

Vaccines for the Prevention of Pneumococcal Disease

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Introduction

Infections caused by *Streptococcus pneumoniae* remain a major public health problem worldwide. Due to large serotype diversity in pneumococcus, vaccines that induce antibody responses against multiple capsular antigens have been developed. At the moment, there are two licensed anti-pneumococcal vaccines for possible use in elderly people: the classical 23-valent pneumococcal polysaccharide vaccine (PPV23)¹ and the 13-valent pneumococcal conjugate vaccine (PCV13), which substituted the PCV7 in children and has been licensed for use in preventing invasive pneumococcal disease (IPD) and pneumonia in people over 50 years old.^{2,3}

Polysaccharide Pneumococcal Vaccine 23 valent (PPV23)

The pneumococcus is surrounded by a polysaccharide capsule. There are more than 90 distinct defined capsular serotypes that vary chemically, in immunogenicity, and clinical impact⁴. PPV23 was first marketed in 1983 and it is commonly recommended for use in high-risk adults and elderly people. This vaccine contains capsular polysaccharide antigens from 23 common pneumococcal serotypes, which account for approximately 90 % of overall IPD infections.^{1,5}

Capsular polysaccharide antigens induce type-specific IgM antibodies (by a T cell-independent mechanism) that enhance opsonization, phagocytosis, and killing of pneumococci. Vaccine immunogenicity is evaluated by measuring functional antibody by opsonophagocytic activity (OPA) or binding of IgG antibody

measured by ELISA. Nevertheless, the levels of circulating antibodies that correlate with protection against pneumococcal disease have not been clearly established. The WHO criteria for evaluation and licensing of new pneumococcal vaccines⁶ recommended a threshold IgG concentration of 0.35 ug/ml to be used as the primary measure to compare the serotype-specific immune responses to new pneumococcal conjugate vaccines or new serotypes added to the current PPV23. However it was emphasized that this threshold antibody concentration does not necessarily predict protection. This threshold correlated best with an OPA titer of 1:8, which has an important role in the evaluation of pneumococcal vaccines and might be used to supplement ELISA antibody concentration measurements.⁶

Antibody response is generally achieved (twofold or greater rise in serotype-specific antibody within 2–3 weeks after vaccination) among immunocompetent adults. Children less than 2 years and immunodeficient persons (AIDS, leukemia, lymphoma, and multiple myeloma) do not consistently develop immunity. High-risk individuals (including 20% of ambulatory elderly people with certain medical comorbidities such as cirrhosis, chronic pulmonary diseases, diabetes mellitus, or chronic nephropathy) may also respond poorly.⁵

As polysaccharide antigens do not induce a T cell-dependent

immune response, there is an absence of memory B cells and this limits the period of vaccine protection. Pre-vaccination levels of antibody titers are generally reached within 5–10 years after the primary dose and an anamnestic immune response does not occur at revaccination. Immune response after revaccination has been controversial. Generally there is a significant increase in antibody levels, although “hyporesponsiveness” (antibody levels lower than after the primary dose) has been reported^{1,5}. At the moment, revaccination is recommended for those persons who received PPV23 before 65 years of age,⁷ but its clinical effectiveness has not been clearly proved⁸. Unfortunately, the immunologic correlates between antibody titers and protection against pneumococcal disease are unknown to date, which largely limits the ability of laboratory studies to predict effectiveness in clinical practice.^{1,8}

PPV23 has the potential to prevent disease and death from invasive pneumococcal infections, but conflicting results have been reported and its effectiveness remains controversial especially when it comes to prevention of pneumococcal pneumonia. More than ten meta-analyses on the efficacy of the polysaccharide vaccine in adults have been published during the past two decades, which reflects the difficulties in reaching a clear conclusion, especially for at-risk populations such as elderly

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people.⁹⁻²⁰ According to most meta-analyses, PPV23 is effective in preventing IPD, but its effectiveness in preventing noninvasive pneumococcal infections and other clinically relevant medical outcomes is uncertain.

