

# Role of pneumococcal vaccination in prevention of pneumococcal disease among adults in Singapore

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**Abstract:** The burden of disease associated with *Streptococcus pneumoniae* infection in adults can be considerable but is largely preventable through routine vaccination. Although substantial progress has been made with the recent licensure of the new vaccines for prevention of pneumonia in adults, vaccine uptake rates need to be improved significantly to tackle adult pneumococcal disease effectively. Increased education regarding pneumococcal disease and improved vaccine availability may contribute to a reduction in pneumococcal disease through increased vaccination rates. The increase in the elderly population in Singapore as well as globally makes intervention in reducing pneumococcal disease an important priority. Globally, all adult vaccines remain underused and family physicians give little priority to pneumococcal vaccination for adults in daily practice. Family physicians are specialists in preventive care and can be leaders in ensuring that adult patients get the full benefit of protection against vaccine-preventable diseases. They can play a key role in the immunization delivery of new and routine vaccines by educating the public on the risks and benefits associated with vaccines. Local recommendations by advisory groups on vaccination in adults will also help to tackle vaccine preventable diseases in adults.

**Keywords:** pneumococcal vaccine, pneumonia, invasive pneumococcal disease, adults

## Pneumococcal disease (PD) in adults

*Streptococcus pneumoniae* or pneumococcus is an important cause of morbidity and mortality in adults and children worldwide.<sup>1</sup> *S. pneumoniae* is a common colonizer of the upper respiratory tract and often spreads to the surrounding mucosal tissue. It causes a wide spectrum of disease and is the most common cause of community-acquired pneumonia (CAP).<sup>2</sup> In most patients, it causes noninvasive disease such as otitis media, sinusitis, and pneumonia. However, in a percentage of patients, the infection spreads into the blood stream resulting in invasive PD (IPD) manifesting as bacteremia, bacteremic pneumonia, or meningitis. The incidence of IPD varies substantially and is affected by factors such as socioeconomic status, age, immune status, genetic background, and geographical location.<sup>2</sup> Pneumococcal pneumonia typically presents with chills, fever, malaise, dyspnea, and a productive cough. Untreated patients can progress to acute respiratory failure, septic shock, multiorgan failure, and death within several days from onset.<sup>3</sup> In adults, there are a number of risk factors commonly implicated in the development of pneumococcal pneumonia including age, chronic lung disease, chronic heart disease, smoking, alcohol consumption, and previous hospitalization for pneumonia.<sup>4</sup>

The capsular polysaccharide of *S. pneumoniae* determines the virulence and provides the antigenic target for natural and vaccine-mediated antibody production. There are more than 90 immunologically distinct serotypes of *S. pneumoniae*, based on the chemical composition of the capsular polysaccharide.<sup>5</sup> Transmission of *S. pneumoniae* occurs through direct contact or via fomites and is facilitated by overcrowding. Colonization begins within a few months of birth and continues throughout adolescence.<sup>6</sup> The probability of adult colonization is directly related to the presence of younger children in the household as adults not exposed to children generally have a lower prevalence of *S. pneumoniae*.<sup>7</sup> There are a limited number of epidemiological studies in Singapore, particularly in relation to serotype prevalence.<sup>8–13</sup> The available seroprevalence data is summarized in Table 1.

Cardiac complications account for one-third of the treatment failure cases in hospitalized pneumonia patients.<sup>14</sup> Numerous cardiac complications independently associated with increased short-term mortality have been reported during the course of CAP (Table 2).<sup>15,16</sup> Although the cause–effect relationship between pneumonia and heart failure might be bidirectional, cardiac arrest occurs in up to 3% of patients admitted to hospital with CAP.<sup>17</sup> In view of the high incidence of complications in patients with pneumonia and the effect on mortality, the possibility of improving the outcomes of these patients by prevention is extremely important.<sup>16</sup>

## PD burden

In Singapore, pneumonia is the third leading cause of death (after cancer and heart diseases) and accounted for 16% of total deaths in 2011.<sup>18</sup> The incidence of pneumonia in adults increases with age all over the world.<sup>19</sup> A US study of 46,237 elderly patients reported 18.2 cases per 1,000 person-years among patients aged 65–69 years, rising to 52.3 cases per 1,000 person-years among patients aged  $\geq 85$  years.<sup>20</sup> Previous estimates of mortality from CAP range from 5.1% for hospitalized and ambulatory patients to 36.5% for patients in intensive care units.<sup>21</sup>

*S. pneumoniae* is the leading cause of vaccine preventable disease. It is estimated that there are 2–4 million cases of pneumonia per year in the US, with *S. pneumoniae* accounting for up to two-thirds of bacterial pneumonia cases.<sup>22</sup> The World Health Organization estimates that 1.6 million die every year from PD.<sup>23</sup> Although the number of IPD cases is similar in the very young and the very old, mortality in elderly patients is disproportionately high.<sup>24</sup> Singapore made IPD a legally notifiable disease under the Infectious Diseases Act in 2010.<sup>25</sup> However, there have been only two retrospective

studies assessing the incidence of PD in adults in Singapore. An analysis by Low et al in hospitalized patients in Singapore examined 4,275 patient records with PD from 1995–2004.<sup>26</sup> The authors found that the mean annual hospitalization rate was 10.9 per 100,000 population but was considerably higher in the young ( $<4$  years; 39/100,000) and in the elderly ( $>75$  years; 95/100,000). The overall mortality rate in this study was 3.2%. The pneumococcal meningitis mortality rate was 23.3% and the pneumococcal pneumonia mortality rate was 2.9%.<sup>26</sup> An analysis of 192 adult cases of IPD in Singapore reported an attributable mortality of 21.4% between 2000–2007.<sup>27</sup>

