



Is there a potential role for protein-conjugate pneumococcal vaccine in older adults?

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EDITORIAL

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Abstract

Longstanding controversy over the efficacy of 23-valent pneumococcal polysaccharide vaccine (PPV23) led to a recommendation by the Joint Committee on Vaccination and Immunisation (JCVI) of the United Kingdom in March 2011, to discontinue routine use of PPV23 in older adults.¹ Following careful review of the evidence and feedback from stakeholders, the JCVI decided to retain the original policy of uniform vaccination of adults >65 years of age, while keeping the subject under continued review. In the United States, the Advisory Committee on Immunization Practices (ACIP) which is also concerned about the efficacy of PPV23 is currently considering a different strategy, i.e. adding 13-valent pneumococcal protein-conjugate vaccine (PCV13) for recommended use in adults, following recent Food and Drug Administration (FDA) approval for this purpose in adults over 50 years of age. It is therefore timely to review the options for prevention of pneumococcal disease in adults.

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality worldwide. Invasive pneumococcal disease (IPD) is a significant cause of morbidity and mortality among persons aged 65 years and older. Pneumococcal disease burden also remains high among adults over 50 years of age. While the precise incidence of non-invasive infection is not known, the Active Bacterial Core Surveillance of the Centers for Disease Control (CDC) identified 27,000 cases of IPD with 4,000 deaths attributable to this disease in the US alone in 2009.² Moreover, there were 242,000 emergency room visits, and 1.4 million hospital days lost due to pneumonia in the US, among adults aged 65 years or older,³ *S. pneumoniae* is believed to be the principal identifiable cause.⁴

Polysaccharide pneumococcal vaccine (PPV23) was introduced in 1983.⁵ It contains capsular polysaccharides from 23 of the 92 known pneumococcal serotypes which, until recently, were responsible for over 80% of all cases of IPD. In the US, the Advisory Committee on Immunization Practices (ACIP) currently recommends PPV23 for all adults over 65 years, and persons 2-64 years old who live in high-risk settings or who suffer from certain co-morbid conditions that increase their risk for pneumococcal disease.⁶ The ACIP recommends revaccination with PPV23 if the first dose was given before the age of 65 and more than five years have elapsed. Most economic evaluations suggest that this public health strategy is cost-effective.^{2, 3, 6} In Australia, under the Australian government's National Immunisation Program, PPV23 is provided free for adults over 65 years, Aboriginal and Torres Strait Islander people over 50 years old, tobacco smokers and anyone over 10 years of age who is adjudged predisposed to IPD. The vaccine was initially recommended once every five years but, in 2010⁷, the Therapeutic Goods Administration (TGA) received 178 reports of adverse reactions, representing about a five-



fold increase over the reported rate in 2009. Therefore, in April 2011, the TGA recommended that physicians not administer a second dose of PPV23 until completion of an investigation of the problem.⁷

Despite these recommendations, the efficacy of PPV23 has remained controversial. The CDC has concluded that overall protection against IPD is about 50-60%,⁸ but expressed uncertainty about protection against non-bacteremic pneumococcal pneumonia, and has not changed its recommendation. A 2008 meta analysis by Moberley et al⁹ found that vaccination with PPV23 was associated with a 53% decrease in all non-bacteremic pneumococcal pneumonia (NBPP), a 74% decrease in all-cause IPD and a 92% decrease IPD specifically due to vaccine types. In 2009, a meta analysis by Huss et al reached a different conclusion. The latter study weighted articles based on statistical, but not necessarily clinical, criteria for excellence; with no more than four to five studies remaining in their analysis, the authors found no benefit from PPV23. The problem with this work is that the two studies to which they gave greatest weight^{10,11} were well designed and executed from epidemiological and statistical points of view, but they based the diagnosis of pneumococcal pneumonia on detection of antibody to pneumolysin in circulating immune complexes – a method that was subsequently shown to be invalid¹². In fact, Orqvist et al¹¹ found five patients with positive blood cultures in the control group and only one in the vaccinated group, but the difference was not significant. The analysis by Moberley et al suggests that PPV23 is an effective agent in preventing non-bacteremic pneumococcal pneumonia as well as IPD. Interestingly, new independent analyses of UK epidemiological data on invasive pneumococcal disease played a role in the JCVI decision to retain the original recommendation for use of PPV23. They concluded that whilst there remains some uncertainty at present, evidence does favour moderate short-term protection. The findings of the new analyses suggest that despite the limited effectiveness of the vaccine the programme remains cost-effective and probably more reasonable than implementing a risk group-based programme. Thus, the JCVI has advised that the existing routine universal PPV23 programme for those aged over 65 years should continue but be kept under review.¹³

The limitations of PPV23 are: (a) questionable effectiveness against non-bacteremic pneumonia; (b) absence of effectiveness for mucosal infections; (c) failure to establish immunologic memory (T-cell independent pathways); (d) limited duration of efficacy; (e) further

diminished efficacy in immune-compromised individuals; and (f) possible hypo-responsiveness following multiple/repeated doses. Of note, following vaccination with PPV23, antibody levels decline after 5–10 years and they decrease more rapidly in some groups than others.⁶ However, the relation of these levels with protection against disease is uncertain limiting the ability to define the need for revaccination on the basis of antibody levels alone.

