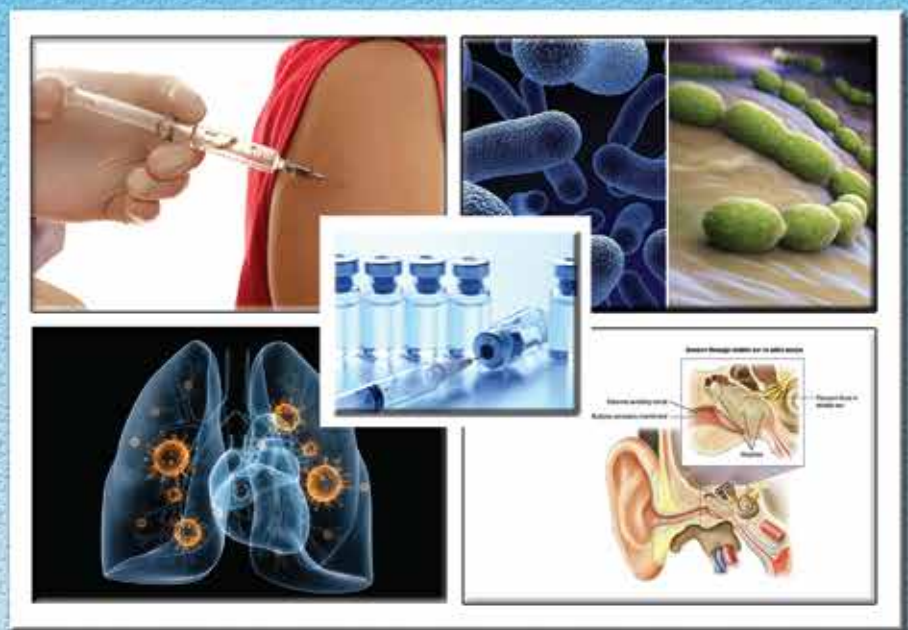


MINISTRY OF HEALTH MALAYSIA

PNEUMOCOCCAL CONJUGATE VACCINE FOR CHILDREN BELOW FIVE YEARS OLD



MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

HEALTH TECHNOLOGY ASSESSMENT REPORT

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MINISTRY OF HEALTH MALAYSIA

Health Technology Assessment Report

PNEUMOCOCCAL CONJUGATE VACCINE FOR CHILDREN BELOW FIVE YEARS OLD

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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- Technical Advisory Committee for Health Technology Assessment.

DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

The human nasopharynx is the reservoir of *Streptococcus pneumoniae*, which is usually carried asymptotically, and is transmitted to other individuals by respiratory droplets. The carrier rate is highest in young children, who most likely carry pneumococci in the nasopharynx at least one time, and are the primary source for its spread within a community. In the host, pneumococci can spread locally from the nasopharynx to cause otitis media or sinusitis, or to the lungs to cause pneumonia. Pneumococci can also cause invasive infections with high mortality. Pneumonia with empyema or bacteraemia, septicaemia and meningitis are invasive pneumococcal diseases (IPD). In Europe and the US, the risk of infection is greatest in children younger than two years old.

Pneumococcal conjugate vaccines (PCVs) containing polysaccharide antigens connected to carrier proteins have been found to be effective in developing an immune response and in reducing nasopharyngeal carriage of vaccine-type pneumococci in infants and children.

Streptococcus pneumoniae is the most common cause of acute otitis media (AOM) and invasive bacterial disease in children, including bacteraemia, meningitis, and pneumonia. With integration of 7-valent pneumococcal conjugate vaccine (PCV7) into the routine childhood immunization schedule, incidence of invasive pneumococcal disease (IPD) in US children declined dramatically. Similar decreases have been noted in Canada, Australia, the United Kingdom, Norway, Spain, Germany, and France after routine PCV7 infant immunization. Another positive impact of PCV7 is indirect protection against vaccine-type pneumococcal carriage among family members living with PCV7-vaccinated children and a reduction in the rate of vaccine-type IPD in the nonvaccinated population. Nevertheless, *S pneumoniae* remains a major cause of morbidity and mortality in children worldwide, particularly in countries in which nonvaccine serotypes such as 1, 3, 5, 6A, and 19A are common. Data collected before and after PCV7 introduction showed that serotypes in PCV7 provided coverage of approximately 80% of IPD-causing isolates in children younger than 5 years in North America, 68% in Europe and up to 65% in Latin America. In Asia, PCV7 coverage ranges from 41.2% in Bangladesh to 81% in China, 76.2% in Japan, and 62% in Thailand.

In Malaysia, the overall under 5 years old death incident rates in 2006 was 0.6 per thousand age specific population and 3.5 per thousand live births. Meanwhile it was reported in 2010 that there were 6 deaths per 1000 live births. Crude birth rate in 2010 was 17.5.

Currently in Malaysia there is no policy on the use of pneumococcal conjugate vaccines to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children.

In 2011, the majority of paediatricians from public and private sectors have come to an agreement to introduce PCV into the National Childhood Immunization programme due to its high efficacy. However, the Committee for Vaccine Use and Cost has suggested that the introduction of PCV into the National Immunization Programme should be further studied in terms of cost-effectiveness. Hence, the information on the cost-effectiveness of two pneumococcal vaccines in the market (PCV10 & PCV13) with different antigenic composition and comparable efficacy is needed.

Therefore this HTA is conducted to review the evidences on the efficacy, safety, effectiveness, cost effectiveness and organizational aspects of PCV10 & PCV13 before introducing them into the National Childhood Immunization programme.

Technical Features

PCV7 is licensed in the United States as Prevnar (Wyeth Pharmaceuticals, Philadelphia, PA). The 10- and 13-valent pneumococcal conjugate vaccines (PCV-10 and PCV-13 respectively) are used to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children. Recently the indication for protecting against pneumonia among children was added for PCV 13. PCV-10 provides coverage against pneumococci and the non-typeable *H. influenzae* (NTHi) protein which may provide protection against otitis media (see table 1 below). The vaccine include serotypes contained in PCV 7 (4,6B,9V,14,18C,19F,23F) plus serotypes:(1,5,7F). PCV-13 includes the serotypes contained in PCV 10 plus serotypes: (3, 6A, 19A). As with PCV7, each of the polysaccharides is covalently conjugated to a common carrier protein, CRM197, a nontoxic variant of diphtheria toxin. PCV13 contains 2.2 µg of each saccharide, except for 4.4 µg of serotype 6B, in 5.0 mM succinate buffer with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose.

Streptococcus pneumoniae (the pneumococcus) is one of the major bacterial causes of acute otitis media (AOM) in children, being responsible for between 30% and 50% of all cases. *Streptococcus pneumoniae* is an antigenically diverse species in which more than 90 serotypes have been identified. However, the prevalence with which the serotypes are recovered from patients with invasive disease varies greatly, presumably because some serotypes have a much greater propensity to cause invasive disease than others. The association of the common childhood serotypes (e.g., types 6B, 9V, 14, 19F, and 23F) with AOM is not necessarily evidence for any special propensity of these to cause AOM, as these serotypes are the ones most commonly carried in the nasopharynx of children and their association with AOM could merely reflect the fact that they are the most likely to gain access to the middle ear from the nasopharynx. Thus, even if all serotypes are equally able to cause AOM, the majority of episodes of this disease would be caused by the most frequently carried childhood serotypes.

Policy Question

Which pneumococcal conjugate vaccine should be recommended into the National Childhood Immunisation programme for children below 5 years old?

