



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Conjugate Pneumococcal Vaccine (13-Valent) for Immunocompromised Populations: A Review of the Clinical Evidence

DATE: 27 March 2014

CONTEXT AND POLICY ISSUES

Streptococcus pneumoniae is a microorganism that can cause a variety of diseases in humans including noninvasive pneumococcal disease, invasive pneumococcal disease (IPD), mucosal diseases (including both pneumonia and community-acquired pneumonia [CAP]), and otitis media.¹⁻³ Morbidity and mortality as a consequence of pneumococcal infections, particularly from invasive diseases such as meningitis and sepsis, are still prevalent in both children and adults.³ Young children, older adults, and persons with immunocompromising conditions remain the most susceptible to pneumococcal infection. In the United States, estimates suggest that the annual burdens of disease caused by pneumococcus in adults 50 years and older are in the area of 30,000 incidents of IPD, 500,000 incidents of CAP, and 25,000 deaths.¹

Vaccines directed against pneumococcus have significantly lowered incidence rates of pneumococcal infection in children and adults since being introduced over two decades ago.¹ Two main pneumococcal vaccine-types are the mainstay of providing protection; a pneumococcal polysaccharide vaccine and pneumococcal conjugate vaccines.¹ The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is directed against 23 of the 93 distinct capsular serotypes found on the polysaccharide capsule surrounding the pneumococcus. These 23 common serotypes had previously accounted for around 90% of IPD infections when this vaccine first came out in 1983.⁴ PPSV23 works by eliciting a T cell-independent immune response that enhances phagocytosis thereby killing the bacterium.⁴ The 13-valent pneumococcal conjugate vaccine (PCV13) is a newer vaccine that conjugates 13 different serotypes (12 of which are similar to PPSV23) to a diphtheria protein component (CRM₁₉₇). Upon vaccination, PCV13 elicits a T cell-dependent immune response that results in enhanced immunogenicity and T cell-dependent memory responses.² While the actual titers necessary to provide protection from pneumococcal infections have not clearly been established, the surrogate measure of opsonophagocytic activity (OPA) geometric mean titers (GMTs) are currently the standardized immune response measurement.⁴

Adults, particularly those that are elderly and immunocompetent, have typically been vaccinated with PPSV23 which has provided satisfactory protection.⁴ The main caveat for its use remains

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the fact that it does not elicit T cell-dependent immune responses, thereby limiting its period of effectiveness due to the absence of memory B cells.⁴ Re-vaccinations are thus required. However, “boosters” with PPSV23 have been observed to occasionally cause “hyporesponsiveness,” whereby the levels of antibodies decrease compared with pre-vaccination levels.⁴

In 2010 in Canada, PCV13 was granted Priority Review Status by Health Canada to ensure an expedited review of the clinical evidence as it appeared to be promising for the prevention of serious, life-threatening, and debilitating disease.⁵ Health Canada subsequently determined that the efficacy, safety, and quality of data was favourable for the immunization against *Streptococcus pneumoniae* in children six weeks old through five years of age.⁵ In the United States, (who also listed the use of PCV13 for their pediatric immunization programs), using the FDA’s Accelerated Approval pathway in which drugs are approved for serious and life-threatening disease based upon the product’s early effectiveness evidence, PCV13 was additionally approved for adults aged 50 years and older for the prevention of pneumonia and invasive pneumococcal disease (IPD) in 2011.^{6,7} Therefore, there are two pneumococcal vaccines that have been approved in the USA for older populations; PCV13 for adults aged 50 years and older and PSV23 for adults aged 65 years and older who have previously received PPSV23 for any indication or if five years had elapsed since their last PPSV23 vaccination.⁶ Currently, the Advisory Committee on Immunization Practices (ACIP) and the World Health Organization do not recommend routine vaccination with PCV13 in older populations due to insufficient evidence.^{6,8} In addition, ACIP does not recommend routine vaccination with PPSV23 in the aforementioned population. However, in 2012, ACIP “recommended routine use of the PCV13 vaccine for adults aged 19 years or older with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants. PCV13 should be administered to eligible adults in addition to the PPSV23 vaccine.”⁷

While some recommendations have been provided; it has also been noted that there is a paucity of evidence surrounding the clinical effectiveness of PCV13 in adults with or without immunocompromising conditions. Therefore, the effectiveness of PCV13 warrants further evaluation.

This report will review the available evidence on the clinical effectiveness of the PCV13 vaccine in adults with HIV infections, sickle cell disease, those who have undergone either hematopoietic stem cell or solid organ transplant, those receiving immunosuppressive treatment, and those who are 65 years of age and older.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of conjugate pneumococcal vaccine (13-valent) in adults with human immunodeficiency virus (HIV) infection?
2. What is the clinical effectiveness of conjugate pneumococcal vaccine (13-valent) in adults who have undergone hematopoietic stem cell transplant?
3. What is the clinical effectiveness of conjugate pneumococcal vaccine (13-valent) in adults who have undergone solid organ transplant?

4. What is the clinical effectiveness of conjugate pneumococcal vaccine (13-valent) in adults who are receiving immunosuppressive treatments?
5. What is the clinical effectiveness of conjugate pneumococcal vaccine (13-valent) in adults with sickle cell disease?
6. What is the clinical effectiveness of conjugate pneumococcal vaccine (13-valent) in adults over the age of 65?

KEY FINDINGS

The PCV13 vaccine was observed to be non-inferior, and for many serotypes superior, when compared with the PPSV23 vaccine in non-immunocompromised adults who are 65 years of age and older. Additional studies are necessary to ensure that PCV13 confers non-inferior immune responses when compared with PPSV23 in more representative older populations, including those that are immunocompromised and those that are residing in either nursing homes or long-term care facilities. There remains a paucity of evidence for the effectiveness of PCV13 in populations of adults with HIV infection, sickle cell disease, those having undergone either hematopoietic stem cell or solid organ transplant, and in those receiving immunosuppressive treatments.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCT), and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 2, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	<p>Adult patients:</p> <ul style="list-style-type: none"> • With HIV infection, • Who have undergone hematopoietic stem cell transplant, • Who have undergone solid organ transplant, • Who are receiving immunosuppressive treatments (e.g. for malignancy), • Who have sickle cell disease, or • Who are over the age of 65
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Intervention	Conjugate pneumococcal vaccine 13-Valent (Pevnar-13; Prevenar 13 [PCV13])
Comparator	No vaccination 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23 [PPV23])
Outcomes	Clinical effectiveness: <ul style="list-style-type: none"> • Immunogenicity • Prevention against pneumococcal infection • Safety
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria or were published prior to January 1, 2009.