Infants and very young children do not produce antibody to purified polysaccharide antigens. To help overcome this problem, a protein-conjugate vaccine to prevent infection due to *Haemophilus influenzae* b was developed in the 1980s and was remarkably successful in eliminating meningitis and bacteremia due to this pathogenic bacterium. By analogy, a protein-conjugate pneumococcal vaccine, first containing 7 capsular serotypes (PCV7) and now containing 13 serotypes (PCV13) has been developed. In the conjugate vaccines, the protein carriers induce a T-cell dependent immune response to the polysaccharides, leading to immunological memory with boosting after repeated injection.⁶ PCV has been successful in reducing disease due to vaccine serotypes. A 90% decline in invasive disease due to vaccine types has been observed among vaccinated children. Conjugate vaccines also prevent colonisation, and their widespread use in children has been followed by a great reduction in pneumococcal disease in non-vaccinated children and adults, an effect that is termed the 'herd effect.' This herd effect reflects the striking decline of vaccine serotypes, formerly among the most common causes of pneumococcal disease, in the population. Unfortunately, this phenomenon has been accompanied by their replacement with strains that are not contained in the vaccine. Examples of replacement strains include 19A, 6A and 33. In the past few years, serotype 19A has become the most common cause of pneumococcal disease in adults in the US.^{14,15} Thus, although the overall incidence of pneumococcal disease is lower than it was before the introduction of PCV7, most strains that now commonly infect children and adults are not included in PCV7; some, but not all, of these common replacement strains are contained in PCV13.

The immunologic properties of conjugate vaccine suggest that PCV might offer advantages over PPV23 in adults. This suggestion has prompted studies to compare surrogate markers of immunity such as antibody levels and opsonic activity for pneumococci after vaccination of healthy or immune-compromised adults with PPV23 and PCV7 or PCV13. These studies have shown that adults



who receive PPV23 have levels of antibody and opsonic activity that are very similar those in adults who receive either PCV7 or PCV13.

No studies have been performed to directly compare the clinical efficacy of PPV23 and PCV. A placebo-controlled trial of PPV23 in patients with AIDS in Uganda showed no protective effective of vaccination.¹⁷ In contrast, a trial by the same investigators of PCV7 in AIDS patients in Malawi¹⁸ showed a 74% decrease in IPD in first year after vaccination; protection fell off rapidly after that. Taken together, these results suggest a possible advantage for conjugate vaccine in AIDS patients in countries with high endemicity of pneumococcal disease. A large study funded by the pharmaceutical industry is currently in progress in the Netherlands comparing PCV13 to placebo in general healthy adults aged 65 years and over living in the community; unfortunately, there is no PPV23 group.¹⁶ Convincing data, as yet unpublished,¹⁹ show that the conjugate vaccine primes the immunologic system, leading to distinctly better short-term responses after repeated administration of either polysaccharide or protein-conjugate pneumococcal vaccine. The possibility that conjugate vaccine might lead to better antibody responses after a single dose and the fairly clear demonstration of immunological priming has led to suggestions that vaccination programs be developed involving multiple doses of pneumococcal vaccine.

There are three potential problems with multiple dosing. First, the enhanced response to revaccination in subjects who initially received PCV7 or PCV13 has been shown at one month, but its duration beyond that not been demonstrated. One study of revaccination after PCV7 in patients who survived pneumococcal pneumonia showed that these initially higher antibody levels do not last even for six months.²⁰ Second, just as the strains covered by PCV7 became uncommon causes of pneumonia in adults within five years after widespread vaccination was begun, there is good reason to believe that vaccination of young children with PCV13 will lead to a similar decrease in the prevalence of disease in adults by the herd effect. In other words, in an era of universal vaccination of children with PCV13, a programme to administer this vaccine to adults would become superfluous. Finally, a public health policy predicated on repeated doses of conjugate vaccine would raise entirely different cost-benefit considerations that would require careful study.

PCV13, can lower the large, potentially preventable burden of adult disease. Observations of mucosal immunity in children suggest opportunity for prevention of non-invasive pneumococcal pneumonia among adults. The flip

side might be the fact that increasing vaccine coverage among the adult population has been difficult, especially if multiple doses of vaccine are being considered. Most importantly, however, the potential herd effects on adults of widespread vaccination of children with PCV13 may mitigate the utility of PCV13 among adults. More data is needed regarding the optimal timing and schedule of revaccination as well as the clinical safety and effectiveness of more than one dose of PPV23.