Objectives

- a) Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in effectiveness and in reducing the development of IPD, pneumonia and otitis media in infants and children?
- b) Are the adverse events of 10-valent and 13-valent pneumococcal conjugate vaccine comparable?
- c) Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in cost-effectiveness?

Methods

Major electronic databases such as Medline, Embase, Pubmed, EBM reviews, HTA databases, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Review, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases were searched up to February 2014. Studies were reviewed separately according to the research questions. Retrieved records were screened for relevance. The search was limited to publication year from 2000-2014. Additional articles were identified by reviewing the bibliographies of retrieved articles and hand searching of journals. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force and data were extracted and narratively presented.

Results and conclusion

Thirty-six studies were included in this review, where one of the studies was a systematic review; one study was a health technology assessment, eleven RCT's, three cross sectional studies and twenty economic evaluation studies. For efficacy/effectiveness, fourteen articles were included, whereby thirteen studies involved PCV13 as the main intervention, with only one study involving PCV 10 as the main intervention and only two studies directly comparing PCV13 and PCV10. For safety, nine articles were included, out of which eight studies had PCV 13 as the main intervention, with only one study that involved PCV 10 as the main intervention and only one study directly comparing PCV13 and PCV10. For cost effectiveness, twenty articles were included with twelve studies that included PCV 13 as the main intervention, six studies that involved PCV 10 as the main intervention while six studies were directly comparing PCV13 and PCV10.

There was fair to good level of evidence to show that PCV7 is no longer cost effective because of increases in invasive diseases caused by nonvaccine serotypes, which reduces the overall direct effects of vaccination. The 10-valent and 13-valent pneumococcal vaccines showed better net health benefits than PCV7. Total programme costs can be lowered by reduction in vaccine prices.

A national immunization program with PCV10 or PCV13 was found to be good value for money and estimated to prevent additional cases of disease among children and save additional costs due to treatment of acute otitis media (AOM) and pneumococcal diseases. Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker either to prevent the severe invasive pneumococcal diseases (IPD) cases only, or prevention of AOM. There was fair to good level of evidence to show that PCV13 was predicted to provide a higher impact on IPD and CAP, while PCV10 was expected to provide a substantially greater reduction in AOM.

Recommendation

Based on the above review, it is recommended that regular surveillance is conducted since changes in serotypes may occur naturally with time and serotypes replacement by nonvaccine serotypes in response to vaccine pressure. The surveillance data is required to determine the usefulness of available pneumococcal vaccines and the need for new vaccine. It is also recommended that local economic evaluation and research should be conducted considering our healthcare systems as well as local costing that will further provide more evidence to support the above strategies.

Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker / policy maker either to prevent the severe IPD cases only, or prevention of AOM. PCV13 was predicted to provide a higher impact on severe invasive pneumococcal diseases (IPD) and community acquired pneumonia (CAP), while PCV10 was expected to provide a substantially greater reduction in acute otitis media (AOM). PCV13 may be the choice to prevent death due to pneumococcal diseases in order to achieve Millenium Development Goal 4 (MDG4). Cost of PCV10 and PCV13 are expensive and our low less than 5 mortality need also to be considered before embarking on the national pneumococcal conjugate vaccination programme. Affordability and sustainability is also an important issue for any national programme. Hence, taking into account our Malaysian scenario, PCV13 should be given for high risk group first before considering giving it for all children below 5 years old.

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ABBREVIATIONS

AOM	acute otitis media
CAP	Community acquired pneumonia
GDP	Gross domestic product
GMC	Geometric mean concentrations
GMT	Geometric mean titers
ICER	Incremental cost-effectiveness ratio
ID	Invasive disease
IPD	invasive pneumococcal diseases
LLOQ	Lowest limit of quantitation
LY	Life years
NIP	National Immunization Program
NTHi	Non-typeable <i>Haemophilus influenzae</i>
OPA	opsonophagocytic activity
PAHO	Pan American health organization
PCV	Pneumococcal conjugate vaccines
PCV 7	7-valent pneumococcal conjugate vaccine
PCV10	10- valent pneumococcal conjugate vaccine
PHiD-CV	10-valent pneumococcal non-typeable <i>Haemophilus influenzae</i> protein D conjugate vaccine
PCV13	13- valent pneumococcal conjugate vaccine
PNP	pneumococcal nasopharyngeal
PSA	Probabilistic sensitivity analyses
QALY	Quality-adjusted life year
RCT	Randomized control trials
WHO	World health organization
YKD	Yukon Kuskokwim Delta

HEALTH TECHNOLOGY ASSESSMENT

10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

CHAPTER 1: BACKGROUND

Description of health problem

The human nasopharynx is the reservoir of *Streptococcus pneumoniae*, which is usually carried asymptomatically, and is transmitted to other individuals by respiratory droplets. The carriage rate is highest in young children, who most likely carry pneumococci in the nasopharynx at least one time, and are the primary source for its spread within a community. In the host, pneumococci can spread locally from the nasopharynx to cause otitis media or sinusitis, or to the lungs to cause pneumonia. Pneumococci can also cause invasive infections with high mortality. Pneumonia with empyema or bacteraemia, septicaemia and meningitis are invasive pneumococcal diseases (IPD). In Europe and the US, the risk of infection is greatest in children younger than two years old.¹⁻⁵

Pneumococcal conjugate vaccines (PCVs) containing polysaccharide antigens connected to carrier proteins have been found to be effective in developing an immune response and in reducing nasopharyngeal carriage of vaccine-type pneumococci in infants and children.⁶

Streptococcus pneumoniae has been the most common cause of acute otitis media (AOM) and invasive bacterial disease in children, including bacteraemia, meningitis, and pneumonia.⁷⁻⁹ With integration of 7-valent pneumococcal conjugate vaccine (PCV7) into the routine childhood immunization schedule, incidence of invasive pneumococcal disease (IPD) in US children declined dramatically.¹⁰⁻¹² Similar decreases have been noted in Canada,^{12,13} Australia,^{12,14-15} the United Kingdom,^{12,16} Norway,^{12,17} Spain,^{12,18,19} Germany,^{12,20} and France^{12,21} after routine PCV7 infant immunization. Another positive impact of PCV7 is indirect protection against vaccine-type pneumococcal carriage among family members living with PCV7-vaccinated children and a reduction in the rate of vaccine-type IPD in the nonvaccinated population.^{12,21,22} Nevertheless, *S pneumoniae* remains a major cause of morbidity and mortality in children worldwide, particularly in countries in which nonvaccine serotypes such as 1, 3, 5, 6A, and 19A are common. Data collected before and after PCV7 introduction show that serotypes in PCV7 provide coverage of approximately 80% of IPD-causing isolates in children younger than 5 years in North America, 68% in Europe and up to 65% in Latin America.^{12,23,24} In Asia, PCV7 coverage ranges from 41.2% in Bangladesh^{12,25} to 81% in China,^{12,25} 76.2% in Japan,^{12,26} and 62% in Thailand.^{12,27}

In Malaysia, the overall under 5 years old death incident rates in 2006 was 0.6 per thousand age specific population and 3.5 per thousand live birth.²⁸ Meanwhile it was reported in 2010 that there were 6 deaths per 1000 live births.²⁹ Crude birth rate in 2010 was 17.5.³⁰⁻³¹

Current service provision

Currently in Malaysia there is no policy on the use of pneumococcal conjugate vaccines to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children.

