporeans.

This 2013 study also estimated the pneumococcal vaccine uptake among the Singapore resident population aged 50 years or older and living in the community. The field work of face-to-face interviews was conducted between Nov 2012 and Oct 2013. A two-staged stratified sampling of a database containing all dwellings was done and the study sample of 3672 residents provided the information on factors associated with uptake of pneumococcal vaccination.

Table 5. Associations between pneumococcal vaccination and socio-demographic and health-related characteristics in representative sample of community living adults 50 years or older, Singapore, 2013

Variable	Adjusted Odds Ratio	(95% CI)	p-Value
Socio-demographic characteristic			
- Marital status (Separated, divorced or widowed)	2.53	(1.16 - 5.54)	<0.0005
- Educational level (A-level, diploma, degree)	1.56	(1.08 - 2.27)	<0.0005
- Monthly household income (S$) >6000	3.18	(1.98 - 5.09)	<0.0005
Health related characteristic			
- Self-rated health (moderate)	0.55	(0.41 - 0.75)	<0.0005
- Self rated health (Bad or very bad)	0.28	(0.11 - 0.66)	0.004
- Regular doctor (yes)	2.19	(1.67 – 2.88)	<0.0005

Source: Ang et al, 2013 [13]
Footnote: Table is abridged version of Table II (on page 5) of paper

Table 5[13] shows the characteristics found to be associated with increased pneumococcal vaccination uptake:

- Socio-demographic characteristics: higher monthly household income, marital status of separated, divorced, or widowed; and higher educational level.
- Health-related characteristics: having a regular doctor, and a trend of moderately good to good self-rated health.

Among the 3672 residents,

- Only 11% "ever had influenza (flu) vaccination in the past year",
- Only 3.9% had been vaccinated against both seasonal influenza and pneumococcal infection.

This important national survey suggests that there may be financial barriers to vaccination which hopefully may be ameliorated by allowing Medisave use for essential vaccines in adults. This has been implemented in Nov 2017[11].

2- Formative research-guided educational intervention to improve the knowledge and attitudes of seniors towards influenza and pneumococcal vaccinations, 2017 [14]

This study is a mixed methods study made up of two components. For the first component, the objectives were to understand the factors influencing the knowledge and attitudes of seniors towards influenza and pneumonia and their respective vaccines; the barriers and facilitations in getting the vaccinations done; and the concerns about vaccine adverse effects and vaccine effectiveness. This was a qualitative study. Four focus discussion groups (FDGs), each with 5 to 13 participants, making a total of 32 participants aged 60 years or older, were conducted. The participants were recruited by care coordinators from Senior Activity Centres (SAC) involved in the study Facilitators were matched with the participants' dialect groups. The content of the question guide used during these FDGs is shown in Table 6.

Table 6. Questions used during focus group discussions with community-dwelling seniors

Theory and constructs of HBM	Questions	
Knowledge and perception of influenza and pneumonia	• What is influenza/pneumonia? • What other names have you heard people use to refer to influenza/pneumonia? • What do you think causes influenza/pneumonia? • How can we prevent getting influenza/pneumonia?	Individual/social factors
Experience with past vaccinations for influenza or pneumonia	• What made you go for vaccination? o How do you feel after receiving your vaccination? • What made you decide not to have the vaccination? • How did your family or friends react towards your decision? • What did your doctor or nurse say about your decision?	
Perceived susceptibility of influenza and pneumonia	• Who do you think are at risk of getting influenza/pneumonia? • Who do you think should go for these vaccinations?	
Perceived severity of influenza and pneumonia	• What do you think are the consequences of getting influenza/pneumonia? • How can we prevent getting influenza/pneumonia?	
Knowledge and perception of vaccination	• What do you know about vaccinations? • What do you think of them?	Vaccine-related factors
Perceived benefits of vaccination	• What did you like about vaccinations? • Who do you think should go for vaccinations? • Why do you think so?	
Perceived barriers to vaccination	• What did you not like about vaccinations? • What are your concerns regarding the vaccinations? o How can we help address your concerns • What do you think about the costs of vaccinations in Singapore? • How can we help you and your friends to receive vaccinations?	
Cues to action	• How can we make it easier for the elderly to get these vaccinations?	
Self-efficacy	• Who would like to receive influenza or pneumococcal vaccinations o Why are you interested to get the vaccine? o What are your reasons for not wanting to get the vaccine?	

Source: Source: Ho et al, 2017 [14] – Table 1
HBM = Health belief model

From the FGDs the discovered knowledge gaps, misconceptions, concerns of vaccine adverse effects and vaccine effectiveness in the participants were noted. A small group interactive educational intervention programme was then created with the aims of filling the discovered knowledge gaps, correcting misconceptions, and addressing concerns on adverse effects and vaccine effectiveness.