*S. pneumoniae* antibiotic resistance has risen dramatically over the last 10–15 years in Singapore. There was a marked increase in antimicrobial nonsusceptibility in children in Singapore in 2008 compared to 1997 (penicillin 27.4% versus 69.5%; erythromycin 33.4% versus 78%; clindamycin 24.5% versus 45.8%; tetracycline 48% versus 67.8%), and multidrug resistance (defined as nonsusceptibility to three or more classes of antibiotics) increased from 33.3% to 74.6%.<sup>11</sup> Penicillin and macrolide resistance to *S. pneumoniae* are a serious concern worldwide, especially in Asian countries.<sup>28</sup> Penicillin-resistant pneumococcal pneumonia is more common in patients with increased risk for mortality, such as those with comorbidities.<sup>29</sup> The probability of penicillin and co-trimoxazole *S. pneumoniae* resistance is increased in human immunodeficiency virus (HIV)-infected patients, associated with receipt of long-term co-trimoxazole prophylaxis. Six serotypes (6A, 6B, 9V, 14, 19F, 23F) account for more than 80% of penicillin-resistant or macrolide-resistant *S. pneumoniae* worldwide.<sup>30</sup>

## Vaccines available in Singapore for prevention of PD

### Polysaccharide vaccines

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) was approved by the Health Sciences Authority (Singapore regulatory body) for use in Singapore in 1988. There are two PPSV23 registered in Singapore: Pneumo 23 by Sanofi Pasteur (Lyon, France), and Pneumovax 23 by MSD (Lyon, France). PPSV23 contains 25  $\mu\text{g}$  of each of the 23 pneumococcal polysaccharide antigens (Table 3). These 23 serotypes accounted for 75.4% of IPD infections in Singapore in 2012.<sup>13</sup> A number of case–control studies have been conducted to assess the effectiveness of PPSV23 in preventing IPD in older adults. Vaccination effectiveness has ranged from 43%–81%.<sup>31</sup> PPSV23 has been found to be effective in healthy individuals  $<75$  years of age, but

Table 1 Singapore pneumococcal seroprevalence data

Study with key findings in PD	Predominant serotype (%)							
	Children				Adults			
	Associated with primary bacteremia	Associated with pneumonia	Associated with meningitis	No specified association	Associated with primary bacteremia	Associated with pneumonia	Associated with meningitis	No specified association
Ling and Tay 1990 <sup>8</sup>	14	6B	6B		1	3	1	
Overall mortality rate was 29.5%.	20	14	19A		11A	4	13	
High incidence in males, extremes of ages, and Indian and Malay races		19A	19F		20	7F	34	
Chong et al 2008 <sup>9</sup>	23F (30.8)	14 (33.9)	14 (30.8)					
Diagnoses at presentation:	14 (26.1)	6B (17.7)	19F (30.8)					
pneumonia 63.3%; bacteremia 17%; meningitis 15.6%; other 4.1%	6B (13)	23F (17.7)						
	15 (7.7)	6A (8.1)						
Hsu et al 2009 <sup>27</sup>								14 (18.2)
Attributable mortality was 21.4%								3 (11.5)
								6B (8.3)
								8 (6.8)
								19F (6.3)
Vasoo et al 2010 <sup>11</sup>								
Dramatic increase in antibiotic resistance over the last 10–15 years in Singapore				6B (16.9)				
				23F (11.9)				
				19F (10.2)				
Singapore Ministry of Health 2012 <sup>12, #</sup>								3* (12.9)
A decrease of 10.8% in invasive PD cases versus 2010				19A (39.7)				14 (11.1)
				14 (15.5)				8 and 19A (9.7)
				6B (13.8)				6B (9.2)
Singapore Ministry of Health 2013 <sup>13, #</sup>								3* (14.9)
PCV7 serotype coverage was modest (35.5%) versus PCV13 (65.9%) and PPV23 (79.3%)				19A (51.6)				7F (7.5)
				6B (22.6)				19A (6.7)
				3 (16.2)				6B (6.7)

**Notes:** <sup>#</sup>Retrospective study from 1977–1986; serotype prevalence in percentage is not available. <sup>†</sup>The latest data from the Singapore Ministry of Health. The report published in 2012 applies to the 2011 period and the 2013 report applies to the 2012 period. <sup>\*</sup>Associated with significantly high case-fatality rates in adults.

**Abbreviations:** PCV7, seven-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV23, 23-valent pneumococcal conjugate vaccine; PD, pneumococcal disease.

**Table 2** Effects of pneumonia on the cardiovascular system

Vascular endothelium and peripheral vessels	Decreased peripheral vascular resistance in most young adults, but increased peripheral vascular resistance in up to one-third of middle-aged adults (no data available for elderly patients); increased concentrations of endothelin-1 and adrenomedullin
Myocardium	Depression of left ventricular function; myocarditis; increased concentrations of troponins, BNP, and ANP
Cardiac rhythm	Acute cardiac arrhythmias
Coronary arteries	Possible acute inflammatory changes in atherosclerotic plaques; possible coronary vasoconstriction
Pulmonary circulation	Increased pulmonary artery pressures
Cardiac autonomic function	Impairment of cardiovascular autonomic reflexes
Coagulation	Increased procoagulant activity
Renal function and fluid and sodium balance	Increased production of vasopressin; decreased ACE activity; water retention; acute kidney injury

**Note:** Reprinted from *The Lancet*, Vol 381, Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA, Acute pneumonia and the cardiovascular system, Pages 496–505,<sup>16</sup> Copyright © 2013, with permission from Elsevier.