In 2011, the majority of paediatricians from public and private sectors have come to an agreement to introduce PCV into the National Childhood Immunization programme due to its high efficacy. However, the the Committee for National Policy and Practice on Immunisation has suggested that the introduction of PCV into the National Immunization Programme should be further studied in terms of cost-effectiveness. Hence, the information on the cost-effectiveness of two pneumococcal vaccines in the market (PCV10 & PCV13) with different antigenic composition and comparable efficacy is needed.

Therefore this HTA is conducted to review the evidences on the efficacy, safety, effectiveness, cost effectiveness and organizational aspects of PCV10 & PCV 13 before introducing them into the National Childhood Immunization programme.

Technical Features

PCV7 is licensed in the United States as Prevnar (Wyeth Pharmaceuticals, Philadelphia, PA). The 10- and 13-valent pneumococcal conjugate vaccines (PCV-10 and PCV-13 respectively) are used to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children. Recently the indication for protecting against pneumonia among children was added for PCV 13. PCV-10 provides coverage against pneumococci and the non-typeable H. influenzae (NTHi) protein which may provide protection against otitis media (see table 1 below). The vaccine include serotypes contained in PCV 7 (4,6B,9V,14,18C,19F,23F) plus serotypes:(1,5,7F).12, 32 PCV-13 includes the serotypes contained in PCV 10 plus serotypes: (3,6A,19A).12,32. As with PCV7, each of the polysaccharides is covalently conjugated to a common carrier protein, CRM197, a nontoxic variant of diphtheria toxin. PCV13 contains 2.2 µg of each saccharide, except for 4.4 µg of serotype 6B, in 5.0 mM succinate buffer with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose.12, 33

Streptococcus pneumoniae (the pneumococcus) is one of the major bacterial causes of acute otitis media (AOM) in children, being responsible for between 30% and 50% of all cases. *Streptococcus pneumoniae* is an antigenically diverse species in which more than 90 serotypes have been identified. However, the prevalence with which the serotypes are recovered from patients with invasive disease varies greatly, presumably because some serotypes have a much greater propensity to cause invasive disease than others. The association of the common childhood serotypes (e.g., types 6B, 9V, 14, 19F, and 23F) with AOM is not necessarily evidence for any special propensity of these to cause AOM, as these serotypes are the ones most commonly carried in the nasopharynx of children and their association with AOM could merely reflect the fact that they are the most likely to gain access to the middle ear from the nasopharynx. Thus, even if all serotypes are equally able to cause AOM, the majority of episodes of this disease would be caused by the most frequently carried childhood serotypes. 6-9, 12, 32-33

Table 1: Serotypes covered by the different Pneumococcal conjugates vaccine

Pneumococcal conjugates vaccine	Serotypes covered by vaccine
PCV7 : Prevenar ; Prevnar)	contain serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F
PCV 10 (decavalent vaccine): Synflorix	Synflorix contains antigen from 10 pneumococcal serotypes: the 7 that are contained in Prevnar (4, 6B, 9V, 14, 18C, 19F, and 23F), with additional three serotypes 1, 5, and 7F. Eight of the ten serotypes are linked to a protein carrier derived from non-typeable <i>Haemophilus influenzae</i> strains.
PCV 13: Prevenar 13 ; Prevnar 13	contain serotypes common to PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) and six are additional serotypes (1, 3, 5, 6A, 7F, and 19A)

CHAPTER 2: DEFINITION OF POLICY QUESTION AND OBJECTIVES

Policy Question

Which pneumococcal conjugate vaccine should be recommended into the National Childhood Immunisation programme for children below 5 years old?

Overall aims and objectives of the assessment

This project aims to provide evidence based guidance on the use of pneumococcal conjugate vaccine to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children, identify and guide the practitioners on the use of pneumococcal conjugate vaccine (PCV) and possibly introduce PCV10 or PCV13 into the National Childhood Immunization programme to be adopted or adapted in Malaysia. In order to do so, certain critical areas of care were identified to be assessed and these objectives were outlined:

1. To undertake a systematic review on the effectiveness or efficacy of using 10-valent and 13-valent pneumococcal conjugate vaccine.
2. To assess the safety and cost effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccines.

These objectives were developed into a series of questions, which were addressed in a review:

- a) Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in effectiveness and in reducing the development of IPD, pneumonia and otitis media in infants and children?
- b) Are the adverse events of 10-valent and 13-valent pneumococcal conjugate vaccine comparable?
- c) Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in cost-effectiveness?

CHAPTER 3: METHODS

Methods of the review, analysis and inclusion criteria has been specified in advance and documented in a protocol.

Search Strategy

The search aimed to systematically identify all literature related to the questions in this review. The last search was conducted in February 2014.

Sources searched

Eight electronic databases were searched from inception: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid); Pubmed; The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases.

In addition to the database searches, articles were identified from reviewing the bibliographies of retrieved articles and hand searching of journals.

Search terms

A combination of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and free text were used. Copies of the search strategies used in MEDLINE are included in Appendix 4 (these were adapted for use in other databases). The search was limited by including search filters for 'human studies'. The search was also limited to publication year from 2000-2014.

Inclusion and exclusion criteria

Eligibility assessment was conducted by two reviewers in an unblinded standardised manner independently using these prespecified inclusion and exclusion criteria.

Inclusion criteria

After discussion with the expert committee, it was agreed that articles were selected for inclusion in this systematic review on the basis of the following criteria:

Study design

For systematic review on clinical effectiveness, systematic reviews, meta-analysis, randomized controlled trials, non-randomised comparative studies and trials with surrogate end points will be included. Additional studies such as cohort, case control, cross sectional will also be taken into consideration especially if the studies are related to safety or adverse events.

Population

Infants and children ≤ 5 years.

Intervention

10-valent or 13-valent pneumococcal conjugate vaccine

Comparators

- a. 7-valent pneumococcal conjugate vaccine
- b. No vaccination

Outcome

One or more of the following outcome measures were assessed

- Efficacy and effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccine protect against
 - i. Invasive pneumococcal disease (IPD)
 - ii. Pneumonia
 - iii. Acute otitis media (AOM)

- Adverse events of 10-valent and 13-valent pneumococcal conjugate vaccine
- Cost-effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccine
 - annual economic and health outcomes of IPD, CAP and AOM
 - cost-utility of the newly available 10-valent and 13-valent conjugated pneumococcal vaccines
 - cost- saving strategy using PCV-13 vaccination / PCV -10 vaccination
 - higher QALY gained with PCV-10 / PCV-13
- Adverse events, safety
- Articles from year 2000

Publication

Full text articles published in English

Exclusion criteria

- i. Animal study
- ii. Narrative review
- iii. Laboratory study
- iv. Non English full text articles

Quality assessment strategy, grading of evidence and conclusion

The validity of the eligible studies was assessed by two reviewers independently using prespecified criteria. For systematic reviews and meta- analysis, the criteria assessed include unbiased selection of articles, heterogeneity of the included studies and publication bias. For RCTs, the criteria assessed were sequence generation, allocation concealment, blinding, explanation on loss to follow up, intention to treat analysis and other potential sources of bias such as funding. For non-randomised studies with comparison, the criteria assessed were random selection of participants, prospective or retrospective study, blinding, and explanation on loss to follow up, control of confounding factors and other potential sources of bias. For economic evaluation, we used two steps to evaluate the risk of bias. First we used the same criteria as RCTs and non-RCTS, then we appraised following Critical Appraisal Skill Programs checklist for economic evaluation.