Critical Appraisal of Individual Studies

Key methodological aspects (both strengths and limitations) relevant to the RCT study design were appraised and summarized narratively. RCTs were appraised using the Downs and Black Checklist⁹ that included assessments of, but not limited to, allocation concealment, blinding, intention to treat analysis, and losses to follow up.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified a total of 316 citations. Of these, 296 citations were excluded during the title and abstract screening and 20 potentially relevant articles were retrieved for full-text review. In addition, 4 potentially relevant reports were retrieved by a grey literature search from other sources (i.e. hand searches, grey literature). Of these, a further 22 reports were excluded upon reading the full text articles. Two RCTs were included in the review.

A PRISMA diagram demonstrating the study selection process is presented in Appendix 1.

Additional references of potential interest are provided in Appendix 2, common acronyms are provided in Appendix 3, and descriptions of study characteristics are provided in Appendix 4.

Summary of Study Characteristics

1. What is the clinical effectiveness of PCV13 in adults with HIV infection?

No evidence was identified regarding the clinical effectiveness of PCV13 in adults with HIV infection.

2. What is the clinical effectiveness of PCV13 in adults who have undergone hematopoietic stem cell transplant?

No evidence was identified regarding the clinical effectiveness of PCV13 in adults who have undergone hematopoietic stem cell transplant.

3. What is the clinical effectiveness of PCV13 in adults who have undergone solid organ transplant?

No evidence was identified regarding the clinical effectiveness of PCV13 in adults who have undergone solid organ transplant.

4. What is the clinical effectiveness of PCV13 in adults who are receiving immunosuppressive treatments?

No evidence was identified regarding the clinical effectiveness of PCV13 in adults who are receiving immunosuppressive treatments.

5. What is the clinical effectiveness of PCV13 in adults with sickle cell disease?

No evidence was identified regarding the clinical effectiveness of PCV13 in adults with sickle cell disease.

6. What is the clinical effectiveness of PCV13 in adults over the age of 65?

Two RCTs were identified regarding the clinical effectiveness of PCV13 in adults over the age of 65.^{10,11} The Juergens et al. trial¹⁰ was a randomized, open-label trial that included 915 healthy adult participants vaccinated with either PCV13 or PPSV23. The main outcome of interest was the measurement of immune response through observations of OPA GMT titers. Subsequent vaccinations at yearly intervals were compared to initial vaccinations in order to determine non-inferiority of the immune responses. PCV13 immune responses were compared with PPSV23 immune responses for non-inferiority by measuring OPA GMTs one month after vaccination. This provided the initial immune responses with which to compare a) the two types of vaccines and b) with subsequent vaccinations. A subsequent vaccination with PPSV23 (in those that had received PCV13) was compared with the initial PCV13 vaccination immune responses to determine if immune responses with the subsequent PPSV23 vaccine were non-inferior. A subsequent vaccination with PCV13 (in those who had received PCV13) was compared with the initial PCV13 immune responses to determine if there was a hypothesized enhanced immune response. The extension study aimed to examine whether a third vaccination with PCV13 (in those initially vaccinated with PCV13 then followed by PPSV23) could enhance the immune response when compared either to the initials PCV13 vaccination or to the PCV13 followed by PPSV23 vaccinations.

The Jackson et al trial¹¹ was a multicenter randomized, modified double blind trial that included 938 participants and examined the immune responses of individual PCV13 and PPSV23 vaccinations and also of subsequent PCV13 and PPSV23 vaccinations that were administered one year later. Initial PCV13 and PPSV23 vaccination-elicited immune responses were observed to determine whether PCV13 was non-inferior to PPSV23. The authors also compared immune responses upon a subsequent vaccination with PCV13 (to those who had previously received PCV13) to the initial PCV13 vaccination. Immune responses were observed in those who received a subsequent PCV13 vaccination (in those who had initially received PPSV23) when compared with an initial PCV13 vaccination. There was also a comparison of immune responses of a subsequent vaccination with PCV13 (in those that had initially received a

PPSV23 vaccination) with those of the initial PCV13 vaccination. Finally, the authors compared the immune responses of a subsequent vaccination with PCV13 (in those previously vaccinated with PCV13) to a subsequent vaccination of PCV13 (in those previously vaccinated with the PPSV23).

Summary of Critical Appraisal

The detailed critical appraisal of the individual randomized controlled trials is summarized in Appendix 5, Table 3.

A total of two RCTs of moderate to good quality met the inclusion criteria for this review.^{10,11} The main limitations observed in both trials^{10,11} included a lack of allocation concealment and no intention-to-treat analysis. In addition, both trials were funded by their respective pharmaceutical company and only one provided a formal declaration of the potential conflicts of interest.¹¹ Additional important limitations included the trial populations not being fully representative of the broader elderly population (e.g. those with co-morbid unstable chronic diseases or those living in nursing homes or long-term care facilities)^{10,11} and trial participants either were vaccinated with PPSV23 in the 5 years prior (potentially affecting the results by the occurrence of “hyporesponsiveness”)¹¹ or their PPSV23 vaccination status was unknown in advance of the 30 days prior to enrollment.¹⁰ Other limitations were noted (Table 3) and are discussed at length in the Limitations section.

Both trials had numerous strengths including clearly defining all aspects of the trial and having the statistical power (recruiting the appropriate number of participants based on appropriate calculations) to detect vaccine responses. In addition, random variability was minimized considering that regular time intervals were used for drawing blood, and the subsequent blood analyses were performed using validated assays on calibrated machines.^{11,12} The participants and investigators in the trial by Jackson et al.¹¹ were appropriately blinded and it appeared that a high percentage of participants actively recorded their adverse events using an e-diary (however, the Jackson et al. trial¹¹ did not specifically report rate of patient participation using an e-diary to record adverse events).

Summary of Findings

1. What is the clinical effectiveness of PCV13 in adults with HIV infection?

No information was identified on the clinical effectiveness of PCV13 in adults with HIV infection.

2. What is the clinical effectiveness of PCV13 in adults who have undergone hematopoietic stem cell transplant?

No information was identified on the clinical effectiveness of PCV13 in adults who have undergone hematopoietic stem cell transplant.