In the Cochrane meta-analysis, Moberley et al¹⁹ supported the recommendation for PPV to prevent IPD in adults. However they mentioned that the evidence from randomized controlled trials was less clear with respect to adults with chronic illness (Lack of effect or lack of power) Further their meta-analysis does not provide compelling evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality. In the WHO meta-analysis, Huss et al. concluded that PPV is not efficacious against either IPD or pneumonia.²⁰

The possible ineffectiveness of PPV23 against pneumonia is an important concern as IPD events are relatively rare (20–60 cases per 100,000 population-years in older adults) and a possible protective effect against CAP is a key point to assess and compare the cost-effectiveness of different anti-pneumococcal vaccination strategies.

Recently, in a large case-controlled study among Spanish individuals over 65 years old, Dominguez et al²¹ reported a PPV23 effectiveness of 24 % against overall CAP. Interestingly, some studies have reported additional benefits from PPV23 vaccination, such as better clinical outcomes (faster resolution of symptoms and lower length of hospital stay) as well as minor severity and mortality observed among patients hospitalized with pneumonia who had previously been vaccinated.²²⁻²⁴ Several studies in North America and European countries concluded that the use of PPV23 was cost-effective in elderly people although the vaccine might only be effective in preventing IPD.²⁵⁻²⁹ However, it must be noted that PPV23

only provides a very incomplete protection and there is a place for a better and more effective vaccine.

Pneumococcal Conjugate Vaccine 13 valent (PCV13)

Given the unmet medical need (poor immunogenicity of PPV23) especially in young children, e efforts were directed to develop a new generation of pneumococcal vaccines with good immunogenicity in this age group. The result was a protein–polysaccharide conjugate vaccine, which contained some selected polysaccharides bound to a protein carrier, rendering the vaccine T cell-dependent and thus making it capable of stimulating antibody responses and priming for a memory response on rechallenge. The first commercially available PCV in 2000 contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F and was indicated in young infants³⁰. In contrast to the polysaccharide vaccine, which had shown only a limited impact on the overall disease burden, PCV7 not only brought about an overwhelming reduction of invasive infections in children, but also produced a considerable indirect effect in reducing pneumococcal diseases in the rest of the population (“herd” protection) by reducing nasopharyngeal carriage of vaccine serotypes^{31,32}. These decreases were primarily attributable to reductions in the incidence of disease caused by PCV7 strains that are also contained in PPV23.³³⁻³⁵ Later, serotype replacement and emerging serotypes were observed,^{32-34,36,37} and PCV13 (including additionally types 1, 3, 5, 6A, 7F, and 19A) was licensed in 2010 to replace the PCV7 for use in children³⁸. Gradually the EMA and FDA approved the use of PCV13 in preventing IPD and pneumonia in people over 50 years old.^{39,40}

PCV13 enhances the immune response in high-risk and elderly people compared to polysaccharide vaccines, owing to its T cell-

dependent mode of action.⁴¹ An important immunological consequence of conjugation of polysaccharide antigen with a carrier protein is that the CD4+ helper T cell fraction contributes to the immunological response. Thus a T cell dependent response is generated, with predominant IgG1 and IgG3 antibodies, instead of the T cell-independent antibody (IgM) response that occurs with simple polysaccharide antigens.⁴² This is an important advantage of the conjugated vaccine, given that the response to polysaccharide antigens is much more variable and age dependent, and antibody levels are therefore more uncertain than with conjugated antigens. Thus, as in young children, potentially immunocompromised adult population groups (such as those with Hodgkin’s disease, cirrhosis, liver or renal transplantation, HIV-infected patients, etc.) and elderly people (many of them with a certain degree of immunosenescence) could benefit from using a conjugate vaccine.

Some studies evaluating the immunogenicity of distinct schemes combining PCV7 and PPV23 in adults have raised questions about a possible hyporesponsiveness when PPV23 was administered before PCVs.⁴³⁻⁴⁶ Clutterbuck et al⁴⁵ reported that prime immunization with PPV23 resulted in a decrease in memory B cell frequency and, furthermore, when immunization with PCV7 is given after PPV23 the memory B cell responses were attenuated. The lack of memory B cell production following PPV23 is consistent with its T cell independent nature and it could explain the limited effectiveness and short-term immunity associated with this vaccine in the elderly.⁴⁵

The immunogenicity of PCV13 has been evaluated in the studies mentioned in Table 1.⁴⁶

The results of the studies are summarized below:

Table 1: Prevenar13 Adult Studies⁴⁶

	Study 1 USA	Study 2 USA, Sweden	Study 3 USA	Study 4 USA	Study 5 Europe
Scope of study	PCV13 vs PPV23 in PPV23-naive adults	PCV13 vs PPV23 in PPV23 pre-immunized adults	Sequential vaccination with PCV13 and PPV23	Concomitant administration with TIV	
Key study objective(s)	Immunogenicity of PCV13 vs PPV23 in adults aged 60–64 y; immunogenicity of PCV13 in adults aged 50–59 y vs adults aged 60–64 y	Immunogenicity of PCV13 vs PPV23 in adults >70 y previously immunized with PPV23	Immunogenicity of PPV23 given 1 y after PCV13 vs initial PPV23 and immunogenicity of PCV13 given 1 y after PPV23 vs initial PCV13 in adults aged 60–64 y	Immunogenicity of PCV13 and TIV when administered concomitantly vs sequentially in adults aged 50–59 y	Immunogenicity of PCV13 and TIV when administered concomitantly vs sequentially in adults aged >65 y
Vaccine groups [no. randomized]	PCV13 (age 60–64 y) [370]; PPV23 (age 60–64 y) [370]; PCV13 (age 50–59 y) [370]	PCV13 [462]; PPV23 [462]	PCV13-PPV23 [478] ^a ; PPV23-PCV13 [223]	PCV13/TIV-PL [550]; TIV/PLPCV13 [550]	PCV13/TIV-PL [580]; TIV/PLPCV13 [580] ^b

^a266 participants from this group received PPV23 1 y after the initial vaccination; ^bThe second vaccination or PL was administered 1mo after the initial vaccination.

Study 1

- PCV13 was non-inferior to PPV23 for all 12 serotypes common to the vaccines when evaluated 1 month post vaccination
- PCV13 was associated with significantly greater immune responses than PPV23 for 8 of 12 serotypes common to the vaccines
- For serotype 6A (not included in PPV23), a higher proportion of PCV13 recipients had a >4-fold increase in the OPA GMT than PPV23 recipients
- The immune response in PPV23-naive adults aged 50–59 years was non-inferior to that in adults aged 60–64 years, as the non-inferiority criterion was met for all 13 pneumococcal serotypes
- The immune response was greater in the participants aged 50–59 years than in participants aged 60–64 years for 9 of 13 serotypes

Inference

PCV13 is preferable (compared to PPV23) in previously unvaccinated adults. More so, if given at an early age of 50 - 59 years

Study 2

- In adults aged >70 years vaccinated with PPV23 at least 5 years previously, the immunogenicity of PCV13 was non-inferior to that of PPV23,

as the non-inferiority criterion was met for all 12 serotypes common to the two vaccines

- For 10 of these 12 serotypes, PCV13 met the pre-specified criterion for superiority over PPV23
- For serotype 6A, a higher proportion of PCV13 recipients had a >4-fold increase in the OPA GMT than PPV23 recipients. The OPA GMT for serotype 6A was also higher in the PCV13 group than the PPV23 group
- As for the younger age group, in adults aged >70 years, OPA GMTs declined during the first year after vaccination, but remained numerically higher than baseline levels for each serotype (statistical analyses not reported)

Inference

- PCV13 is preferable (compared to PPV23) in previously PPV23 vaccinated patients

Study 3

- PCV13 did not diminish the response to subsequent PPV23, as immune responses for the 12 serotypes in common in participants who received PPV23 after PCV13 were non-inferior to those following a single dose of PPV23
- For six of the serotypes in common, the immune response was greater in participants who

received PPV23 after PCV13

- When PCV13 was administered 1 year after PPV23 versus initial vaccination with Prevenar13, the immune response was lower for all 12 serotypes common to the two vaccines.

Inference

- If, both PCV13 and PPV23 are to be used, Prevenar13 should be given first.

Study 4

- In adults aged 50–59 years, concomitant administration of PCV13 with TIV produced antibody responses that were non-inferior to sequential administration for each of the three TIV strains.
- Concomitant administration was also non-inferior to sequential administration in terms of IgG responses for all 13 serotypes (based on ELISA)
- In post hoc analyses, a non-inferiority criterion based on OPA GMC ratios was met for 8 of 13 serotypes

Inference

- PCV13 may be given concomitantly with TIV in adults aged 50-59 years.