The quality of the evidence was later graded according to US/Canadian Preventive Services Task Force grading system (see Appendix 5).⁸ Caution in interpretation should be encouraged since the grades chosen to indicate the strength of evidence cannot be interpreted as the ultimate truth. It is also important to note that when scientific evidence is concluded as being insufficient, this does not necessarily mean that the given method has no effect.

Data extraction strategy

Data from included studies were extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements were resolved through discussion. A third person, whose decision is final, was consulted if disagreements persist after discussion.

Information was extracted from each included trial on (1) characteristics of trial participants (2) the trials inclusion and exclusion criteria (3) type of intervention (4) type of control used (5) outcome measures.

Data synthesis

All the data extracted were summarized in evidence table. The evidence was presented to a multidisciplinary expert committee member. Data were assessed for suitability for pooling with regards to the intervention, study design, populations, comparators and outcome. Due to methodological and clinical heterogeneity of the studies, a narrative synthesis was used.

The overall search results were presented in Chapter 4. The detailed results were presented in Chapter 5 according to the research questions.

CHAPTER 4: OVERALL SEARCH RESULTS

The electronic searches identified 3609 articles. Out of these 3609 articles, 2045 articles were duplicates. Two reviewers screened 1564 titles and abstracts. A total of 92 full text articles were retrieved for assessment. Thirty-six articles met our inclusion and exclusion criteria.

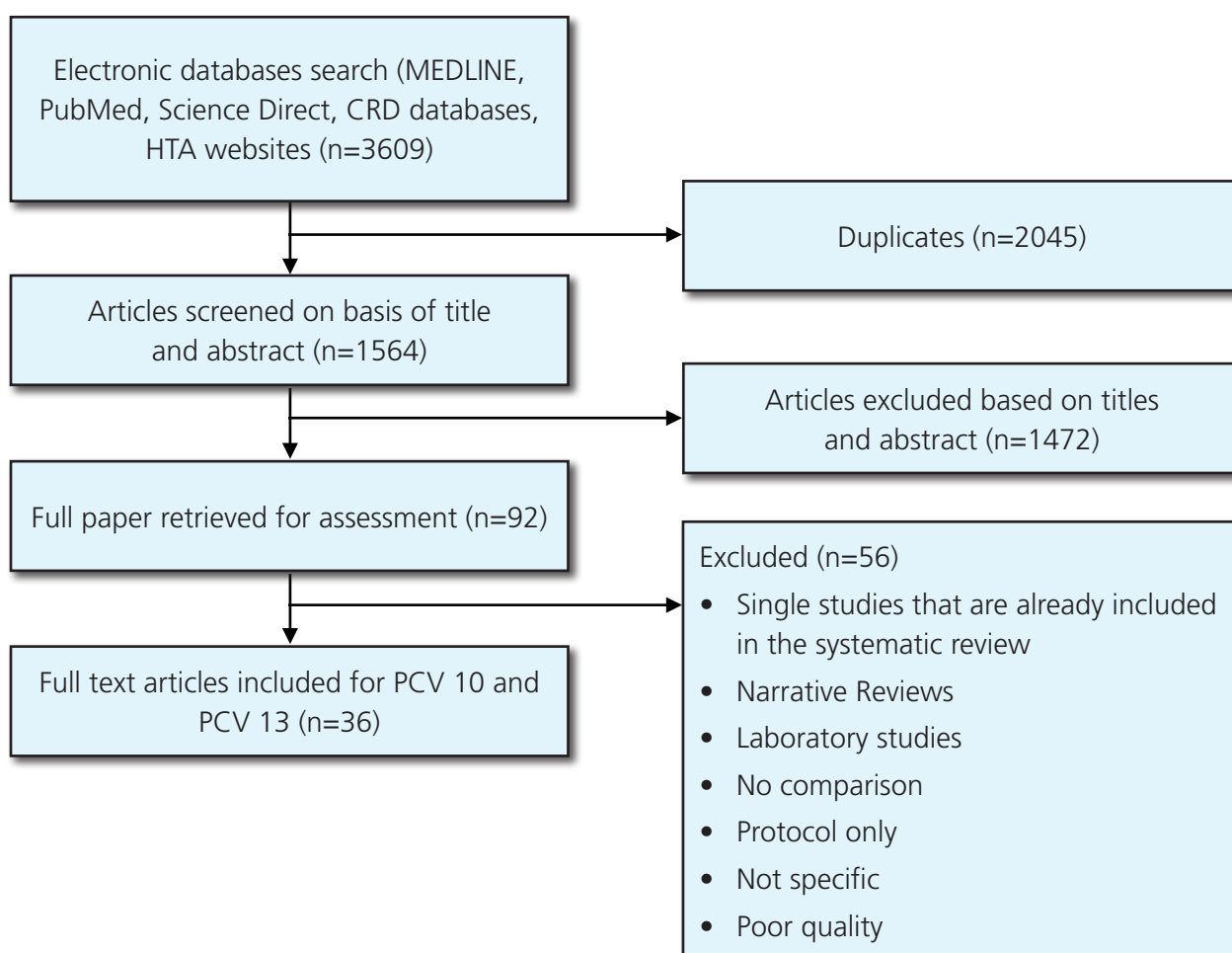
For efficacy/effectiveness, fourteen articles were included, whereby thirteen studies involved PCV13 as the main intervention, with only one study involving PCV 10 as the main intervention and only two studies directly comparing PCV13 and PCV10. For safety, nine articles were included, out of which eight studies had PCV 13 as the main intervention, with only one study that involved PCV 10 as the main intervention and only one study directly comparing PCV13 and PCV10. For cost effectiveness, twenty articles were included with twelve studies that included PCV 13 as the main intervention, six studies that involved PCV 10 as the main intervention while six studies were directly comparing PCV13 and PCV10.

A flow diagram showing the number of articles identified, retrieved and included in the review is presented in Figure 1.

The evidence tables of these studies were presented in Appendix 6. The excluded studies were listed in Appendix 7.

The characteristics of included studies are discussed in the relevant chapters.

Figure 1: Flow chart of study selection



CHAPTER 5: 10-VALENT AND 13- VALENT PNEUMOCOCCAL CONJUGATE VACCINES

A) EFFICACY/ EFFECTIVENESS

Clinical Effectiveness

Cohen R et al did a study to assess the effect of the implementation of PCV13 on pneumococcal nasopharyngeal (PNP) carriage in young children with AOM (acute otitis media).³⁴ Between October 2010 and May 2011, 58 pediatricians distributed throughout France took part in this prospective study. Among 943 children enrolled (mean age, 13.4 months), 651 had received at least 1 dose of PCV13 and 285 received PCV7 only (reference group). The result showed that:

- In comparing PCV13-vaccinated children versus children exclusively vaccinated with PCV7,
 - Overall pneumococcal nasopharyngeal (PNP) carriage was 53.9% for PCV13-vaccinated children versus 64.6% for children exclusively vaccinated with PCV7, $P < 0.002$)
 - carriage of serotypes not in PCV7 was 9.5% for PCV13-vaccinated children versus 20.7% for children exclusively vaccinated with PCV7, $P < 0.0001$
- The carriage rates were also significantly lower in PCV13-vaccinated patients than in patients only vaccinated by PCV7:
 - serotypes 19A (7.5% for PCV13-vaccinated children versus 15.4%, for children exclusively vaccinated with PCV7, $P < 0.001$)
 - serotype 7F (0.5% for PCV13-vaccinated children versus 2.8% for children exclusively vaccinated with PCV7, $P < 0.002$)
 - serotype 6C (3.7% for PCV13-vaccinated children versus 8.4% for children exclusively vaccinated with PCV7, $P < 0.003$)

This study suggested that in young children (lesser than 2 years) with AOM, PCV13 has an impact on overall PNP carriage, as well as on serotypes 19A, 7F, and 6C. (This study was supported by Pfizer Pharmaceuticals France. The authors mentioned that they had no other funding or conflicts of interest to disclose).

