

# Pneumococcal Vaccines – a Real World Perspective

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## Cost-Effectiveness of Pneumococcal Vaccination

In the last decade, coinciding with the widespread use of PPV23 in elderly people, numerous cost-effectiveness analyses were performed in different settings.<sup>1-10</sup> Interestingly, although IPD has a relatively small incidence, these studies generally concluded that PPV23 vaccination strategy was a cost-effective intervention, even if the vaccine only prevents IPD.

In the last few months, given recent EMA and FDA approval for the use of PCV13 to prevent IPD and pneumococcal pneumonia in people over 50 years old,<sup>11,12</sup> the potential cost-effectiveness of PCV13 vaccination in adults has been assessed in some simulation/projection studies<sup>13-16</sup>. Interestingly, similar to PPV23, all published studies assessing cost-effectiveness of PCV13 for high-risk and older adults concluded in favor of vaccination.<sup>13-16</sup>

In the USA, in a microstimulation projection model, the cost-effectiveness of adult vaccination strategies using PCV13 compared with PPV23 was assessed by Smith et al.<sup>16</sup> According to their results, in the base case scenario, administration of PCV13 as a substitute for PPV23 in current recommendations (i.e., vaccination at age 65 years and at younger ages if comorbidities are present) cost US\$28,900 per quality adjusted life year (QALY) gained compared with no vaccination and was more cost effective than the currently recommended PPV23 strategy. Adding PPV23 at age 75 years to PCV13 at ages 50 and 65 years gained 0.00002 QALYs, costing

US\$496,000 per QALY gained.

The CDC does not recommend routine revaccinations with PPV23 in the general population over 65 years old because of insufficient data on clinical benefit, particularly the degree and duration of protection and safety.<sup>17,18</sup> Nevertheless, PCV13 efficacy against nonbacteremic pneumococcal pneumonia in adults and magnitude of possible indirect effect from PCV13 childhood vaccination) should be considered before a well-informed decision can be made.

## Implications for Clinical Practice

Pneumococcal infections remain a major cause of morbidity and mortality throughout the world.

Key differences between PPV23 and PCV13 are summarized in Table 1.

The main advantage of PCV13 is that it is effective against pneumonia than PPV23. The main shortcoming of PPV23 is that it may be less effective than PCV13 against vaccine-type infections but a major advantage is that it may provide protection against additional serotypes.<sup>19-22</sup>

PPV23 offers an efficacy of approximately 50-70% against IPD. A protective effect against CAP has not been clearly demonstrated. Major limitations are that the immune response after PPV23 can be weak in some individuals (especially among immunocompromised people or

those with major comorbidities), it does not elicit long-lasting immunity, and no anamnestic effect occurs at revaccination. Given the good immune response and efficacy observed in children, the use of the conjugate vaccine (PCV13) has been approved for preventing IPD and pneumonia in adults over 50 years old. In contrast with the polysaccharide vaccine (T cell-independent immune response), protein-polysaccharide conjugate vaccines promise to enhance the immune response owing to their T cell dependent mode of action. Efficacy data of PCV13 proven in children (approximately 80 % against vaccine-type IPD and 6-27% against pneumonia) suggest that PCVs promote a potentially better efficacy than PPV23 in high-risk and elderly people. Recently with the CAPiTA study, the PCV13 efficacy data is available and strongly supports the use of this vaccine to prevent pneumococcal pneumonia and IPD in older adults.<sup>23</sup>

Apart from its possible better efficacy than PPV23, the relatively low serotype coverage of PCV13 is an important shortcoming of routine use of PCV13 alone in adult populations. A sequential strategy using both PCV13 and PPV23 vaccines could be a way to achieve greater effectiveness among high-risk people (anatomic or functional asplenia, immunodeficiencies, leukemia, lymphoma, multiple myeloma, transplantations, nephrotic syndrome or chronic renal failure, and immunosuppressive therapy).