As the data on conjugate vaccine in adults is currently limited, the numbers of doses needed in the elderly, the safety of repetitive doses, and the benefits and cost-effectiveness of PCV13 in adults have yet to be established. Thus, as long as the PPV23 contains more serotypes than PCVs, and the safety and efficacy of PCVs in adults is not established, continuing use of PPV23 in persons aged over 65 years remains a recommended public health strategy, especially because strains covered by PCV13 are likely to be greatly reduced in the population in the near future. Pneumococcal conjugate vaccines, inducing immunologic memory would allow an amnestic response to revaccination and might provide longer, more durable protection against infection. While such a possibility is theoretically appealing, the limited data available from older adults receiving PCV have not been promising (see Table 1).

For now, because of its low cost and proven effectiveness, use of PPV23 should remain a public health priority, especially in older adults. Future attention should be directed to the development of vaccines that utilise conserved pneumococcal protein antigens. Pneumolysin is present in all pneumococci; inoculation of purified pneumolysin into the trachea of rodents produces all the stigmata of bacterial pneumonia. Artificial 'knockout' of the capacity to generate this toxin renders pneumococci relatively avirulent, and antibody to it is highly protective in experimental animals. There are also surface-expressed proteins, such as PspA (pneumococcal surface protein A), antibodies to which might enhance opsonisation and phagocytosis. Trials of these proteins as vaccines are currently under progress in humans. Further studies are needed to warrant changes in current recommendations. As of now, it is important to advocate the continuation of present vaccine policies while simultaneously advancing research on protein vaccines.

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PEER REVIEW

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CONFLICTS OF INTEREST

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Not applicable



Table 1: Overview of head-to-head PCV versus PPV23 studies in adults.

Authors	Country	Year	Age	N	Study subjects	Regimens	Results (IgG ELISA ± OPA)*	
deRoux et al. ²¹	Germany	2008	≥ 70 y	219	100% naïve	PCV7: 1y→PCV7: 1m PCV7: 1y→PPV23: 1m PPV23: 1y→PCV7: 1m	ELISA: PCV7 IgG superior for 6/7 serotypes (4, 6B, 9V, 18C, 19F, 23F). OPA: PCV7 superior for 5/7 serotypes (4, 9V, 14, 18C, 23F).	
Dransfield et al. ²²	USA	2009	≥ 40 y	120	COPD - Naïve or > 5 yr	PCV7: 1m PPV23: 1m	ELISA: PCV7 > PPV23 for 5/7. OPA: PCV7 > PPV23 for 4/7.	
Goldblatt et al. ²³	UK	2009	50-80 y	599	100% prior PPV; no PPV within 5 yrs	PCV7: 6m PPV23: 6m PCV7: 6m→PPV23: 6m PCV7: 6m→PCV7: 6m	ELISA: PCV7 superior for 3/7 serotypes (4, 9V, 23F). Other types comparable.	
Jackson et al. ²⁴	USA	2007	70-79 y	219	all > 5 y since 1 st PPV23	PPV23: 5+y→PPV23: 1y+1m PPV23: 5+y→PCV7: 1y+1m PCV7 dose arms: 0.1, 0.5, 1, 2 ml . Then 0.1 ml PPV23 after 1 y	ELISA & OPA: PPV23 ~ PCV7 0.5 ml for 7/7 serotypes. OPA superior for 9V, 23F in 0.5 ml arm. Dose-response for PCV7 across arms. Year 1 values: PCV7 ~ PPV23.	
Miernyk et al. ²⁵	USA	2009	55-70 y	86	Alaska natives - 100% naïve	PPV23: 2m PCV7: 2m→PPV23: 2m PCV7: 6m→PPV23: 2m	ELISA: PCV7 ~ PPV23 (4, 6B, 14, 19F). OPA similar; only serotype 1 higher for PPV23.	
Musher et al. ²⁰	USA	2008	mean 63 y	66	Patients with prior pneumococcal pneumonia- 24% naïve	PCV7: 6m→PPV23: 4-8w+6m PPV23: 6m→PCV7: 4-8w+6m after 1 st and 2 nd doses	ELISA & OPA: Prior PPV within 1-5 y, peak 1 ≥ peak 2. Prior PPV > 5 y, no suppression for PPV & PCV. IgG & OPA in both groups approach baseline levels 6 m after 2 nd dose	
Peñaranda et al. ²⁶	Spain	2010	median 44 y	202	HIV+ on HAART	PCV7: 4w→PPV23: 4w PPV23: 4w	PCV7 ~ PPV23 for 7/7 PCV7/PPV23 ~ PPV23 for 7/7	
Ridda et al. ²⁷	AUS	2009	60-100 y	241	100% naïve	PCV7: 6m PPV23: 6m	ELISA: PCV7 ~ PPV23 (4, 6B, 18C, 19F)	
Scott et al. ²⁸	USA	2008	20-50 y	30	Japanese descent - 100% naïve	PCV13: 1m PPV23: 1m	ELISA: PCV13 ~ PPV23 for 12/12 serotypes	
O'Brien ⁶	USA	2009	In healthy adults: "the preponderant failure to see an antibody boost or persistence of antibody following combined PCV-PPV23 may reveal the limits of the adult immune system. lack of clear benefit of PCV over PPV23"					

*OPA=opsonophagocytic activity

*ELISA= Enzyme-Linked Immunosorbent Assay