**Abbreviations:** ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide.

protection wanes after 5 years.<sup>31</sup> Unlike conjugate vaccines, PPSVs have not been shown to interrupt carriage and therefore do not have the potential for herd effects.<sup>32–35</sup> There is no discernible impact of PPSV23 on population incidence of IPD, and the older and high-risk individuals are less likely to benefit.<sup>36</sup> However, based on vaccine efficacy estimates, PPSV23 is still considered a cost-effective intervention for the low-risk elderly.<sup>31,37</sup>

Overall, PPSV is quite a safe vaccine with minimal side effects, even in pregnancy.<sup>32</sup> The Advisory Committee on Immunization Practices (ACIP) states that a pneumococcal vaccine may be administered at the same time as an influenza vaccine (by separate injection in the other arm) without an increase in side effects or decreased antibody response to either vaccine.<sup>38</sup> Recent studies indicated asthma as an independent risk factor for IPD, and the risk among persons with asthma was at least double that among controls.<sup>39</sup> Similarly, smoking

**Table 3** 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

**Abbreviations:** PCV7, seven-valent pneumococcal conjugate vaccine; PCV10, ten-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

was determined to be the strongest independent risk factor for IPD in immunocompetent, nonelderly adults.<sup>40</sup> Consequently, in 2008, ACIP recommendations for PPSV23 were expanded for smokers and asthma patients.<sup>41</sup> However, in some countries where PPSV23 is officially recommended, the estimated vaccination uptake is very low (around 2% in Switzerland).<sup>42</sup> A recent survey in Switzerland among general practitioners revealed little priority for pneumococcal vaccination in daily practice, especially in comparison with the importance of other vaccinations, namely influenza. This low level of priority may be supported by the fact that general practitioners rarely ever experience a case of severe PD in their daily work. Insufficient evidence from PPSV23 clinical trials and existing epidemiologic data may have enhanced the lack of attention given to pneumococcal vaccination in general practice.<sup>42</sup>

## Conjugate vaccines

In an effort to improve the immunogenicity of vaccines, pneumococcal conjugate vaccines (PCVs) were developed. The advantages of the conjugate vaccines are related to the way the antibodies are produced by the body. PCV induces a T-cell-dependent response which results in plasma cells producing immunoglobulin G but also produces memory B-cells. This T-cell-dependent response elicits immunological memory, and therefore primes the immune system for either natural exposure or subsequent booster vaccination. The latter observation may be considered a surrogate for exposure to the polysaccharide during a “natural” infection.<sup>43</sup> There is no decrease in the immune response seen with revaccination with conjugate vaccines, as they produce immunoglobulin G rather than just immunoglobulin M.<sup>44</sup> Memory B-cells ensure boosting of the effect with revaccination. Memory B-cells are not produced in response to most free polysaccharide vaccines and, in fact, may be depleted post-vaccination, resulting in hyporesponsiveness.<sup>38,45</sup>

Seven-valent PCV (PCV7), which included the purified capsular polysaccharides of seven serotypes conjugated to a nontoxic variant of diphtheria toxin known as CRM197, was developed in 2000 (Table 3).<sup>46</sup> PCV7 was licensed for children in Singapore in 2002 and PCV7 vaccination officially became part of the National Childhood Immunization Program (NCIP) in October 2009.<sup>13</sup> After PCV7 was introduced in the US, rates of IPD caused by the seven serotypes have decreased substantially even among the unvaccinated population.<sup>47</sup> The indirect benefits of vaccination, or herd effects, likely result from reduced nasopharyngeal carriage of pneumococcus in PCV7-vaccinated children and reduced transmission from children to unvaccinated children and

adults.<sup>48</sup> Surveillance data has shown reduction in IPD, pneumonia, and acute otitis media in young children after the introduction of PCV7 in many different geographic locations.<sup>23,30</sup> A clinical trial in Malawi in predominantly HIV-infected adults documented significant protection from PCV7. In this study, survivors of pneumococcal pneumonia were randomized to receive PCV7 or placebo and were followed up thereafter for a mean of 1.2 years. The rates of protection were 74% in HIV-infected persons.<sup>49</sup> PCV7 has also been shown to induce a superior immune response in patients with chronic obstructive pulmonary disease when compared with PPSV23.<sup>50</sup>

In order to provide improvements in serotype coverage and potentially reduce the remaining IPD burden, further improvements in conjugate vaccines were released. A ten-valent PCV using recombinant nontypeable *Haemophilus influenzae* protein D as the conjugate was registered in Singapore and has been available since April 2010 (Table 3). A 13-valent PCV (PCV13) was approved for children in Singapore in 2010 and was introduced in the NCIP of Singapore in December 2011.<sup>13</sup> PCV13 received Health Sciences Authority approval for expanded use in adults aged >50 years for the prevention of pneumonia and IPD on February 7, 2012.