3. What is the clinical effectiveness of PCV13 in adults who have undergone solid organ transplant?

No information was identified on the clinical effectiveness of PCV13 in adults who have undergone solid organ transplant.

4. What is the clinical effectiveness of PCV13 in adults who are receiving immunosuppressive treatments?

No information was identified on the clinical effectiveness of PCV13 in adults who are receiving immunosuppressive treatments.

5. What is the clinical effectiveness of PCV13 in adults with sickle cell disease?

No information was identified on the clinical effectiveness of PCV13 in adults with sickle cell disease.

6. What is the clinical effectiveness of PCV13 in adults over the age of 65?

Immune Responses

Both trials examined immune responses using OPA GMTs of the PCV13 and PPSV23 vaccines after initial and subsequent vaccinations, but baseline titers were not reported.^{10,11} Results will be presented according to vaccine type and administration order for clarity.

Detailed immune responses are presented in Appendix 6, Tables 4 and 5.

PCV13 compared with PPSV23

PCV13 OPA immune responses were observed to be non-inferior for the majority of PCV13 serotypes (an exception being serotype 7F¹⁰) when compared to an initial PPSV23 vaccine.¹⁰ In addition, most of the PCV13 serotype OPA GMTs were statistically significantly higher when compared with PPSV23 (exceptions being serotypes 3,¹¹ 7F,¹⁰ 14^{10,11}). In a post-hoc analysis of different age ranges performed by Jackson et al.¹¹, it was determined that PCV13 OPA GMT responses were greater than those after initial PPSV23 administration for most serotypes, and were similar in both the 70 to 74 and the 75 to 79 age sub-groups. The immune responses were observed to be slightly lower in participants from the those that were 80 years and older.¹¹

PCV13/PPSV23 compared with initial PPSV23

Statistically significantly higher OPA responses were observed for seven of the 12 common serotypes when comparing the immune responses of the PCV13 vaccine followed a year later by the PPSV23 vaccine with the initial PPSV23 vaccination. All other serotypes were non-inferior.¹⁰

PCV13/PCV13 compared with initial PCV13

Immune responses for five of the 13 serotypes did not meet the non-inferiority criteria (eight were observed as non-inferior) after a subsequent dose of PCV13 when compared to an initial dose of PCV13 in the Juergens et al. trial.¹⁰ This effect was also observed in a trial by Greenberg et al.¹³ whereby lower immune responses of seven of the 13 serotypes were observed after subsequent PCV13 doses in pneumococcal vaccine-naïve adults aged 60-64 years. Jackson et al.¹¹ observed OPA GMTs to be non-inferior for most of the serotypes (with the exception of serotypes 4 and 5 which were statistically significantly lower) after a second dose of PCV13 when compared to the initial PCV13 dose. Contrary to the Juergens et al. trial¹⁰, they also observed statistically significantly greater responses in serotypes 6A, 6B, and 23F.¹¹

PCV13/PPSV23/PCV13 compared with either initial PCV13 or PCV13/PPSV23 (Extension Study)

The extension study was performed to observe if subsequent vaccination with PCV13 might overcome normally observed lower PPSV23 immune responses (after prior PSV13 vaccination).¹⁰ Priming with PCV13 did not enhance the immune response at a one year interval after PPSV23 vaccination.¹⁰

PCV13/PCV13 compared with initial PPSV23

OPA GMT immune responses were observed to be non-inferior for all 12 common serotypes following the administration of the second PCV13 dose when compared to the initial PPSV23 dose. In addition, statistically significantly greater responses were observed in nine of the 12 common serotypes and also for serotype 6A.¹¹

PPSV23/PCV13 compared with initial PCV13

Statistically significantly lower OPA GMT immune responses were observed in all of the 13 serotypes after the administration of PCV13 that followed an initial PPSV23 vaccination when compared to an initial PCV13 vaccination.¹¹

PCV13/PCV13 compared with PPSV23/PCV13

The immune response was statistically significantly greater in 12 of the 13 serotypes following the two PCV13 administration when compared to the PCV13 following an initial PPSV23 vaccination.¹¹

Safety

Vaccination 1 (Year 0)

Compliance in completing the 14 day post-vaccination e-diary was high among the elderly participants in one trial¹⁰ while participation was not reported in the other.¹¹ After the first vaccination (Year 0), localized adverse events were reported as occurring in a larger proportion of participants administered PPSV23 when compared with PCV13.^{10,11} The most common localized reactions were the same in both trials and included redness, pain, and swelling at the injection site along with limitation of arm movement.^{10,11} Some systemic adverse events (such as fever, chills, vomiting, joint pain, and decreased appetite) were similar across vaccination types;^{10,11} exceptions included the appearance of a rash which was increased in those receiving PPSV23^{10,11} and a significantly higher percentage of participants reporting fatigue and new and aggravated generalized muscle pain post-PPSV23.¹¹ Serious adverse events occurring after the initial vaccination ([1.3% and 0.3% for PCV13 and PPSV23, respectively]¹⁰ and [none reported after one and six months post-vaccination]¹¹ were determined not to be related to either study vaccine.

Vaccination 2 (one year after Vaccination 1)

Incidences of local reactions after the second vaccination (of those participants who were vaccinated with PCV13 at Year 0) were lower after a subsequent vaccination with PCV13 when compared with PPSV23 (20.1% and 28.1%, respectively).¹⁰ No significant differences in

localized or systemic adverse events were observed in the Jackson et al. trial between groups initially vaccinated with either PCV13 or PPSV23 followed a year later with PCV13,¹¹ with the exception of a significantly higher incidence of vomiting that was observed in those receiving PPSV23/PCV13 relative to those receiving PCV13/PCV13 (3.1% versus 0.4%).¹¹ Systemic events were generally similar between vaccination types in the Juergens et al. trial and no serious adverse events of those reported (in four participants) were found to be related to either vaccine.¹⁰ In contrast to this, Jackson et al. reported an incidence of idiopathic thrombocytopenia purpura (in a man initially administered PPSV23) 132 days after the second vaccination, this time with PCV13, which was thought to be vaccine related.¹¹ Deaths occurred in both trials but were determined to be unrelated to the study vaccines.^{10,11}

Vaccination 3 (one year after Vaccination 2)