The content of this intervention programme created had the following features: "Basic facts on influenza and pneumonia were explained to address the misconceptions of their causes and transmission routes. The severity of these illnesses, as compared to the common cold, and the susceptibility of the seniors to respiratory illnesses were highlighted. The use, benefits and effectiveness of influenza and pneumococcal vaccines were explained in lay language by the HA [health

assistants] to the seniors [course participants], and the safety of vaccines was emphasized." [14]

The second component of this study was a quantitative study. The educational programme described above was taught to a total of 655 seniors in the participating SACs. Of these 604 (92.2%) consented to participate in the second component of this study which consisted of pre- and post-intervention quantitative surveys.

The respondents in the second component of this study had these characteristics: "The median age of participants was 73 years (interquartile range, IQR 68-77), with majority being female, of Chinese ethnicity, and having received no formal education or only up to primary school education. Majority resided in 1 or 2-room government housing flats. The most common chronic diseases present were hypertension (61.9%), hyperlipidemia (57.8%) and diabetes mellitus (26.5%)" [14] .

Results of the pre- and post-intervention surveys given to participants in the educational intervention programme are shown in Table 8[14].

Table 8. Results from Pre- and Post-intervention surveys given to participants in educational intervention events (N = 604)

Survey Questions	No of pairs	Case/control pairs				Odds Ratio (OR)	95% Confidence intervals	P value
		+/+	+/-	-/+	-/-			
Knowledge								
1) Influenza is the same illness as the common cold (False)	602	174	210	72	146	2.92	2.22-3.87	<0.0001
2) Pneumonia is an infection of the lungs with symptoms such as fever, cough with phlegm and difficulty in breathing (True)	602	394	145	25	38	5.80	3.78-9.26	<0.0001
3) Pneumonia is the same illness as tuberculosis (False)	603	240	190	51	122	3.73	2.72-5.18	<0.0001
4) Pneumonia will not cause death (False)	602	183	174	99	144	1.76	1.37-2.27	<0.0001
5) Vaccinations can help to protect me from diseases such as influenza (True)	598	493	86	15	4	5.73	3.29-10.89	<0.0001
6) Washing my hands will not help prevent the spread of influenza (False)	600	215	199	98	88	2.03	1.59-2.61	<0.0001
7) Vaccinations against pneumonia should be taken every year (False)	600	44	193	38	325	5.08	3.57-7.40	<0.0001
8) Most of the side effects of vaccination are mild and will go away in a few days. (True)	601	388	157	31	25	5.06	3.43-7.71	<0.0001
9) Young children and the elderly are not recommended to go for vaccination (False)	595	313	164	56	62	2.93	2.15-4.04	<0.0001
Attitudes								
10) I believe I am at risk of getting diseases such as influenza and pneumonia.	592	263	194	64	71	3.03	2.27-4.09	<0.0001
11) If I feel healthy and well, I don't think I need to get pneumonia vaccinations.	594	288	168	65	73	2.58	1.93-3.50	<0.0001
12) I believe that getting vaccinations is an effective way to prevent such diseases such as influenza and pneumonia.	600	529	55	11	5	5.00	2.59-10.59	<0.0001

Source: Ho et al, 2017 – Table 4 [14]

Of note are the following:
Pre-intervention survey – "the questions with the highest proportion of incorrect answers asked participants whether pneumococcal vaccinations should be taken yearly [518 incorrect answers (85.8%)]; whether influenza is the same as the common cold [356 incorrect answers (58.9%)], and whether pneumonia could result in death [318 incorrect answers (52.6%)]. The median pre-intervention total knowledge score (maximum of 9) was 5 (interquartile range, IQR 4-5), while the median total attitude score (maximum score 3) was 2 (IQR 1-3)." [14]

Post-intervention survey – "participants were 1.76 – 5.80 times as likely as pre-intervention to answer individual knowledge questions correctly (p <.0001 for all questions) (Table 4) [Table 8 in this paper]. They were also five times as likely to agree that vaccinations were effective in preventing infectious diseases (OR = 5.00, 95% CI 2.59-10.59, p<.0001). The median total knowledge score improved to 7 (IQR 5-7) (p<.0001)." [14]

The conclusions that could be drawn from this study are firstly, formative research through FGDs are effective in engaging and getting a true understanding of influenza, and pneumonia and vaccination to prevent these. The use of facilitators with dialect language skills matching the participants' dialects was clearly important; secondly, to address knowledge gaps, misconceptions and concerns, a purpose built educational programme that improved knowledge, correct misconceptions, and addressed concerns of vaccine adverse effects and vaccine effectiveness was able to improve knowledge and attitudes towards vaccinations. This study has much to offer as a model for adaptation in future endeavors of promoting uptake to pneumococcal and influenza vaccinations[14].

DISCUSSION

This review on pneumococcal vaccination in the adult has highlighted several areas for the practitioner to add to his or her current knowledge and skills base on pneumococcal vaccination in adults. The increasing population of survivors of middle age diseases in Singapore is an important reminder of the growing importance of pneumococcal disease in older people. It is also a reminder that pneumococcal disease is vaccine preventable.