PCV13 comprises “13” *S. pneumoniae* polysaccharide serotypes, including the existing seven in PCV7 and six additional serotypes (Table 3). The immunogenicity of PCV13 has been evaluated in a number of trials in healthy infants in comparator studies versus PCV7 and when coadministered with other vaccines.<sup>51</sup> Noninferiority in terms of the proportion of responders 1 month after the final dose of the primary series of PCV13 versus PCV7 has been demonstrated for six of the seven common serotypes in one pivotal study<sup>52</sup> and in five of the seven in another.<sup>53</sup> The remaining six serotypes in PCV13 also demonstrated robust immune responses.<sup>52,53</sup> Importantly, functional antibodies were elicited against all 13 serotypes contained in PCV13 after primary vaccination.<sup>52,53</sup> Recently, the results of first randomized PCV13 versus PCV7 pediatric trial results were published. PCV13 resulted in lower acquisition and prevalence of nasopharyngeal colonization than PCV7 for four additional PCV13 serotypes, and serotypes 6C and 19F. It was comparable with PCV7 for all other common serotypes.<sup>10</sup> Evidence for PCV13 protective effectiveness against IPD is also beginning to emerge in many industrialized countries such as England, Wales, Germany, and the US.<sup>53</sup> These findings predict vaccine effectiveness through both direct and indirect protection. PCV13 immunogenicity and safety was also demonstrated either alone or

with concomitant administration of a trivalent inactivated influenza vaccine in adults aged  $\geq 65$  years who were naive to PPSV23.<sup>54</sup>

A meta-analysis of all available published data from controlled clinical trials of PCV (any valency) found the efficacy of PCV in the reduction of IPD was 89% for disease due to vaccine serotypes and 63%–74% for disease due to all serotypes. The efficacy to prevent acute otitis media by vaccine serotypes was 55%–57% and 29% to prevent otitis media involving all serotypes. However, the efficacy to prevent clinical pneumonia was only 6%–7%, although it was 29%–32% to prevent radiograph-confirmed pneumonia.<sup>55</sup>

## PCV13 for the prevention of PD in adults

Despite multiple studies conducted for more than 30 years, the efficacy and effectiveness of PPSV23 in adults remain a subject of controversy.<sup>36</sup> In a World Health Organization-commissioned meta-analysis and a review of randomized controlled trials, the results of the randomized controlled trials of PPSV23 are consistent with a protective effect against IPD and all-cause pneumonia among generally healthy young adults and, to a lesser extent, in the general population of elderly people.<sup>56,57</sup> However such trials have not demonstrated that PPSV23 is efficacious against either IPD or all-cause pneumonia in populations at higher risk, such as individuals with underlying conditions that increase their risk of PD or highly immunosuppressed individuals of any age.<sup>57,58</sup>

The availability of PCV13 in adults, however, sometimes creates a unique dilemma for clinicians as it is unusual to have availability of a new pediatric vaccine for a disease that is important in adults.<sup>59</sup> Further complicating the situation is the lack of clear evidence regarding the relative benefits of PCV13 compared with PPSV23 in adults. However, several lines of evidence suggest the possibility that PCV13 may be more efficacious in adults than PPSV23.<sup>59</sup> Relative absolute efficacy of the PCV13 and PPSV23 vaccines can be best demonstrated by randomized controlled trials; however, performing such trials is extremely difficult and expensive. Documenting an organism-specific effect for pneumococcal pneumonia can be quite challenging. Randomized trials of pneumococcal vaccine must be extremely large to have adequate statistical power. Cohort and case-control studies, although cheaper and logistically easier, can introduce bias from known and unknown confounders.<sup>59</sup> Hence, the development of surrogate markers for vaccine efficacy has been critical. Enzyme-linked immunosorbent assay can be used to measure anti-pneumococcal immunoglobulin G



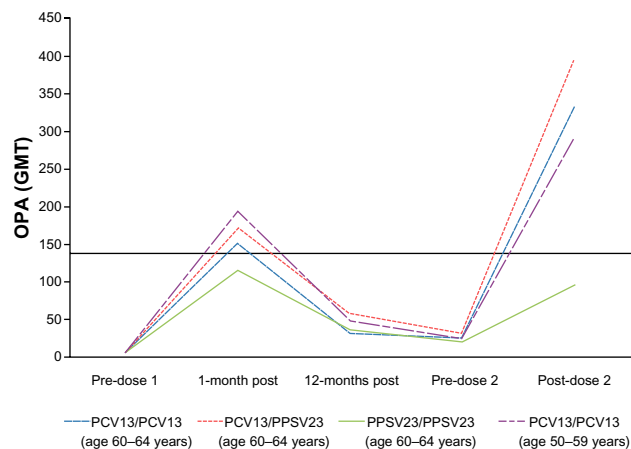
antibodies, but cannot distinguish between functional and nonfunctional antibodies.<sup>60</sup> Opsonophagocytic activity of pneumococcal polysaccharide antibodies in vitro is a measure of antibody functional activity and has been shown to correlate with immune protection more than enzyme-linked immunosorbent assays.<sup>61,62</sup> This is because opsonophagocytic activity is the mechanism of protection against PD, and hence it is the most appropriate assay for comparing antibody responses elicited by vaccines as well as for comparing the responses to various dosing regimens.<sup>43</sup>

The clinical program of PCV13 was designed to show that it could induce a T-cell-dependent response that could then be recalled or boosted by either natural exposure or a subsequent vaccination, or both.<sup>43</sup> Pivotal Phase III clinical trials with PCV13 in adults have been performed in two populations aged  $\geq 50$  years: those who were naive to previous vaccination (Study 004)<sup>63,64</sup> and those who had been previously vaccinated with PPSV23 but not within the past 5 years (Study 3005).<sup>65</sup> An opsonophagocytic activity titer that correlates with protection has not been defined. Based on matching immunogenicity to efficacy results from several infant PCV7 or nine-valent PCV efficacy trials, a PCV13/PPSV23 geometric mean titer ratio was determined.<sup>63–65</sup> If the lower 95% confidence interval of the ratio was  $>0.5$  for serotypes in common, then the response was considered similar or noninferior. If, however, the lower 95% confidence interval was  $>1.0$ , then the response was considered to be statistically significantly higher or superior.<sup>43,63–65</sup>