For the most part, both localized and systemic adverse events were not reported as frequently after the third vaccination (extension study) of PCV13 (following the initial PCV13 as the first vaccination and PPSV23 as the second vaccination); the notable exception to this being a slight increase in those with decreased appetite.¹⁰ There were two serious adverse events reported and both were determined to be unrelated to the study vaccine.¹⁰

Limitations

A total of two randomized controlled trials of moderate to good quality met the inclusion criteria for this review.^{10,11} The main limitations observed in both trials^{10,11} included a lack of allocation concealment and no intention-to-treat analysis. In addition, both trials were funded by their respective pharmaceutical company yet only one provided conflict of interest declarations.¹¹

It was apparent that one trial¹¹ included participants that were somewhat representative of the elderly population from which they were recruited especially with regard to co-morbidities such as chronic diseases. However, the authors of this same trial also noted the lack of representation of minorities within its included participants and that their patients were not immunocompromised (i.e. had stable chronic disease), which may limit generalizability.¹¹ The trial by Juergens et al.¹⁰ included healthy participants aged 65 years and older, excluding patients that were residing in either nursing homes or long-term care facilities. Their justification included the fact that the trial was designed to provide preliminary immunogenicity and safety data to support the use and development of the pediatric PCV13 in older populations; thus not including participants with confounders such as co-morbidities was appropriate.¹⁰ In addition, there was a higher proportion of female participants in the Juergens et al. trial¹⁰ which could introduce minor population bias.

Participants in the Jackson et al. trial¹¹ had all received the PPSV23 vaccine in the five years preceding the commencement of the trial. Although participants in the Juergens et al. trial¹⁰ were not allowed to have received the PPSV23 vaccine 30 days prior to the trial start, there was no description of whether these patients had actually received this vaccine prior to that. As PPSV23 does not elicit a T-cell dependent immune response thereby not conferring antibody “memory” (through memory B-cell activation), immune response reactivation via subsequent vaccination has remained controversial.⁴ Literature has reported that “hyporesponsiveness” (induction of lower levels of antibody titers after the primary dose) has sometimes occurred upon subsequent PPSV23 vaccination.⁴ Observing this distinct possibility, it remains uncertain whether the immune responses of participants receiving an initial dose of PPSV23 would have been confounded by the potential for “hyporesponsiveness.”

Non-inferiority and superiority margins are important when comparing newer vaccines to those that are currently accepted for a particular indication. Both trials used a non-inferiority margin of 0.5 and a superiority margin of 1.00 yet provided no explanation regarding this decision as to why these values were used.^{10,11}

The Juergens et al. trial¹⁰ examined immune responses upon administration of the PCV13 vaccine containing aluminum phosphate. However, at the time this trial was ongoing, the formulation did not include polysorbate 80. Polysorbate 80 was later incorporated into the PCV13 vaccine to combine with the aluminum phosphate in order to provide protection against vaccine product aggregation, thereby protecting against protein and antigenicity loss.¹⁰ It is not known whether the omission of polysorbate 80 had any significant effect on the immunogenicity observed in this study; thus this could have potentially confounded the results.

The time interval of one year between vaccinations observed in these trials may not be indicative of real world vaccination regimens in older adults. While children have been reported to benefit from close vaccination intervals,⁸ the adult immune system does not necessarily respond in the same manner, particularly upon vaccination with the polysaccharide vaccine¹⁴. Decreased immune responses observed in these trials may have been due to already present high circulating antibody titers which could have interfered with subsequent vaccinations.¹⁰ This seemed to be corroborated in a study by Jackson et al.¹⁵ whereby longer intervals between vaccinations with PCV13 (comparing it to the initial PCV13 vaccination) had comparable, if not statistically significantly increased, titers for many serotypes.

Finally, effectiveness information was limited to immunological data (i.e. opsonophagocytic activity geometric mean titers) and information on reduction in pneumonia rates or other clinical outcomes is lacking.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

As the risk increases for the development of both pneumonia and IPD in older adults, it remains important that vaccine effectiveness be continually examined in populations at risk of *Streptococcus pneumoniae* infection. Currently, two vaccines have been approved by the FDA for protection against pneumococcal diseases; PCV13 for the prevention of pneumonia and IPD in adults 50 years and older and PPSV23 for adults aged 65 years and older who have previously received this vaccine for any indication.⁶ Health Canada has only approved PCV13 vaccinations to be included as part of the standard child vaccination program.⁵

Numerous trials have been completed in older adults in an attempt to examine the effectiveness and further develop the pediatric PCV13 for routine use in that population.^{10,11} In this review, PCV13 opsonophagocytic immune responses for all PCV13 serotypes (except serotype 7F) were observed to be non-inferior when compared PPSV23 in adults 65 years of age and older either previously vaccinated with PPSV23 or not, with many serotypes showing superiority in eliciting immune responses. These results mirror the effects observed in another similar pivotal trial whereby non-inferiority of PCV13 (for all 12 common serotypes) and even superiority of OPA immune responses (in eight of the common serotypes) were observed when compared to PPSV23 in PPSV23-naïve participants between the ages of 60 and 64 years with stable non-immunocompromising chronic conditions.¹⁶ In addition, the safety profiles of both vaccines are similar with localized and systemic adverse events being described as mild to moderate and tolerable.^{10,11} While it is encouraging that almost all serotypes elicited non-inferior immune responses when compared to PPSV23, there remain important issues to consider. First, PCV13

does not contain all of the serotypes in PPSV23, thereby not providing protection against those only found in PPSV23. Second, while PCV13 does have the advantage of being a conjugate vaccine, therefore stimulating a T-cell dependent immune response and provoking memory B cells to enable a prolonged period of protection,⁴ there still exists the ongoing possibility of serotype replacement.³ The main reason for the addition of six more distinct serotypes to PCV13 (which was originally developed as PCV7), was the observation that serotypes not included in the vaccines were beginning to cause pneumococcal disease upon widespread use of PCV7.³ Third, the order of vaccination appears to be important. While PPSV23 immune responses were reported to be significantly increased after a prior vaccination with PCV13 when compared to PPSV23 (thereby lending credence to the conjugate-vaccine immune memory response and enhancement capabilities),¹⁰ the opposite response was observed when PCV13 vaccination was given subsequent to an original PPSV23 vaccination (and compared to an initial PCV13 vaccination response).¹¹ This may be due to the mechanism of action of the polysaccharide vaccine whereby a T cell-independent immune response may not elicit strong enough immunological memory upon subsequent vaccination or exposure to the targeted organism. In addition, immune responses of PCV13 vaccination followed by a subsequent PCV13 vaccination did not meet the non-inferiority criteria for five of the 13 serotypes, indicating the possibility of an antagonistic effect.