Study 5

- In adults aged >65 years, the concomitant administration group was non-inferior to the sequential group in antibody response to two of three TIV

antigens. For serotypes A/H1N1 and B, the concomitant administration group met the non-inferiority criterion, whereas for serotype A/H3N2, the lower limit of the 95%CI was -10.4%, which just exceeded the pre-specified limit of -10%

- Both the concomitant and the sequential administration groups met EMA vaccine guideline criteria for all three TIV serotypes
- For all pneumococcal serotypes except for 19F, concomitant administration of PCV13 with TIV was non-inferior to sequential administration, based on GMC ratios. However, for all 13 serotypes, the GMC was numerically higher in the sequential administration group. In the absence of an established correlate of protection based on the GMC, the clinical significance of this is unknown.

Inference

- PCV13 may be given concomitantly with TIV in adults aged >65 years.

Thus considering the above studies, one can say that according to data, the immunogenicity of PCV13 in older adults (naive or previously vaccinated with PPV23) seems good. As the level of vaccine-induced pneumococcal antibody in adults that correlates with protection against clinical disease, including IPD or pneumococcal pneumonia, has not been established to date, clinical implications of these immunogenicity data are uncertain.

Safety and Tolerability

PCV13 was generally well tolerated by older adults participating in immunogenicity trials⁴⁶, with most adverse events being of mild to moderate severity⁴⁷. In adults previously vaccinated with PPV23, PCV13 recipients had significantly ($p < 0.05$) lower rates of new muscle pain, fatigue and rash

than PPV23 recipients, although the clinical relevance of these small but significant between-group differences is uncertain.

In PCV13 and PPV23 recipients, injection-site pain was the most frequent local reaction to vaccination, occurring in >50 % of vaccines.⁴⁷ Limitation of arm movement, injection-site redness or swelling occurred in 10–31 % of participants across treatment groups and were significantly ($p < 0.05$) less common in PCV13 than PPV23 recipients in the previously vaccinated with PPV23 group. Serious adverse events reported within 1 month of initial vaccination occurred in 0.2–1.4 % of PCV13 recipients and 0.4–1.7 % of PPV23 recipients. During the period 1–6 months following initial vaccination, serious adverse events occurred in 1.2–5.8 % and 2.4–5.5 % in the respective groups. One individual developed erythema multiforme 34 days after a second dose of PCV13.⁴⁷ Across trials, 12 of 5,667 PCV13 recipients (0.21 %) and 4 of 1,391 PPV23 recipients (0.28 %) died, with all deaths occurring within the period from day 3 to day 309 following vaccination⁴⁷. Two of 12 deaths in PCV13 recipients occurred within 30 days of vaccination (one from cardiac failure and one from peritonitis).

In adults aged ≥ 65 years, coadministration of PCV13 with TIV was associated with a higher rate of systemic adverse events occurring within 14 days than sequential administration of the vaccines [60.1 % vs. 48.5 %; difference 11.6 % (95 % CI 5.4, 17.8)].⁴⁸ Concomitant and sequential administration of the PCV13 and TIV vaccines were associated with generally similar rates of local reactions of any grade [46.9 % vs. 46.6 %; difference 0.3 % (95 % CI -6.0, 6.7)].⁴⁸ The majority of these reactions were mild. There were no reports of vaccine-related serious adverse events during the course of this study

A major consideration in using a PCV in elderly people would be

whether conjugate vaccine would have the same effectiveness in adult and elderly individuals as in children. It would not be appropriate to extrapolate pediatric data on efficacy to elderly persons, considering that the predominant forms of IPD are different in elderly people (mainly pneumonia) and children (mainly nonfocal bacteremia).^{49,50} Thus, the most important attribute of a pneumococcal vaccine for adults would be the effective prevention of both bacteremic and nonbacteremic pneumonias.

From these data it cannot be predicted how effective the conjugate vaccine would be in adults and elderly people. The magnitude of possible vaccine efficacy against pneumonia (bacteremic and nonbacteremic cases) is a key point in evaluating the potential health benefits of both PPV23 and PCV13 vaccination in adults. In contrast to the polysaccharide vaccine, subjects immunized with the conjugate vaccine are at lower risk of nasopharyngeal colonization with serotypes contained in the vaccine.³²

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