Azzari C et al did a study between April 2008 and March 2011, involving a total of 144 patients with pneumococcal meningitis/sepsis ($n = 43$) or pneumonia ($n = 101$) from 83 participating centers.³⁵ The median age of participants was 4.1 years old. The objective was to assess the potential serotype coverage of three pneumococcal conjugate vaccines (7-, 10- and 13-valent) against bacteraemic pneumococcal pneumonia and meningitis/sepsis in Italian children. Inclusion: all children 0–16 years with a confirmed diagnosis of meningitis/sepsis (the most severe IPD) or bacteraemic pneumonia (the most common IPD), admitted to Paediatric Hospitals or Paediatric wards of general hospitals in Italy during study period. The outcomes of the study were:

- 83 participating centers located in 19 of 20 Italian regions were serotyped. The 10 most prevalent serotypes were 1 (29.9%), 3 (16.0%), 19A (13.2%), 7F (8.3%), 5 (4.2%), 14 (4.2%), 6A (3.5%), 6B (3.5%), 18C (3.5%), 19F (3.5%).
- Serotype coverage for PCV7 was 19.4%, PCV10 was 61.8% and PCV13 was 94.4% and with no statistical difference between pneumonia and meningitis/sepsis. Hence, PCV10 would provide potential coverage for about 62% of the serotypes identified, while PCV13 would provide coverage of more than 94% (86% for meningitis/sepsis and nearly 100% for pneumonia).

The author suggested that the introduction of PCV13 could have a significant added benefit in reducing the burden of pneumococcal disease in Italian children below 2 years as well in older children. (The research has been partially supported by the Italian Department of Health; Italian Center for Disease Control and Prevention (grant 117-19.01.07-#6728 to C.A.). The authors do not have any conflict of interest).

Hortal M et al did a pre and post vaccination study using population-based surveillance in Uruguay, from January 1st 2009 to June 30th 2011.³⁶ PCV7 was included into the National Immunization Program (NIP) in March 2008 using a 2 + 1 dosing schedule. In March 2010, PCV13 replaced PCV7. The objective was to compare the incidence of consolidated pneumonia hospitalization in children less than five years of age before and after pneumococcal conjugate vaccine implementation. One thousand five hundred and forty two (1542) hospitalised patients under five years of age were enrolled. Mean age was 18.1 ± 15.6 months, 52% were males, 89% of families lived in urban areas but in area with dwelling and poverty condition. About 40% of patients had been hospitalized previously with acute respiratory diseases. The surveillance was carried out at the same four hospitals in previous pre vaccination study. The outcomes of the study were:

- 1224 were hospitalized with pneumonia (430 consolidated Pneumonias and 794 non consolidated pneumonias). In 48 consolidated pneumonias, *S.pneumoniae* etiology was recognized.
- A significant reduction (44.9%) of incidence rate of consolidated pneumonia in post vaccinated patients aged 12–23 months was observed with PCV -7 vaccinations.
- Pleural effusion was recorded in 89 patients.
- In March 2010, PCV13 replaced PCV7. Compliance of PCV7/13 globally was 92% but the vaccination status varied among the surveyed patients because two catch-ups were carried out in addition to the routine cohort vaccination. From 2009 1st semester to 2011, 1st semester incidence rates decline reached 59%.

According to the author, to date, the ongoing surveillance documented a significant decline on incidence of hospitalizations for consolidated pneumonia in children younger than 24 months of age, suggesting the success of the 2 + 1 vaccination schedule. (This study is supported by an irrestrictive grant from Pfizer Inc.).

Immunogenicity

Esposito S et al did a randomised controlled trial which compared the safety and immunogenicity of PCV13 with those of PCV7 when given as part of the pediatric vaccination schedule recommended in Italy.³⁷ A total of 606 subjects were randomly assigned to receive either PCV13 or PCV7 at 3, 5, and 11 months of age; all subjects concomitantly received diphtheria-tetanus-acellular pertussis hepatitis B-inactivated polio-Haemophilus influenzae type B (DTaP-HBV-IPV/Hib) vaccine. The study showed that:

- Overall, the safety profile of PCV13 was similar to that of PCV7. Most of the local reactions in the two vaccine groups were mild in severity and lasted 1 or 2 days. No statistically significant differences between vaccine groups were observed after doses 1 and 2 of the infant series or after the toddler dose. There was no significant differences between vaccine groups in the incidence of systemic events.
- The response to DTaP-HBV-IPV/Hib antigens was substantially the same with both PCV13 and PCV7. PCV13 elicited antipneumococcal capsular IgG antibodies to all 13 vaccine serotypes, with notable increases in concentrations seen after the toddler dose.
- For concomitant antigens, 95% CIs for the proportion of responders and for the difference in proportions (PCV13 - PCV7 reference) were calculated, with noninferiority declared if the lower bound of the two-sided 95% CI for the difference in proportions was greater than -10%. All of the 95% CI lower limits for the differences between PCV13 and PCV7 responses exceeded -10%, indicating that the responses to concomitant vaccine antigens when given with PCV13 vaccination were not inferior to those when given with PCV7 after both the infant series and the toddler dose.
- Despite a lower immunogenicity for serotypes 6B and 23F after the primary series of PCV13, responses to the seven common serotypes were comparable between the PCV13 and PCV7 groups when measured after the toddler dose. PCV13 also elicited substantial levels of OPA activity against all 13 serotypes following both the infant series and the toddler dose.

- PCV13 appeared comparable to PCV7 in safety profile and immunogenicity for common serotypes, demonstrated functional OPA responses for all 13 serotypes, and did not interfere with immune responses to concomitantly administered DTaP-HBV-IPV/Hib vaccine.

(This study was supported by a grant from Wyeth Vaccines Research (protocol 6096A1-500), which was acquired by Pfizer Inc. in October 2009).

Bryant KA (Kristina) et al did a randomised controlled trial whereby the safety and immunogenicity of PCV7 were compared with those of 13-valent PCV (PCV13), which contains saccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to CRM (a nontoxic variant of diphtheria toxin).¹² Infants were randomly assigned to receive PCV13 or PCV7 at ages 2, 4, and 6 months with other vaccines. Post-third-dose antibodies to each pneumococcal polysaccharide were measured by immunoglobulin G enzyme-linked immunosorbent assay. Antibacterial functional antibodies were measured by opsonophagocytic assay (OPA). The result showed that:

- Subjects received PCV13 (n = 122) or PCV7 (n = 127). For the 7 common serotypes included in PCV13 and PCV7, 88.3% to 99.1% of vaccinated infants in both groups achieved antibody concentrations of $\geq 0.35 \mu\text{g/mL}$ 1 month after the third dose, and there were no significant differences between treatment groups.
- For the 6 additional serotypes only in PCV13, 97% to 100% of PCV13-vaccinated infants achieved similar levels of pneumococcal antipolysaccharide IgG concentrations 1 month after the third dose.
- Geometric mean antibody concentration for PCV13 recipients ranged from 1.32 $\mu\text{g/mL}$ (serotype 23F) to 4.26 $\mu\text{g/mL}$ (serotype 14).
- The ratio of OPA geometric mean titers for the 7 shared serotypes (PCV13:PCV7) ranged from 0.6 to 1.4, suggesting no clinically meaningful differences.
- For PCV13-only serotypes, OPA geometric mean titers were significantly higher in the PCV13 group than in the PCV7 group.
- Local reactions and systemic events were similar between groups.