Further studies are required to assess the immunogenicity of PCV13 in adults with various conditions (those with HIV or sickle cells disease, those who have undergone hematopoietic stem cell transplant or solid organ transplant, or those receiving immunosuppressive treatments) as there is currently a paucity of evidence. Patients with inflammatory conditions, such rheumatic diseases and inflammatory bowel disease, often receive immunosuppressive agents such as methotrexate and anti-tumour necrosis factor.¹⁷ Of potential interest, in one study by Agarwal et al.,¹⁷ PPSV23 immune responses were observed to be diminished in several studies whereby patients (with inflammatory conditions) were treated with methotrexate monotherapy or methotrexate in combination with anti-tumour necrosis factor therapy and subsequently vaccinated with PPSV23. This suggests that methotrexate negatively effects antibody production upon vaccination with PPSV23.¹⁷

Therefore, at present, PCV13 serotype immune responses have been observed to be non-inferior, and in some cases superior, in adults aged 65 and older when compared to PPSV23. Whether this immune response will occur in a more representative elderly population (for instance in those with immunocompromising or unstable chronic diseases, or those residing in nursing homes and long-term care facilities) and adult populations with immunocompromising conditions, remains to be seen.

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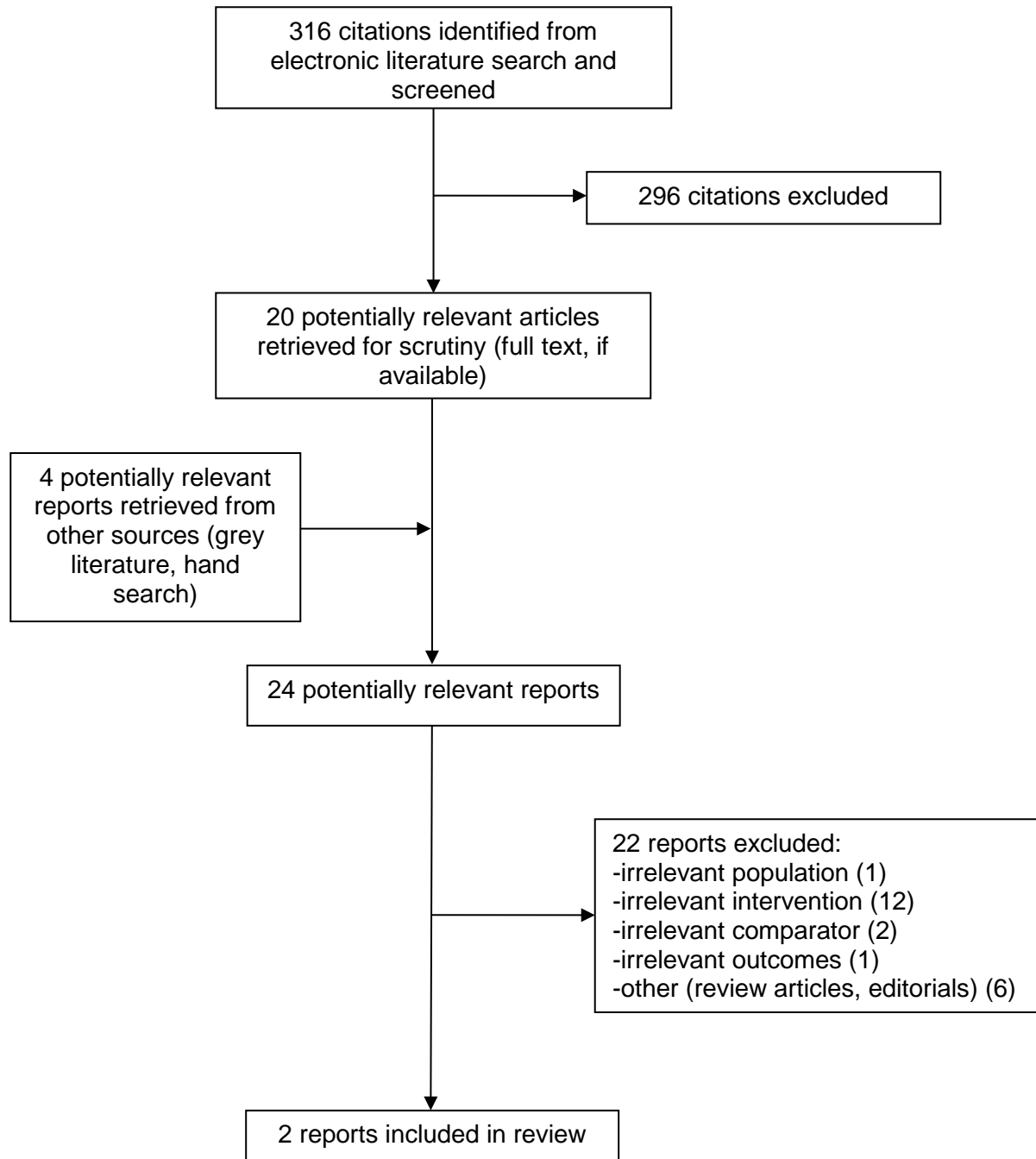
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REFERENCES

1. Paradiso PR. Pneumococcal conjugate vaccine for adults: a new paradigm. Clin Infect Dis [Internet]. 2012 Jul [cited 2014 Mar 5];55(2):259-64. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3381637>
2. Scott LJ, Sanford M. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed): a guide to its use in older adults. Drugs Aging. 2012 Oct;29(10):847-55.
3. Jefferies JM, Macdonald E, Faust SN, Clarke SC. 13-valent pneumococcal conjugate vaccine (PCV13). Hum Vaccin. 2011 Oct;7(10):1012-8.
4. Vila-Corcoles A, Ochoa-Gondar O. Preventing pneumococcal disease in the elderly: recent advances in vaccines and implications for clinical practice. Drugs Aging. 2013 May;30(5):263-76.
5. Summary basis of decision (SBD) for ^{Pr}Pprevnar® 13 [Internet]. Ottawa: Health Canada; 2010. [cited 2014 Mar 25]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2010_prevnar13_122881-eng.php
6. Centers for Disease Control and Prevention (CDC). Licensure of 13-valent pneumococcal conjugate vaccine for adults aged 50 years and older. MMWR Morb Mortal Wkly Rep. 2012 Jun 1;61(21):394-5.
7. 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 Oct 12;61(40):816-9.
8. WHO Publication. Pneumococcal vaccines WHO position paper - 2012 - recommendations. Vaccine. 2012 Jul 6;30(32):4717-8.
9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Feb 11];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>
10. Juergens C, de Villiers PJ, Moodley K, Jayawardene D, Jansen KU, Scott DA, et al. Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine formulations with and without aluminum phosphate and comparison of the formulation of choice with 23-valent pneumococcal polysaccharide vaccine in elderly adults: A randomized open-label trial. Hum Vaccin Immunother. 2014 Feb 27;10(5).
11. Jackson LA, Gurtman A, Rice K, Pauksens K, Greenberg RN, Jones TR, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2013 Aug 2;31(35):3585-93.