S. pneumoniae is an important pathogen in community acquired pneumonia (CAP). CAP is still a major cause of morbidity and mortality in Singapore especially among elderly and immunocompromised individuals. In these patients, presentation can be atypical and a high index of suspicion is needed in primary care physicians.

Two pneumococcal vaccines are available for adult vaccination, namely, the PPSV23 and PCV13. Of the two, PCV13 is more immunogenic although it has not been used for a very long time whereas PPSV23's protection is less immunogenic but covers a broader range of strains. PCV13 is able to reduce nasal carriage of *S. pneumoniae* which may be important in preventing disease. Table 1 is a useful table for comparison of the PPSV23 vaccine and the conjugate vaccines like PCV13.

The current pneumococcal vaccine immunization strategy recommended by ACIP in the US and by our local vaccine experts including the College of Family Physicians[8] is to continue with the use of PPSV23 and add to this PCV13 to enhance the vaccine protection. In a patient who has not been vaccinated with pneumococcal vaccines before, the first vaccine to administer is PCV13 first followed by PPSV23 a year later. In patients given PPSV23 before, PCV13 is given to complete the protection. Figure 2 and 3 explain this.

Cost effectiveness studies in Singapore by Ang et al have shown the pneumococcal conjugate vaccines (PCV7, PhiD10, and PCV13) are cost effective in children especially if they are able to generate herd immunity. Similar studies are pending for adults.

Uptake of pneumococcal vaccines is currently low and is a

concern. Characteristics associated with increased pneumococcal vaccination uptake in a study were: higher monthly income; marital status of separated, divorced, or widowed; higher educational level; and having a regular doctor trend of moderately good to good self-rated health. Absence of these characteristics can provide cues to action in daily practice as triggers to recognize patients who may be at risk of pneumococcal disease and need improvement of their pneumococcal vaccine knowledge and also help to overcome barriers to vaccination such as costs.

There may be a need to close knowledge gaps and correct misconceptions, and address concerns of vaccine adverse effects and vaccine effectiveness in the local community. The formative research-guided educational intervention by Ho et al has shown the effectiveness of discovering gaps by focus group discussion and designing intervention to deal with these discovered gaps. This research highlights the importance of listening to our patients to determine what are the barriers to effective preventive interventions including vaccination.

CONCLUSIONS

- The increasing population of adults surviving childhood and middle aged diseases in Singapore is an important reminder of the growing importance of pneumococcal disease in older people. It is also a reminder that pneumococcal disease is vaccine preventable.
- Pneumococcal disease in adults can be divided into invasive pneumococcal diseases and non-invasive pneumococcal diseases.
- *S. pneumoniae* is an important pathogen in community acquired pneumonia (CAP) and 10 – 30% of non-invasive pneumococcal pneumonias can progress to bacteraemic pneumonia or pneumonia with empyemas.
- Two pneumococcal vaccines are available for adult vaccination, namely, the PPSV23 and PCV13.
- The current pneumococcal vaccine immunization strategy recommended by ACIP and Singapore experts is to administer the PCV13 first followed by PPSV23 a year later in pneumococcal naïve patients. In patients given PPSV23 before, PCV13 is given to complete the protection.
- Uptake of pneumococcal vaccines is currently low. Characteristics associated with increased pneumococcal vaccination uptake were: higher monthly income; marital status of separated, divorced, or widowed; higher educational level; having a regular doctor trend of moderately good to good self-rated health; and
- A two component research-guided educational intervention study showed effective intervention outcomes. This emphasizes the importance of understanding barriers that our patients face in trying to increase pneumococcal vaccination rates.

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LEARNING POINTS

- **The increasing population of survivors of childhood and middle age diseases in Singapore is an important reminder of the growing importance of pneumococcal disease in older people as well as traditional risk groups in children and immunocompromised young adults.**
- **It is also a reminder that pneumococcal disease is vaccine preventable.**
- **Pneumococcal disease in adults can be divided into invasive pneumococcal diseases and non-invasive pneumococcal diseases.**
- **Two pneumococcal vaccines are available for adult vaccination, namely, the PPSV23 and PCV13.**
- **The current pneumococcal vaccine immunization strategy recommended by ACIP is to administer the PCV13 first followed by PPSV23 a year later in pneumococcal naïve patients. In patients given PPSV23 before, PCV13 is given to complete the protection.**
- **Uptake of pneumococcal vaccines is currently low in Singapore and many countries.**
- **Patients with low uptake risk factors are cues to action to providers to close their patients' knowledge gaps and to promote pneumococcal vaccinations. The introduction of Medisave allowability since Nov 2017 for pneumococcal vaccination, has the potential to significantly increase the rate of vaccination and thereby reduce the morbidity and mortality due to pneumococcal disease in Singapore.**