The study showed that PCV13 was well tolerated and immunogenic, with most infants developing antipolysaccharide antibody concentrations of $\geq 0.35 \mu\text{g/mL}$, as well as OPA responses, to each of the 13 serotypes. (This study was sponsored by Wyeth).

Kim DS et al did a study whereby the immunogenicity and safety of 13-valent and 7-valent pneumococcal conjugate vaccines (PCV13 and PCV7) were compared when administered with routine vaccines at six sites in Korea.³⁸ Healthy infants (n = 180) were randomly assigned (1:1) to receive PCV13 or PCV7 at 2, 4, 6 (infant series) and 12 months (toddler dose). Immune responses one month after the infant series and toddler dose were measured by enzyme-linked immunosorbent assay and OPA assay. IgG antibody geometric mean concentrations and OPA functional antibody geometric mean titers were calculated. Safety was also assessed. The results showed that:

- For each of the 7 common serotypes, the proportion of subjects achieving IgG concentrations $\geq 0.35 \mu\text{g/mL}$ (ie, the proportion of responders) was similar and $\geq 97.6\%$ in both the PCV13 and PCV7 vaccine groups; $\geq 92.3\%$ achieved lowest limit of quantitation (LLOQs), except for serotype 19F which was lower (78.6%).
- IgG geometric mean concentrations (GMCs) and OPA GMTs were generally similar across groups, but there was a trend toward lower responses in the PCV13 group for some serotypes.
- For the 6 additional serotypes unique to PCV13, the proportion of responders in the PCV13 group was 100% for all serotypes except serotype 6A (97.6%); $\geq 96.0\%$ achieved LLOQs.
- IgG GMCs and OPA GMTs were notably higher in the PCV13 group than in the PCV7 group.
- Although PCV7 elicited IgG responses to nonvaccine serotypes 5 and 19A, OPA functional antibody responses were minimal (GMTs: 4 and 7, respectively).

- In contrast, PCV7 elicited both IgG and OPA functional responses (GMT 492) to serotype 6A; however, the OPA responses were 4.5-fold less than those in response to PCV13.
- For the 7 common serotypes, PCV13 generally resulted in an increase in immune responses after the toddler dose. For serotype 14, however, which showed the highest IgG response after the infant series (GMC 14.83 µg/mL), the posttoddler response (GMC 11.51 µg/mL) was less than that after the infant series; in contrast, the OPA GMTs were higher after the toddler dose (GMT increase from 1236 to 1542). For 5 of the 6 additional serotypes, the toddler dose of PCV13 resulted in increases in IgG GMCs; the exception was serotype 3, which showed similar IgG GMCs postinfant series (1.60 µg/mL) and posttoddler dose (1.65 µg/mL). However, OPA GMTs for serotype 3 showed a notable increase from after the infant series to after the toddler dose (GMT increase from 153 to 256).
- These observations are consistent with at least some protection by PCV7 against 6A-mediated invasive pneumococcal disease, but no cross-protection for serotypes 5 and 19A. The toddler dose elicited higher IgG and OPA responses than postinfant series responses for most serotypes; however, for serotypes 3 and 14 only OPA responses were increased posttoddler dose.
- Vaccine safety profiles were similar. Incidence of systemic events was generally similar in both groups. Fever was mostly mild, and there was no cases of severe fever.

(This study was sponsored by Wyeth, which was acquired by Pfizer in October 2009).

Silfverdal et al did a phase 3 open label study that evaluated immunogenicity and safety of PCV13 in Swedish infants and toddlers previously given one or two doses of PCV7 during infancy.³⁹ Healthy infants previously given PCV7 at ages 3 months (group 1; n = 118) or 3 and 5 months (group 2; n = 116) received PCV13 at ages 5 (group 1) and 12 months (both groups). IgG responses were assessed one month after each PCV13 dose and before the 12-month dose. Local reactions and systemic were assessed one month after each PCV13 dose and before the 12-month dose. Results were as shown below:

- One month after the 5-month dose, serotype-specific IgG GMCs were 1.56–4.70 µg/ml for PCV7 serotypes except for serotypes 6B (0.40 µg/ml) and 23F (0.57 µg/ml). For the 6 additional serotypes, GMCs were 0.72 – 1.88 µg/ml except for serotype 6A (0.28 µg/ml).
- For PCV7 serotypes, the proportions of subjects with pneumococcal serotype-specific IgG concentrations $\geq 0.35\mu\text{g/ml}$ were 92.2% – 99.1%, except for serotypes 6B (53.0%) and 23F (62.6%). Proportions for the six additional serotypes were 80.9%–100.0%, except for serotype 6A (36.8%).
- Post-12-month dose, IgG GMCs for the PCV7 serotypes were 2.93 – 9.63 µg/ml (group 1) and 3.33–9.30µg/ml (group 2); and for the 6 additional serotypes, 1.85 –14.65µg/ml (group 1) and 1.34 – 13.16 µg/ml (group 2).
- GMCs increased by >4-fold in both groups from pre- to post-12-month dose. Proportions of subjects in group 1 with pneumococcal serotype-specific IgG concentrations $\geq 0.35\mu\text{g/ml}$ (WHO-designated postprimary reference antibody level) post-5-month dose were 92.2% – 99.1% for most PCV7 serotypes except 6B (53.0%) and 23F (62.6%) and 80.9% – 100.0% for most of the six additional serotypes except 6A (36.8%).
- Local reactions and fever were mostly mild or moderate.

From the study it was found that PCV13 was immunogenic and safe in infants and toddlers previously partially immunized with PCV7. Even a single dose in an infant or toddler induces an immune response to the six additional serotypes. (This study was sponsored by Wyeth, which was acquired by Pfizer Inc in October 2009).

Weckx LY et al did a phase III, randomized, multicenter, double-blind study in Brazil whereby the primary objective of the study was to compare pneumococcal immune responses induced by PCV13 with those induced by PCV7, measured one month after the infant series and also to observe for any adverse events (AEs) after PCV13 vaccination relative those after PCV7.⁴⁰ Healthy infants (n=354) aged 1 month (28–54 days) were enrolled. Subjects were randomly assigned in a 1:1 ratio (177 in each group) to receive either

PCV13 or PCV7. Blood samples were collected 27–56 days after both the infant series (1 month after dose 3 of PCV7 or PCV13), and toddler dose (age 13 months).