12. Cluster of severe acute respiratory syndrome cases among protected health-care workers--Toronto, Canada, April 2003. *MMWR Morb Mortal Wkly Rep* [Internet]. 2003 [cited 2014 Mar 27];52(19):433-6. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5219a1.htm>
13. Greenberg RN, Gurtman A, Frenck RW, Strout C, Jansen KU, Trammel J, et al. Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults 60-64 years of age. *Vaccine*. 2014 Mar 5.
14. Musher DM, Sampath R, Rodriguez-Barradas MC. The potential role for protein-conjugate pneumococcal vaccine in adults: what is the supporting evidence? *Clin Infect Dis* [Internet]. 2011 Mar 1 [cited 2014 Mar 5];52(5):633-40. Available from: <http://cid.oxfordjournals.org/content/52/5/633.full.pdf+html>
15. Jackson LA, Gurtman A, van CM, Frenck RW, Treanor J, Jansen KU, et al. Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older. *Vaccine* [Internet]. 2013 Aug 2 [cited 2014 Mar 21];31(35):3594-602. Available from: <http://www.sciencedirect.com/science/article/pii/S0264410X13005860?via=ihub>
16. Jackson LA, Gurtman A, van CM, Jansen KU, Jayawardene D, Devlin C, et al. Supplementary data: Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. *Vaccine*. 2013 Aug 2;31(35):3577-84.
17. Agarwal N, Ollington K, Kaneshiro M, Frenck R, Melmed GY. Are immunosuppressive medications associated with decreased responses to routine immunizations? A systematic review. *Vaccine*. 2012 Feb 14;30(8):1413-24.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

Lujan M, Burgos J, Gallego M, Falco V, Bermudo G, Planes A, et al. Effects of immunocompromise and comorbidities on pneumococcal serotypes causing invasive respiratory infection in adults: implications for vaccine strategies. *Clin Infect Dis*. 2013 Dec;57(12):1722-30.

[PubMed: PM24065334](#)

Schwarz TF, Schmoele-Thoma B. Assessment of functional antibacterial opsonophagocytic antibodies elicited by 13-valent pneumococcal conjugate vaccine administered concomitantly with trivalent influenza vaccine in a randomized clinical trial in adults aged ≥ 65 years. *Vaccine*. 2013 Jan 2;31(2):291-4.

[PubMed: PM23123107](#)

Schwarz TF, Flamaing J, Rumke HC, Penzes J, Juergens C, Wenz A, et al. A randomized, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged ≥ 65 years. *Vaccine*. 2011 Jul 18;29(32):5195-202.

[PubMed: PM21619909](#)

Unpublished Clinical Trial and Associated Reference

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT00744263, Study evaluating the efficacy of a 13-valent pneumococcal conjugate vaccine (13vPnC) in adults (CAPITA); 2013 [cited 2007 Feb 22]. Available from:

<http://www.clinicaltrials.gov/ct2/show/record/NCT00744263?term=Capita+AND+vaccine&rank=1>

Mangen MJ, Bonten MJ, de Wit GA. Rationale and design of the costs, health status and outcomes in community-acquired pneumonia (CHO-CAP) study in elderly persons hospitalized with CAP. *BMC Infect Dis*. 2013 Dec 19 [cited 2014 Mar 6];13:597. Available from:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880048/>

APPENDIX 3: Acronyms of Commonly Used Terms

ACIP	Advisory Committee on Immunization Practices
CAP	community-acquired pneumonia
AIPO ₄	aluminum phosphate
FDA	Food and Drug Administration
GMC	geometric mean concentrations
GMT	geometric mean titers
IPD	invasive pneumococcal disease
OPA	opsonophagocytic activity
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
PCV13/PCV13	initial administration of PCV13 followed by administration of PCV13 one year later
PCV13/PPSV23	initial administration of PCV13 followed by administration of PPSV23 one year later
PCV13/PPSV23/PCV13	initial administration of PCV13 followed by administration of PPSV23 on year later followed by PCV13 administration one year after that
PPSV23/PCV13	initial administration of PPSV23 followed by administration of PCV13 one year later

APPENDIX 4: Characteristics of Included Studies

Table 2: Summary of Randomized Controlled Trials

Author, Year	Population Trial Design, N, Country	Intervention, Duration	Outcomes	Quality assessment		
				AC	DB	ITT
Juergens et al., 2014 ¹⁰	<p>Healthy men and women aged ≥65 y^a; could be on anticoagulants^b</p> <p>OL (3 arms) + ES (OL, single arm)</p> <p>OL (N=915)</p> <ul style="list-style-type: none"> PCV13 n=309 PPSV23 n=301 PCV13-AIPO₄ n=305 <p>ES (N=105)</p> <p>South Africa</p>	<p>OL:</p> <p>Year 0^c</p> <ul style="list-style-type: none"> PVC13 PCV13-ALPO₄ PPSV23 <p>Year 1^d (n=267 randomized from PCV13 arm)</p> <ul style="list-style-type: none"> PCV13 (n=136) PSV23 (131) <p>ES:6</p> <p>Year 2^e (n=105); coming from PCV13/PPSV23 arm</p> <ul style="list-style-type: none"> PCV13 	<p>PCV13 OPA GMTs</p> <p>PPSV23 OPA GMTs</p>	No	No	NR
Jackson et al., 2013 ¹¹	<p>Adults ≥70 y^g who had received 1 dose of PPSV23 at least 5 y before enrollment</p> <p>DB^f</p> <p>N=938</p> <p>Multicenter (46 in US; 7 in Sweden)</p>	<p>Year 0^c:</p> <ul style="list-style-type: none"> PCV13 PPSC23 <p>Year 2^d:</p> <ul style="list-style-type: none"> PCV13 (from PCV13 arm, n=391) PCV13 (from PPSV23 arm, n=404) 	<p>PCV13 OPA GMTs</p> <p>PPSV23 OPA GMTs</p>	NR	DB ^f	NR

AC = allocation concealment; DB = double blind; ES = extension study; GMT = geometric mean titers; ITT = intention-to-treat; NR = not reported; OL = open label; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV13-AIPO₄ = 13-valent pneumococcal conjugate vaccine without aluminum phosphate; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; RCT = randomized controlled trial; US = United States; y = years.