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**Table 1: Key differences between PPV23 or PCV13 in elderly people**

Vaccine	Advantages	Disadvantages
PPV23	<ul style="list-style-type: none"> <li>• Long experience (licensed in 1983)</li> <li>• Not expensive</li> <li>• At present, relatively high serotype coverage for IPD in elderly (60–70 %)</li> <li>• Considerable efficacy proven against IPD (50–70 %) in immunocompetent elderly</li> <li>• Cost-effective proven for elderly people even if it only prevents IPD</li> </ul>	<ul style="list-style-type: none"> <li>• T cell-independent immune response (IgM antibody produced, response declines in 3–5 years and no anamnestic response at revaccination)</li> <li>• Decrease in memory B cell frequency after PPV23</li> <li>• Weak immunogenicity in some individuals</li> <li>• Unclear (null to small) efficacy against nonbacteremic pneumococcal pneumonia. No effect on nasopharyngeal carriage</li> <li>• No efficacy demonstrated in reducing nasopharyngeal carriage</li> <li>• No impact proven in reducing overall pneumococcal disease burden</li> </ul>
PCV13	<ul style="list-style-type: none"> <li>• T cell-dependent immune response (larger duration and boosting effect at revaccination)</li> <li>• High efficacy (80–90 %) against vaccine type IPD proven in children</li> <li>• Significant efficacy against pneumococcal pneumonia (CAPIITA study)</li> <li>• Potential efficacy in reducing nasopharyngeal carriage</li> <li>• Considerable impact in reducing all pneumococcal disease burden shown by prior PCV7</li> </ul>	<ul style="list-style-type: none"> <li>• Short experience (approved in 2011)</li> <li>• Expensive</li> <li>• At present, relatively small serotype coverage for IPD in the elderly (30–40 %)</li> <li>• Future reduction of vaccination impact in adults/elderly (because of probable indirect effects from PCV13 pediatric use)</li> </ul>

<sup>a</sup>Most advantages listed for PCV13 are primarily effects seen in young children

The best possible sequence should be PCV13 followed by PPV23 for naive individuals or alternatively it could be a single dose of PCV13 for those subjects previously vaccinated with PPV23. The serotype replacement phenomenon cannot be fully overcome by increasing the number of serotypes in the vaccine; therefore new technologies, such as protein-based vaccines, are greatly needed. Protein-based vaccine offers the potential advantage of a serotype-independent protection and several are in various stages of investigation. According to some experts a common protein vaccine with broad protection against pneumococcus could be available in the next 5–10 years.<sup>24,25</sup>

#### The current position of pneumococcal conjugate vaccine in older adults

PCV13 is approved in several countries worldwide, including the US, EU and India,<sup>26,27</sup> for use in adults aged  $\geq 50$  years for the

prevention of pneumonia<sup>27</sup> and/or invasive disease,<sup>26,27</sup> caused by *S. pneumoniae* serotypes included in the vaccine.

On December 30, 2011, US-FDA approved PCV13 for prevention of pneumonia and invasive disease (IPD) caused by PCV13 serotypes among adults aged 50 years and older. The US-FDA approved PCV13 for an adult indication under the Accelerated Approval pathway, which allows the agency to approve products for serious or life-threatening diseases. Approval of PCV13 for adults was based on immunogenicity studies that compared antibody responses to PCV13 with antibody responses to PPV23, a vaccine that provides protection against IPD but for which no consensus exists regarding protection against non-bacteremic pneumococcal pneumonia.<sup>28</sup>

At the ACIP meetings, the recommending body identified two critical gaps in evidence needed

to support a recommendation for routine PCV13 use among adults.

- No available data demonstrated clinical efficacy of PCV13 against pneumococcal pneumonia in adults.
- Full impact of routine PCV13 vaccination among children on the incidence of pneumococcal disease caused by PCV13 serotypes in adults was not known at that time. i.e. herd effect (The recommending body debated that if herd effects of similar magnitude to that of PCV7 are observed from the introduction of PCV13, the potential benefit of vaccinating adults with PCV13 is likely to be reduced substantially)

But based on the immunogenicity, safety data and going by the pediatric experience the ACIP (June 2012) recommended routine use of PCV13 for adults aged  $\geq 19$  years with (**high risk**) immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants<sup>29</sup> ACIP recommended PCV13 to be given first followed by PPV23 in recommended schedules. The ACIP decision to recommend PCV13 use (**routine**) among older adults was deferred until data became available on the efficacy of PCV13 against non-invasive pneumococcal pneumonia among adults.