Study 004<sup>63</sup> was conducted in two age cohorts who had never received a pneumococcal vaccine previously: those aged 50–59 years and 60–64 years. At 1 month following the first dose, the response to a single dose of PCV13 was at least as good as the response to PPSV23 for all of the serotypes (noninferior) and statistically significantly higher for nine of the 13 serotypes. The overall superior response to a single dose of PCV13 was seen consistently throughout the clinical program. The response to a dose of PCV13 in those aged 50–59 years (mean age 54 years) was superior to the response in the 60–64 years cohort for eight of the twelve serotypes common to both vaccines and for serotype 6A, a serotype unique to PCV13, indicating the importance of age as a factor in the immune response. In the follow-up of Study 004<sup>64</sup> conducted about 4 years later, the adults aged 60–64 years initially given PCV13 received PCV13 or PPSV23, and those initially given PPSV23 received another PPSV23. All adults aged 50–59 years were revaccinated with PCV13. Initial vaccination with

PCV13 established an immune state that resulted in recall of anti-pneumococcal responses upon subsequent vaccination with either a conjugate or free polysaccharide vaccine. In contrast, initial vaccination with PPSV23 resulted in an immune state in which subsequent PPSV23 administration yielded generally lower responses compared with the initial responses. Figure 1 shows the pattern of the immune response to serotype 1, which is illustrative of the sequences for the majority of serotypes.

Study 3005<sup>65</sup> enrolled PPSV23 exposed individuals (mean age 77 years) to receive either PCV13 or PPSV23 again. The pattern of the immune response was essentially the same as that seen in the PPSV23-naive adults (Study 004), although the magnitude of the response was somewhat lower in these older individuals. The response to PCV13 was at least as good as the response to PPSV23 and was statistically significantly higher for eleven of the 13 serotypes. Subjects were reimmunized 1 year later with PCV13, regardless of whether they had received PCV13 or PPSV23 the previous year. Subjects who had previously received a dose of PCV13 had a response that was at least noninferior to the first dose. In contrast, subjects who had received PPSV23 a year previous had a significantly reduced response to PCV13 (Figure 2 shows the pattern of

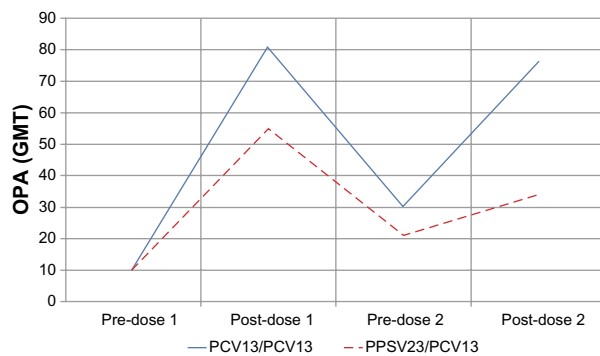


**Figure 1** Functional immune responses for pneumococcal serotype 1 (GMT) in the pivotal noninferiority trial (Study 004) measured pre- and post-vaccination using a functional OPA assay.

**Notes:** Antibodies were determined before first vaccination (pre-dose 1), 1 month after vaccination (1 month post), and 12 months after first vaccination (12 months post); and before the second vaccination 3–4 years later (pre-dose 2) and 1 month after the second vaccination (post-dose 2). An OPA titer that correlates with protection has not been defined. The dark straight line at GMT ~140 represents the minimum GMT peaks attained following first dose of PCV13 to help understand amplification of response following revaccination. This demonstrates that PCV13 primed the immune system for a booster response to subsequent vaccination with either vaccine. In contrast, the PPSV23 vaccine inhibited the response to a second dose of the same vaccine, and this was seen for all of the serotypes (serotype 1 is shown in figure as an example).

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**Abbreviations:** GMT, geometric mean titer; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.



**Figure 2** Functional immune responses for pneumococcal serotype 1 (GMT) in the pivotal noninferiority trial (Study 3005) measured pre- and post-vaccination using a functional OPA assay.

**Notes:** Study 3005<sup>65</sup> enrolled PPSV23 exposed individuals (mean age 77 years) to receive either PCV13 or PPSV23 again. Subjects were reimmunized 1 year later with PCV13 regardless of whether they had received PCV13 or PPSV23 the previous year. Antibodies were determined before first vaccination (pre-dose 1), 1 month after vaccination (post-dose 1), before the second vaccination (pre-dose 2), and 1 month after the second vaccination (post-dose 2). Study 3005 showed that PPSV23 also blunted the response to a dose of the conjugate vaccine (serotype 1 is shown in figure as an example).

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**Abbreviations:** GMT, geometric mean titer; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

responsiveness to serotype 1 as an example). In summary, although Study 004 in vaccine-naïve adults showed that PPSV23 blunted the response to a second dose of the same vaccine, Study 3005 showed that PPSV23 also blunted the response to a dose of the conjugate vaccine.