^a No known or suspected immunodeficiency or suppression; no history of S. pneumonia infection within 5 years prior to the study enrollment; no serious chronic illness with cardiac, pulmonary, or renal failure; no evidence of severe cognitive impairment (mini-mental examination score ≤21); also could not be residents of either a nursing home or long-term care facility.

^b "Participants on anticoagulants were eligible unless current use contraindicated intramuscular injection."

^c Year 0 = Vaccination 1.

^d Year 1 = Vaccination 2; one year after Vaccination 1.

^e Year 2 (ES) = Vaccination 3; one year after Vaccination 2.

^f Modified double blind." PCV13 and PPSV23 were dispensed and administered by unblinded study staff member who were not involved in subsequent participant assessments. All other study staff members and participants were blinded to the vaccine administered at enrollment."

^g "Pre-existing chronic conditions (e.g. cardiovascular, pulmonary, liver disease including alcoholic liver disease and alcoholism, renal and urinary disorder or diabetes mellitus). Disease has to be stable, defined as not requiring significant change in therapy or hospitalization for worsening disease 12 weeks prior to vaccination."

APPENDIX 5: Critical Appraisal of Clinical Studies

Table 3: In Depth Critical Appraisal of Included Randomized Controlled Trials

Author, Year	Strengths	Limitations
Juergens et al., 2014 ¹⁰	<ul style="list-style-type: none"> • Clearly defined study objectives, patient characteristics, interventions, and outcomes • Analysis of blood by validated assays and at specific time intervals (random variability not an issue) • High compliance of 14 day e-diaries to assess safety • Study had statistical power to detect clinically important effects 	<ul style="list-style-type: none"> • OL design, no AC or blinding (patients or investigators), and ITT NR • Participant vaccination with PPSV23 prior to 30 days before enrollment NR • Participants not necessarily representative of entire population from which they were recruited; also higher percentage of female patients • 0.02% polysorbate 80 (now included in the updated vaccine) was not added at the time of the study • Short 1 year intervals between vaccinations • Funded by pharmaceutical company (Pfizer) • Conflicts of interest NR
Jackson et al., 2013 ¹¹	<ul style="list-style-type: none"> • Clearly defined study objectives, patient characteristics, interventions, and outcomes • Patients and laboratory staff adequately blinded • Analysis of blood by validated assays and at specific time intervals (random variability not an issue) • Participants more representative of population from which they were recruited in terms of chronic diseases • Study had statistical power to detect clinically important effects • Conflicts of interest declared 	<ul style="list-style-type: none"> • AC and ITT NR • Patients all had PPSV23 vaccination in the 5 year period prior to enrollment; thus more potential for vaccine hyporesponsiveness • Low number of participants from minorities • Short 1 year intervals between vaccinations • Funded by pharmaceutical company (Pfizer)

AC = allocation concealment; ITT = intention-to-treat; NR = not reported; OL = open label; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

APPENDIX 6: Summary of Results from Clinical Studies

Table 4: Immune Responses (OPA GMT Ratio [95% CI]) in Healthy Older Patients (≥65 years) Vaccinated with PCV13 or PSSV23¹⁰

Sero-type	Open-label Study			Extension Study	
	Vaccination 1 ^a	Vaccination 2 ^c	Vaccination 2 ^d	Vaccination 3 ^e	Vaccination 3 ^f
	PCV13 relative to PPSV23 ^b	PCV13/PPSV23 relative to PPSV23 ^b	PCV13 dose 1 vs PCV13 dose 2 ^{b,h}	PCV13/PPSV23/PCV13 vs PCV13 ^b	PCV13/PPSV23/PCV13 vs PCV13/PPSV23 ^b
1	2.22 (1.65-2.99)	2.02 (1.40-2.93)	0.7 (0.54-0.92)	0.4 (0.28-0.56)	0.4 (0.34-0.57)
3	1.91 (1.52-2.41)	1.77 (1.32-2.37)	0.6 (0.51-0.71)	0.8 (0.67-1.01)	0.8 (0.66-0.95)
4	1.73 (1.33-2.26)	0.97 (0.68-1.38)	0.5 (0.41-0.58)	0.6 (0.44-0.72)	1.0 (0.76-1.22)
5	3.24 (2.30-4.56)	2.07 (1.34-3.21)	0.4 (0.35-0.55)	0.4 (0.32-0.53)	0.7 (0.57-0.80)
6A ^g	7.14 (5.00-10.20)	2.88 (1.78-4.66)	0.8 (0.60-1.15)	0.6 (0.45-0.91)	2.0 (1.39-2.84)
6B	2.81 (2.02-3.91)	1.63 (1.08-2.45)	0.9 (0.76-1.16)	0.8 (0.56-1.01)	1.3 (1.11-1.63)
7F	0.65 (0.46-0.90)	0.89 (0.59-1.33)	0.8 (0.61-1.15)	0.4 (0.25-0.65)	0.3 (0.18-0.41)
9V	3.36 (2.22-5.09)	1.81 (1.01-3.26)	0.5 (0.35-0.78)	0.3 (0.16-0.40)	0.4 (0.27-0.68)
14	0.88 (0.63-1.23)	0.81 (0.54-1.21)	0.6 (0.43-0.73)	0.6 (0.40-0.78)	0.7 (0.57-0.83)
18C	2.50 (1.83-3.41)	1.42 (0.94-2.15)	0.5 (0.42-0.63)	0.5 (0.40-0.65)	0.8 (0.66-1.03)
19A	1.73 (1.35-2.23)	1.21 (0.90-1.64)	0.6 (0.54-0.75)	0.4 (0.30-0.48)	0.7 (0.58-0.78)
19F	2.11 (1.48-2.99)	2.06 (1.37-3.12)	0.9 (0.70-1.27)	0.5 (0.35-0.67)	0.6 (0.47-0.73)
23F	2.95 (2.02-4.31)	2.27 (1.42-3.63)	1.4 (1.02-1.85)	1.3 (0.86-1.86)	1.5 (1.18-1.94)

CI = confidence interval; GMT = geometric mean titers; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; vs = versus.