The outcomes were as shown below:

- Immune responses to the common serotypes 1 month after the infant series;
 - The proportion of subjects with serotype-specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$ was comparable in the PCV13 ($\geq 94.2\%$) and PCV7 ($\geq 93.0\%$) groups
 - IgG Geometric mean concentration (GMC)s were comparable in the PCV13 and PCV7 groups
- Immune responses to the additional serotypes after the infant series
 - For the 6 additional serotypes, the proportion of responders ranged from 1.3% (serotype 7F) to 98.7% (serotype 19A) in the PCV7 group
 - For serotypes 1, 3, 5, 6A, and 7F, the response rates in the PCV13 group were significant compared with the PCV7 group
 - For serotype 19A, response rates were comparable in both PCV13 (99.4%) and PCV7 (98.7%) groups
 - IgG GMCs for the six additional serotypes were higher in the PCV13 group than the PCV7 group
- Immune responses to the common serotypes after the toddler
 - Dose IgG GMCs were comparable in both groups for the 7 common serotypes after the toddler dose, with exception of serotype 19F
 - Immune responses to the additional serotypes after the toddler dose
 - IgG GMCs for the six additional serotypes were higher in the PCV13 group
- Concomitant vaccine immunogenicity
 - The proportion of subjects achieving PT, FHA, and PRN antibody levels of ≥ 5 EU/mL and pertussis antigens one month after the infant series and toddler dose were similar between the PCV13 and PCV7 groups
 - Reported local reactions and systemic events were similar in both groups

The study showed that PCV13 provide comparable protection for the seven common serotypes and added protection against the six additional serotypes. (This study was sponsored by Wyeth, which was acquired by Pfizer Inc. in October 2009).

Huang LM et al did a randomized, multicenter, double-blind study in Taiwan. The objective was to evaluate the immunogenicity and safety of PCV13 compared to PCV7.⁴¹ Subjects (n= 168) that were day 42-98 healthy infants were randomly assigned in a 1:1 ratio (84 in each group) to receive PCV13 or PCV7 at 2, 4 and 6 months (infant series), and 15 months (toddler dose). Concomitant study vaccines were diphtheria, tetanus, acellular pertussis (DTaP), inactivated poliovirus (IPV) and Haemophilus influenzae type b (Hib), administered at 2 and 4 months; and DTaP-IPV-Hib combined with hepatitis B virus (HBV) administered at 6 months. Blood samples were obtained 28 – 42 days after the infant series and toddler dose. The outcomes were as shown below:

- Immune responses to the common serotypes after the infant series
 - The proportion of subjects with serotype-specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$ was similar in both groups ($\geq 95\%$)
 - IgG GMCs were high in both groups, generally lower in PCV13
- Immune responses to the additional serotypes after the infant series
 - For the 6 additional serotypes, the proportion of responders higher in PCV13 group (exception 19A)

- IgG GMCs higher in PCV13 than PCV7 as shown in the table below:

Sereotypes	IgG GMC level for infant series (PCV13)	IgG GMC level for infant series (PCV7)
serotype 4	2.89 µg/mL (95% CI; 2.45 - 3.42 µg/mL)	4.64 µg/mL (95% CI; 4.00 -, 5.37 µg/mL)
serotype 6B	4.37 µg/mL (95% CI;3.58 - 5.33 µg/mL)	4.82 µg/mL (95%CI; 4.09 - 5.67 µg/mL)
serotype 9V	1.97 µg/mL (95% CI;1.70 - 2.27 µg/mL)	2.92 µg/mL (95% CI; 2.55 - 3.34 µg/mL)
serotype 14	9.76 µg/mL (95% CI;8.34 - 11.43 µg/mL)	11.59 µg/mL (95%CI 9.79 - 13.71 µg/mL)
serotype 18C	2.39 µg/mL (95% CI;2.04 - 2.82 µg/mL)	3.07 µg/mL (95% CI; 2.64 - 3.56 µg/mL)
serotype 19F	3.60 µg/mL (95% CI; 3.00 - 4.32 µg/mL)	4.77 µg/mL (95% CI; 4.17 - 5.47 µg/mL)
serotype 23F	1.93 µg/mL (95% CI;1.56 - 2.37 µg/mL)	3.25 µg/mL (95% CI; 2.78 - 3.80 µg/mL)
serotype 1	4.14 µg/mL (95% CI 3.45 - 4.96 µg/mL)	0.02 µg/mL (95% CI; 0.02 - 0.02 µg/mL)
serotype 3	1.20 µg/mL (95% CI 1.00 - 1.45 µg/mL)	0.05 µg/mL (95% CI; 0.04 - 0.06 µg/mL)
serotype 5	2.47 µg/mL (95% CI 2.09 - 2.92 µg/mL)	0.43 µg/mL (95% CI; 0.35 - 0.53 µg/mL)
serotype 6A	4.57 µg/mL (95% CI 3.92 - 5.34 µg/mL)	0.79 µg/mL (95% CI; 0.63 - 0.99 µg/mL)
serotype 7F	3.67 µg/mL (95% CI 3.14 - 4.29 µg/mL)	0.04 µg/mL (95% CI; 0.03 - 0.05 µg/mL)
serotype 19A	3.69 µg/mL (95% CI 3.20 - 4.24 µg/mL)	2.46 µg/mL (95% CI; 2.13 - 2.84 µg/mL)

➤ Immune responses to the common serotypes after the toddler

- PCV13 higher immune response for all serotypes than postinfant series as shown in table below:

Sereotypes	IgG GMC level for post-infant series (PCV13)	IgG GMC level for post-infant series (PCV7)
serotype 4	4.06 µg/mL (95% CI;3.34 - 4.93 µg/mL)	6.34 µg/mL (95% CI;5.26 - 7.65 µg/mL)
serotype 6B	13.62 µg/mL (95% CI;11.08 - 16.73 µg/mL)	413.28 µg/mL (95% CI;10.87 - 16.21 µg/mL)
serotype 9V	3.18 µg/mL (95% CI;2.66 - 3.80 µg/mL)	3.88 µg/mL (95% CI;3.27 - 4.60 µg/mL)
serotype 14	8.17 µg/mL (95% CI;6.53 - 10.22 µg/mL)	12.04 µg/mL (95% CI;9.90 - 14.63 µg/mL)
serotype 18C	3.67 µg/mL (95% CI;3.00 - 4.49 µg/mL)	4.87 µg/mL (95% CI;4.01 - 5.90 µg/mL)
serotype 19F	8.07 µg/mL (95% CI;6.58 - 9.90 µg/mL)	7.41 µg/mL (95% CI;6.16 - 8.92 µg/mL)
serotype 23F	5.51 µg/mL (95% CI;4.46 - 6.81 µg/mL)	7.97 µg/mL (95% CI;6.55 - 9.68 µg/mL)
serotype 1	7.62 µg/mL (95% CI;6.30 - 9.21 µg/mL)	0.02 µg/mL (95% CI;0.02 - 0.02 µg/mL)
serotype 3	1.29 µg/mL (95% CI;1.09 - 1.53 µg/mL)	0.05 µg/mL (95% CI;0.04 - 0.06 µg/mL)
serotype 5	4.57 µg/mL (95% CI;3.87 - 5.39 µg/mL)	0.43 µg/mL (95% CI 0.35 - 0.53 µg/mL)
serotype 6A	11.55 µg/mL (95% CI;9.66 - 13.81 µg/mL)	0.79 µg/mL (95% CI 0.63 - 0.99 µg/mL)
serotype 7F	5.91 µg/mL (95% CI;4.95 - µg/mL)	0.04 µg/mL (95% CI 0.03 - 0.05 µg/mL)
serotype 19A	8.82 µg/mL (95% CI;7.45 - 10.43 µg/mL)	2.46 µg/mL (95% CI 2.13 - 2.84 µg/mL)

➤ Local reactions and systemic events were similar in both groups. No adverse events, deaths or discontinuation due to adverse events

The study suggested that PCV13 could offer broader serotype protection in preventing pneumococcal disease in Taiwanese children. There was similar safety profile between PCV13 and PCV7. (This study was sponsored by Wyeth, which was acquired by Pfizer in October 2009).