A randomized placebo-controlled trial (CAPIITA trial) was conducted in the Netherlands amongst approximately 85,000 adults aged  $\geq 65$  years during 2008–2013 to verify and describe further the clinical benefit of PCV13 in the prevention of pneumococcal pneumonia. The results of the CAPIITA trial demonstrated 45.6% (95% confidence interval [CI] = 21.8%–62.5%) efficacy of PCV13 against vaccine-type pneumococcal pneumonia, 45.0% (CI = 14.2%–65.3%) efficacy against vaccine-type nonbacteremic pneumococcal pneumonia, and 75.0% (CI = 41.4%–

**Table 2: New ACIP recommendations for the use of PCV13 and PPV23<sup>30</sup>****Pneumococcal vaccine-naïve persons**

- Adults aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown
- One dose PCV13 followed by a dose of PPV23
- PPV23 should be given 6–12 months after PCV13
- If PPV23 cannot be given during this time window, the dose of PPV23 should be given during the next visit
- The two vaccines should not be co-administered, and the minimum acceptable interval between PCV13 and PPV23 is 8 weeks

**Previous vaccination with PPV23**

- Adults aged ≥65 years who have previously received ≥1 doses of PPV23
- Should receive a dose of PCV13 if they have not yet received it
- A dose of PCV13 should be given ≥1 year after PPV23.
- For those for whom an additional dose of PPV23 is indicated, it should be given 6–12 months after PCV13 and ≥5 years after the most recent dose of PPV23

90.8%) efficacy against vaccine-type IPD among adults aged ≥65 years.<sup>30</sup>

In June 2014, the results of CAPiTA trial became available and were presented to ACIP. The evidence supporting PCV13 vaccination of adults was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework and determined to be type 2 (moderate level of evidence); the recommendation was categorized as a Category A recommendation. So finally on August 13, 2014, ACIP recommended routine use of PCV13 among adults aged ≥65 years.<sup>30</sup>

## The New ACIP Recommendations

Both PCV13 and PPV23 should be **routinely** administered in series to all adults aged ≥65 years. The recommendations for routine PCV13 use among adults aged ≥65 years will be re-evaluated in 2018 and revised as needed. ACIP recommendations for use of PCV13 (**high risk**) in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants remain unchanged

The recommendations for usage of both the vaccines are mentioned below as well as in Table 2.

The new ACIP recommendations strongly support the usage of

PCV13 as a routine vaccine in the adult population for prevention of pneumococcal disease. CAPiTA study data did help justify the place of PCV13 in the adult vaccination schedule. ACIP recommendations have laid down the sequence of administration of both pneumococcal vaccines e.g. it is PCV13 that has to be used first followed by PPV23 (because of the strong immune response produced by the PCV). CDC believes that the implementation of PCV13 is cost effective for the immediate future. Clinicians now have guidance on the use of PCV13 in adults 65+ as well as in adults with immunocompromised conditions. These ACIP recommendations as well as the MMWR document can serve as a valuable reference to other vaccine technical committees as they consider their own policy decisions

Pharmacoeconomic and public health impacts are important considerations in making decisions on vaccination schedules in contemporary healthcare settings. A recent analysis conducted from the US healthpayer perspective and using a Markov simulation model predicted that PCV13 vaccination in lieu of PPV23 vaccination would result in reductions in cases of IPD (by ~15,000 cases) and nonbacteraemic pneumonia (by 1.2 million cases) and considerable savings in total healthcare (~US\$3.5 billion) and societal (~US\$7.4 billion) costs, based on the

assumption that the effectiveness of PCV13 vaccination is similar to that of PCV7 vaccination in children.<sup>31</sup>

## Disclosure

Speaker's bureau: Pfizer, MSD, Sanofi, Novartis, Ranbaxy. Advisory board: Pfizer, MSD, Novartis.

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