At the current time there is no clinical efficacy data regarding PCV13 efficacy in adults. The ongoing CAP Immunization Trial in Adults (CAPiTA) hopes to establish the efficacy of PCV13 in the prevention of pneumococcal CAP, non-bacteremic pneumococcal CAP, and IPD in community-dwelling elderly adults.<sup>66</sup> Although CAPiTA is the largest vaccine efficacy placebo-controlled trial ever conducted in older adults worldwide, it does not include PPSV23 as an active comparator. The uncertainty surrounding the efficacy of PPSV for the prevention of noninvasive pneumococcal pneumonia made it very difficult to design an appropriate study and the required study size would likely have been prohibitive and made it logistically unfeasible.<sup>66</sup> Recently, it was announced that CAPiTA has completed pneumonia case accrual and top-line results are expected in early 2014.<sup>67</sup> The principal disadvantages of PCVs are their lesser breadth of coverage and the appearance of replacement strains. Although it is possible that with the widespread use of PCV13 new replacement strains will be those contained in PPSV23, it is also possible that altogether new strains may emerge not covered by any current vaccine. As per the Singapore Ministry of Health data published recently

in 2013, the latest potential coverage rates of PCV13 and PPSV23 for adult IPD in 2012 were 67.9% and 75.4%, respectively.<sup>13</sup>

## Is direct protection of adults with PCV13 required despite indirect benefits of herd effect?

The strongest argument against the routine use of PCV13 in adults, whether they be healthy or immunocompromised, comes from the fact that routine PCV vaccination of children has also reduced the incidence of conjugate vaccine serotype disease in older adults.<sup>31</sup> In PCV7-vaccinated children, the incidence of IPD was reduced by >90%. Not only was the effect in vaccinated children dramatic with widespread use of this vaccine, IPD in children who had not been vaccinated and in adults of all ages also decreased substantially. This phenomenon is called the herd effect: vaccinating a critical number of members of a population, especially with an agent that reduces colonization and infection, protects those who are unvaccinated.<sup>68</sup> Herd effect is not the same as herd immunity. Herd immunity means that the immune system of unvaccinated persons has been affected by contact with a live vaccine strain or virus. For example, an unvaccinated person can develop immunity to poliovirus by being exposed to vaccine virus shed by a vaccinated person after receiving live oral polio vaccine.<sup>69</sup> Herd effect, unlike herd immunity, does not affect the immune system of unvaccinated persons. Unvaccinated individuals remain susceptible to infection if they come into contact with persons capable of transmitting disease.<sup>69,70</sup> Herd effect will not be seen immediately after the introduction of a new vaccine. For most infectious diseases, there is a threshold of vaccine coverage (uptake) that must be achieved for a herd effect to be seen. It takes time to reach that threshold.<sup>71</sup> Herd effect is also dependent on the degree of vaccine coverage (uptake) in children. For example, herd effects with PCV have not been observed in countries with a low vaccine uptake. Furthermore, today's society is highly mobile. Even if an individual is a member of a population (herd) in which vaccine uptake is high, he or she will lose that protection upon leaving the herd and moving to another herd in which vaccine uptake is low. Furthermore, immunocompromised individuals are at much higher risk for IPD.<sup>72</sup>

Cohen et al studied the herd effects of pediatric use of PCV7 on the adult population with and without HIV infection. Declines in cases of IPD were observed in both groups; however, because of the high pre-PCV7 incidence of IPD in adults with HIV, the remaining disease burden was high despite a significant herd effect.<sup>73</sup> From 2004–2007, the incidence of IPD

in HIV-positive adults was 385 per 100,000. The incidence of IPD was approximately 40 times as high among adults with HIV infection as among adults without HIV infection, which called for more aggressive prevention measures.<sup>73</sup> This study served as the basis for the ACIP recommendation on the use of PCV13 in adults who have immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants.<sup>74</sup>

A well-defined herd effect has also been observed in the US, UK, and Australia after introduction of PCV7 into their NCIPs.<sup>68,75,76</sup> However, even after implementation of nationwide vaccination programs in France, Spain, and The Netherlands, analyses of epidemiological statistics in these countries showed significant serotype replacement and little evidence of a herd effect.<sup>77–80</sup> It is hypothesized that serotype replacement has a disproportionate effect on herd effect due to the differing serotype distributions in the pediatric and adult populations.<sup>81</sup> Therefore, the assumption that Singapore would experience a robust herd effect similar to that seen after implementation of PCV7 vaccination in the US (30% of direct effect) was modified by the Singapore Ministry of Health.<sup>82</sup> Given that negligible herd effects had been seen in most European investigations, there would be no guarantee of reductions in PD in the unvaccinated population; hence, there seems a need for direct protection of adults. The herd effect is also dependent on the degree of vaccine coverage (uptake) in children. For example, herd effects with PCV have not been observed in countries with a low vaccine uptake.<sup>71</sup> Based on 2011 data from the Singapore National Immunization Registry, the vaccination uptake for pneumococcal vaccines (PCV7 and/or PCV13) was only 52% for children aged 1 year.<sup>13</sup> So far, no significant changes in pneumococcal population dynamics related to herd effects of PCV13 have been observed in Singapore.<sup>13</sup> However, PCV13 was included in the Singapore NCIP <2 years ago; hence, it might be also too early to document herd effects.

## International recommendations for the use of pneumococcal vaccines in adults

In 2013, the US ACIP<sup>83</sup> recommended vaccination with PPSV23 for all adults aged  $\geq 65$  years and all adults <65 years with chronic lung disease, chronic cardiovascular diseases, diabetes mellitus, chronic renal failure, nephrotic syndrome, chronic liver disease (including cirrhosis), alcoholism, cochlear implants, cerebrospinal fluid leaks, immunocompromising conditions, functional or anatomic asplenia, residents of nursing homes or long-term care facilities, and adults who smoke cigarettes.

Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis. When cancer chemotherapy or other immunosuppressive therapy is being considered, the interval between PPSV23 and initiation of immunosuppressive therapy should be  $\geq 2$  weeks. Vaccination during chemotherapy or radiation therapy should be avoided. Guidance on PPSV23 revaccination is outlined in Table 4.