Bolded italics demonstrated a statistically significantly greater OPA response of PCV13 compared with PPSV23.

Bolding demonstrated a statistically significantly greater OPA response when 1) initial PCV13 dose was compared to that administered a year later (Vaccination 2^d column); and 2) in the extension study when PCV13/PPSV23/PCV13 titres were compared with PCV13/PPSV23 titres (Vaccination 3^f column).

Italics demonstrated a statistically significantly lower OPA when comparing 1) PCV13 with PPSV23 (Vaccination 1^a column); 2) PCV13 dose 1 compared with PCV13 dose 2 (Vaccination 2^d column); 3) extension study whereby PCV13/PPSV23/PCV13 was compared with PCV13 (Vaccination 3^e column); 4) extension study whereby PCV13/PPSV23/PCV13 was compared with PCV13/PPSV23 (Vaccination 3^f column).

^a Year 0; first vaccination; vaccination with either PCV13 or PPSV23.

^b One month post-vaccination.

^c Year 1 (one year after first vaccination); second vaccination; vaccination with PPSV23 after having either PCV13 or PPSV23 as the first vaccination.

^e Year 2; third vaccination; extension study; comparing PCV13 administered after PCV13 (Year 1) followed by PPSV23 (Year 2) to PCV13 at Year 0.

^f Year 2; third vaccination; extension study; comparing PCV13 administered after PCV13 (Year 1) and PPSV23 (Year 2) to PCV13 (Year 0) followed by PPSV23 (Year 1).

^g Serotype 6A is present in PCV13 but not in PPSV23.

^h Compared dose 1 (Year 0) to dose 2 (Year 1) of PCV

Table 5: Immune Responses (OPA GMT Ratio [95% CI]) in Older Patients (≥70 years) Vaccinated with PCV13 or PPSV23¹¹

Serotype	Vaccination 1 ^a	Vaccination 2 ^c	Vaccination 2 ^d	Vaccination 2 ^e	Vaccination 2 ^f
	PCV13 vs PPSV23 ^b	PCV13/PCV13 vs PCV13 ^b	PCV13/PCV13 vs PPSV23 ^b	PPSV23/PCV13 vs PCV13	PCV13/PCV13 vs PPSV23/PCV13
1	1.5 (1.17-1.88)	1.0 (0.85-1.10)	1.4 (1.10-1.76)	0.4 (0.33-0.54)	2.2 (1.74-2.82)
3	1.1 (0.91-1.35)	1.0 (0.91-1.11)	1.1 (0.91-1.34)	0.6 (0.49-0.74)	1.7 (1.36-2.03)
4	2.7 (1.93-3.74)	0.8 (0.68-0.92)	2.3 (1.66-3.25)	0.5 (0.36-0.67)	1.8 (1.29-2.42)
5	2.0 (1.55-2.63)	0.8 (0.73-0.94)	1.6 (2.21-2.06)	0.6 (0.44-0.76)	1.4 (1.03-1.79)
6A ^g	9.6 (7.00-13.26)	1.2 (1.03-1.40)	12.1 (8.92-16.44)	0.6 (0.44-0.83)	2.1 (1.54-2.77)
6B	3.0 (2.21-4.13)	1.2 (1.02-1.35)	3.8 (2.78-5.07)	0.6 (0.42-0.78)	2.2 (1.61-2.94)
7F	1.5 (1.07-2.18)	0.8 (0.65-1.01)	1.2 (0.80-1.67)	0.5 (0.34-0.71)	1.5 (1.05-2.24)
9V	2.0 (1.36-2.97)	0.9 (0.69-1.15)	1.8 (1.18-2.62)	0.4 (0.27-0.59)	2.2 (1.47-3.32)
14	1.0 (0.73-1.33)	0.9 (0.79-1.05)	0.8 (0.62-1.13)	0.7 (0.51-0.95)	1.2 (0.89-1.68)
18C	1.9 (1.42-2.50)	1.1 (0.97-1.23)	2.0 (1.53-2.69)	0.6 (0.43-0.74)	1.9 (1.45-2.49)
19A	1.8 (1.43-2.20)	1.0 (0.89-1.07)	1.7 (1.37-2.10)	0.7 (0.56-0.86)	1.4 (1.11-1.68)
19F	1.6 (1.17-2.06)	1.0 (0.83-1.15)	1.5 (1.09-1.93)	0.5 (0.40-0.72)	1.7 (1.30-2.30)
23F	3.7 (2.69-5.09)	1.9 (1.60-2.14)	7.3 (5.36-9.82)	0.6 (0.39-0.78)	3.6 (2.57-4.93)

CI = confidence interval; GMT = geometric mean titers; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; vs = versus.

Bolded italics demonstrated a statistically significantly greater OPA response of PCV13 compared with PPSV23.

Bolding demonstrated a statistically significantly greater OPA response following the second vaccination of PCV13 when compared with 1) PCV13 administered at Year 0 (Vaccination 2^c column); 2) PCV13 administered at Year 0 (Vaccination 2^d column); 3) PCV13 administered at Year 0 – keeping in mind the initial administration of PPSV23 initially/PCV13 (Vaccination 2^e column); and the two combinations compared with each other (Vaccination 2^f column).

Italics demonstrated a statistically significantly lower OPA response following the second vaccination of PCV13 compared with PPSV23 at Year 0.

^a Year 0; first vaccination; vaccination with either PCV13 or PPSV23.

^b One month post-vaccination.

^c Year 1 (one year after first vaccination); second vaccination; vaccination with PCV13 after having PCV13 as the first vaccination versus PCV13 at Year 0.

^d Year 1 (one year after first vaccination); second vaccination; vaccination with PCV13 after having PCV13 as the first vaccination versus PPSV23 at Year 0.

^e Year 1 (one year after first vaccination); second vaccination; vaccination with PCV13 after having PPSV23 as the first vaccination versus PCV13 at Year 0.

^g Serotype 6A is present in PCV13 but not in PPSV23