There were no specific local/international recommendations for use of PCV13 in adults until June 2012 when the ACIP in the US made their recommendations for adults aged >19 years with immunocompromising conditions, functional or anatomical asplenia, cerebrospinal leaks, or cochlear implants (Table 5).<sup>74</sup> In 2013, ACIP added guidance for the first time on the timing of administration of PCV13 relative to the PPSV23 in adults.<sup>83</sup> In the conditions when

**Table 4** Advisory Committee on Immunization Practices 2013 updates/highlights related to pneumococcal vaccination in adults

### Updates for PCV13

- Adults  $\geq 19$  years\* with immunocompromising conditions who have not previously received PPSV23 or PCV13 should receive a single dose of PCV13 followed by a dose of PPSV23  $\geq 8$  weeks later.
- Adults  $\geq 19$  years with immunocompromising conditions who have previously received one or more doses of PPSV23, should receive a single dose of PCV13  $\geq 1$  year after the last dose of PPSV23 was received.
- Recommendations for the second dose of PPSV23 remain unchanged ( $\geq 5$  years after the first dose in adults aged 19–64 years with immunocompromising conditions and a single dose after age 65 years for all who received first dose before age 65 or later if  $\geq 5$  years have passed since the previous dose).
- When cancer chemotherapy or other immunosuppressive therapy is being considered, the interval between PPSV23 vaccination and initiation of immunosuppressive therapy should be  $\geq 2$  weeks. Vaccination during chemotherapy or radiation therapy should be avoided.
- No direct guidance on the timing of PCV13 in relation to chemotherapy or radiation therapy. But in general, PCV13 should be given first and  $\geq 8$  weeks before PPSV23 when both PCV13 and PPSV23 are indicated in adults.
- PCV13 has not yet been recommended for routine vaccination of older adults, but recommends PPSV23 for all adults aged  $\geq 65$  years.

### Updates for PPSV23 (on revaccination)

- One-time revaccination 5 years after the first dose is recommended for persons aged 19–64 years with chronic renal failure or nephritic syndrome; functional or anatomic asplenia (eg, sickle cell disease or splenectomy); and for persons with immunocompromising conditions.
- Persons who received one or two doses of PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if  $\geq 5$  years have passed since their previous dose.
- No further doses are needed for persons vaccinated with PPSV23 at or after age 65 years.

**Notes:** \*PCV13 is licensed by the US Food and Drug Administration and Singapore Health Sciences Authority for use in adults  $\geq 50$  years of age only. Data from the Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention.<sup>83</sup>

**Abbreviations:** PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.



**Table 5** Advisory Committee on Immunization Practices 2012 recommendations on medical conditions or other indications for administration PCV13 and PPSV23 for adults aged  $\geq 19$  years,\* by risk group

Risk group	Underlying medical condition	PCV13	PPSV23	
		Recommended	Recommended	Revaccination 5 years after first dose
Immunocompetent persons	Chronic heart disease <sup>†</sup>		✓	
	Chronic lung disease <sup>‡</sup>		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leak	✓	✓	
	Cochlear implant	✓	✓	
	Alcoholism		✓	
	Chronic liver disease, cirrhosis		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathy	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓
Immunocompromised persons	Congenital or acquired immunodeficiency <sup>¶</sup>	✓	✓	✓
	Human immunodeficiency virus infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin's disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression**	✓	✓	✓
	Solid organ transplant	✓	✓	✓
Multiple myeloma	✓	✓	✓	

**Notes:** \*All adults aged  $\geq 65$  years should receive a dose of PPSV23 regardless of previous history of vaccination with pneumococcal vaccine. <sup>†</sup>Including congestive heart failure and cardiomyopathy, excluding hypertension. <sup>‡</sup>Including chronic obstructive pulmonary disease, emphysema, and asthma. <sup>¶</sup>Including B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease). \*\*Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy. Reprinted from Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2012;61(40):816–819.<sup>74</sup>

**Abbreviations:** PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

both PCV13 and PPSV23 are indicated in adults, a dose of PCV13 should be given first. For those that require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and  $\geq 5$  years since the most recent dose of PPSV23.<sup>83</sup> Although ACIP recommends PCV13 for adults aged  $\geq 19$  years with the specific medical conditions noted above. However, PCV13 is currently licensed by the US Food and Drug Administration and Singapore Health Sciences Authority for use among only in adults aged  $\geq 50$  years (Table 4).<sup>83</sup> On May 30, 2013, the Committee for Medicinal Products for Human Use, European Medicines Agency adopted a positive opinion recommending PCV13 for active immunization for the prevention of invasive disease caused by *S. pneumoniae* in adults  $\geq 18$  years of age as well.<sup>84</sup>

## Cost-effectiveness of pneumococcal vaccines

The costs associated with the treatment of CAP are considerable, although it is difficult to determine accurate

cost-effectiveness data. A study conducted in a large urban hospital in the US showed that median hospital costs were \$8,654 and \$9,441 for CAP mediated by penicillin-susceptible and penicillin nonsusceptible *S. pneumoniae*, respectively.<sup>85</sup> Several years ago, before the widespread introduction of PCV7 vaccination for children, the cost-effectiveness of PPSV23 vaccination to prevent IPD was evaluated in ten Western European countries (PPSV23 was given concomitantly with influenza vaccine). PPSV23 was found to be acceptably cost-effective in all ten countries studied. However, while encouraging, these studies may not be relevant in countries that have introduced widespread vaccination of children with PCVs.<sup>31</sup>

There are few Asian cost-effectiveness studies of conjugate vaccines but all conclude that the inclusion of indirect or herd effects is essential to a positive assessment. PCV7 in children was found to be cost-effective when including herd effects in Hong Kong,<sup>86</sup> but not cost-effective when herd effects were excluded in a Korean study.<sup>87</sup> Similarly, in the US, PCV13 has been estimated to be highly cost-effective if

herd effects were included,<sup>88</sup> but studies in The Netherlands excluding herd effects do not support this conclusion.<sup>81</sup> A US cost-effectiveness study indicated PCV13 vaccination was favored compared with PPSV23 when substituted using the current recommendations, but the analysis was sensitive to assumptions about PCV13 effectiveness against non-bacteremic pneumococcal pneumonia and the magnitude of potential indirect effects from childhood PCV13 on pneumococcal serotype distribution.<sup>89</sup> Another US study found that one dose of PCV13 is more cost-effective for immunocompromised individuals than previous vaccination recommendations and may be more economically reasonable than current recommendations depending on life expectancy and vaccine effectiveness in the immunocompromised. However, the findings were based on the assumption that both vaccines prevented IPD, but only PCV13 prevented non-bacteremic pneumonia.<sup>90</sup>

## Pneumococcal vaccine utilization for adults

In Singapore, as well as globally, all adult vaccines remain underused.<sup>91–92</sup> Rates of vaccination of adults have consistently fallen behind vaccination rates for children and adolescents.<sup>92</sup> The Centers for Disease Control and Prevention estimated that 40,000–50,000 vaccine-preventable deaths occur every year in the US and estimates the health care burden of vaccine-preventable diseases at \$10 billion.<sup>92</sup> The Centers for Disease Control and Prevention analyzed data from the 2010 National Health Interview Survey to assess adult vaccination rates and found them to be low for most routinely recommended vaccines. Only three vaccines are included in Healthy People 2020 – pneumococcal, herpes zoster, and hepatitis B (for health care personnel). These uptakes are well below the respective target levels. The uptake for pneumococcal vaccine in 2010 was only 59.7% for persons aged >65 years (Healthy People 2020 target: 90%) and 18.5% for persons at high risk aged 18–64 years (Healthy People 2020 target: 60%).<sup>92,93</sup>

In 2005, the World Health Organization estimated that 1.6 million people died of PD throughout the world, mainly the elderly and small children.<sup>23</sup> In 2005 in the US, more than 40,000 cases and more than 4,400 deaths from IPD were estimated. More than half of these cases occurred in adults for whom the PPSV was indicated.<sup>94</sup> Sustained declines in IPD have occurred among adults with acquired immunodeficiency syndrome in the US, but incidence remains high 7 years after PCV7 introduction. More aggressive efforts, including use of new PCVs in HIV-infected adults have been

suggested to reduce IPD among HIV-infected adults.<sup>73</sup> It is difficult to extrapolate from these conditions to conditions in the developed world, but the results suggest that, even in the developed world, patients with acquired immunodeficiency syndrome might respond to PCV.<sup>36</sup> Combination of the public seasonal flu vaccination campaign with a campaign for pneumococcal vaccination has been suggested to increase the pneumococcal vaccination rate.<sup>42</sup>

While there is less data in Asia regarding adult vaccine uptake compared to Western countries, several studies suggest there is significant PD in Singapore and vaccination should impact on reducing disease.<sup>9,26,27</sup> The increase in the elderly population globally and in Singapore makes intervention in reducing PD an important priority. Family physicians are specialists in preventive care and can be leaders in ensuring that adult patients get the full benefit of protection against vaccine-preventable diseases. Standing order programs, which allow for vaccination without an individual physician order, are one of the most effective mechanisms to achieve high pneumococcal vaccination rates in adults.<sup>95–96</sup> Since December 2010, one of the largest public hospitals piloted an innovative pre-discharge vaccination program for the first time in Singapore. This hospital-wide initiative integrates influenza and pneumococcal vaccination into standardized pre-discharge procedure for inpatients with appropriate medical indications. Patients and families may opt out, if desired. Pharmacists screen patients for indications and contraindications according to a pre-approved checklist and a vaccine is administered on the day of discharge by the nurse. This program enabled over 100 patients per month to get vaccinated who would not otherwise have received the vaccines. Such programs would be very useful if implemented nationwide to achieve maximum coverage and penetration for adult vaccination.<sup>91</sup>

## Conclusion

Improving the vaccination rates may contribute to a reduction in morbidity and mortality associated with PD affecting adults. Advances in vaccine production have provided both conjugate- and polysaccharide-based vaccines enabling wider serotype coverage and providing greater access to those in need. Studies indicate that conjugate vaccination of children can interrupt the transmission of pneumococci to adults and may prevent disease among adults, but there are also clear benefits of direct vaccination in adult populations. A significant burden of disease remains, particularly in immunocompromised and some immunocompetent adults with comorbidities; this remaining burden of disease may

warrant a direct vaccination approach. It would be reasonable to conclude that for pneumococcal pneumonia prevention most high-risk adult patients may be best served by a combination of PCV13 and PPSV23, provided that PCV13 is given first. However, unless official country guidelines address potential advantages of PCV13 in adults especially in high-risk patients, physicians may be reluctant to consider it in routine clinical practice. There is a need for urgency about potential missed opportunities to prevent morbidity and death from PD in adults. Although reassessing local policy regarding pneumococcal vaccination in adults will require careful analysis of available information, advisory groups are encouraged to tackle this issue at the earliest opportunity.

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