Vanderkooi OG et al did a phase III, randomised, multicenter, double-blind study in Canada.⁴² The objective was to evaluate the immune and safety responses to concomitant routine childhood vaccines when given with PCV13, compared with PCV7. Subjects (n=603), that were healthy infant, day 42 - 98 were randomized 1:1 (300 in PCV13 group, 303 in PCV7 group) to receive either PCV13 or PCV7 at 2, 4 and 6 months (primary infant series) followed by toddler booster at 12 months. Routine concomitant vaccines were diphtheria, tetanus, acellular pertussis, inactivated poliovirus, Haemophilus influenza type b at 2, 4, and 6 months; meningococcal C conjugate at 2, 6, and 12 months; and measles, mumps, and rubella and varicella vaccines at 12 months of age. Blood draws were performed at 7 and 13 months. Immune responses were measured against selected concomitant vaccines; meningococcal C conjugate, Haemophilus influenza type B and pertussis. The outcomes were:

- There were no statistically significant differences between the groups in responses to Hib, pertussis, or meningococcal C after primary or booster vaccinations
- Response to concomitant vaccine antigens – similar in both vaccines, 2.4% lower in PCV13 (meningococcal C antigen)
- Specific IgG concentration $\geq 0.35 \mu\text{g/mL}$ were achieved for most serotypes in $\geq 90\%$ infants with the exception of serotype 3 (79.6%) and 5 (87.0%), and after the fourth dose, $\geq 98\%$ in toddler achieved serotype – specific antibody concentrations with the exception of serotype 3 (84.8%)
- After the fourth dose, 98% to 100% of subjects achieved serotype-specific antibody concentrations $\geq 0.35 \mu\text{g/mL}$, except for serotype 3 (85%)
- Local reactions and systemic events were similar in both groups
- No adverse events, deaths or discontinuation due to adverse events

The study showed no differences between PCV7 and PCV13 on immune responses elicited by selected routine childhood vaccines concomitantly administered (measles, mumps, rubella and varicella were not assessed). The safety profile of PCV13 was similar to PCV7. (The study was supported by Wyeth Pharmaceuticals, Collegeville, PA which was acquired by Pfizer Inc. in October 2009).

Scott P et al did a systematic review and meta analysis. Search was done on twelve databases and trial registries up to March 2010.⁴³ The authors selected randomised controlled trials (RCTs), cohort and case-control studies making direct comparisons between PCV schedules with 2 primary (2p) or 3 primary (3p) doses, with (+1) or without (+0) a booster dose. They extracted data on clinical, nasopharyngeal carriage and immunological outcomes and used meta-analysis to combine results where appropriate. The studies compared 10-valent PCV with 7-valent PCV. The results showed that:

- Seropositivity levels (antibody concentration $\geq 0.35 \mu\text{g/ml}$) following 3p and 2p PCV schedules were high for most serotypes (5 RCTs).
- Differences between schedules were generally small and tended to favour 3p schedules, particularly for serotypes 6B and 23F; between-study heterogeneity was high.
- Seropositivity levels following 3p+1 and 2p+1 schedule were similar but small differences favouring 3p+1 schedule were seen as below:
 - ELISA seropositivity at threshold $0.35 \mu\text{g/ml}$, about age 6 months, for serotype 6B [prevalence differences 0.21; (95% CI; 0.08, 0.33)] and for serotype 23F [prevalence differences 0.17; (95% CI; 0.06, 0.28)]
 - ELISA threshold $0.35 \mu\text{g/ml}$, one month after booster dose, age about 12 months, for serotypes 6B [prevalence differences; 0.07 (95% CI; 0.02, 0.12) and 23F [prevalence differences; 0.04 (95% CI; -0.00, 0.09)]
- adjusted odds ratios (aOR) for disease caused by serotypes included in the vaccine were reported as:
 - 3p+0 versus 2p+0, aOR 1.5 (95%CI; 0.54–4.35);
 - 3p+0 versus 2p+1, aOR 1.5 (95%CI; 0.15–14.6);

- 3p+1 versus 3p+0, aOR 0 (95%CI 0–0.87);
- 3p+1 versus 2p+1, aOR 0 (95%CI 0–10.1).

(This project received funding from the World Health Organization).

Snape MD et al did a phase III, randomised, double blind, active-controlled study. The objective of the study was to assess the immunogenicity and tolerability of PCV13 given according to a reduced dose schedule.⁴⁴ The study was conducted from October 2006 to October 2008. It was performed in the United Kingdom across nine sites. Randomisation was done by a web-based system with a block size of four each sites separately. Participants and relevant staff were blinded during the study. Infants (n=286) were randomised in this study, whereby 141 were assigned to receive PCV13 and 145 to receive PCV7. The PCVs were given at 2, 4, and 12 months of age. The results showed that:

- After primary immunisation, the percentage of PCV13 recipients with serotype-specific IgG concentration > 0.35µg/mL for the six non-PCV7 serotypes ranged from 79.2% (serotype 6A) to 97.2% (serotype 1).
- No more than 17.5% of PCV 7 recipients reached this threshold for five of these six serotypes.
- At 13 months of age, >97% of PCV13 recipients had pneumococcal serotype-specific serum IgG concentrations ≥0.35µg/mL for each vaccine serotype except serotype 3 (88.2%),
- Following immunisation with PCV 13 at 2 and 4 months of age, OPA titers of > 1.8 were seen in > 88% of participants for each of the 13 vaccine serotypes but four types of serotypes the percentages were below 50%.
- At 5 months, 110/114 (96.5%) of PCV13 recipients and 100/102 (98.0%) of PCV7 recipients had serum anti-PRP (Hib) IgG concentration ≥0.15 µg/mL (differences, 1.5%; 95%CI; - 7.1%, -3.7%), while 119/120 (99.2%) and 117/118 (99.2%), respectively, had meningococcal C serum bactericidal assay titers of ≥1:8. All PCV13 recipients and 110/113 (97.3%) of PCV7 recipients had IgG concentrations against fimbrial agglutinogens of ≥2.2 EU/mL; IgG concentrations for the remaining pertussis antigens were ≥5 EU/mL for all participants.
- Local reactions and systemic events were similar in the PCV13 and PCV7 groups.

A schedule of 2, 4, and 12-month course of PCV13 was immunogenic for all 13 vaccine serotypes and was well tolerated. (This study was supported by Wyeth Pharmaceuticals, Collegeville, PA which was then acquired by Pfizer Inc in October 2009, who/which also acted as study sponsor).

Vaccination Schedule

Singleton R et al did an open-label clinical trial whereby PCV13 impact was assessed using existing Alaska-wide IPD surveillance.⁴⁵ In 2009, 372 eligible Yukon Kuskokwim Delta (YKD) children aged less than 5 years were offered PCV13 and received ≥1 dose of PCV13 during the study between January 30, 2009, and March 25, 2010. Study subjects received PCV13 vaccinations as appropriate for their age and prior vaccination history in accordance with the following groups:

- Group 1: Subjects aged 6 weeks to <10 months with no prior doses of PCV7
- Group 2: Subjects aged <12 months with 1 prior dose of PCV7
- Group 3: Subjects aged <12 months with 2 prior doses of PCV7

(Note: recruitment of subjects aged <12 months with 3 prior doses of PCV7 was delayed until age 12 months).

- Group 4: Subjects aged ≥12 months to <2 years.
- Group 5: Subjects aged ≥2 years to <5 years.

Serotype-specific anti-pneumococcal IgG levels were measured postinfant series and posttoddler dose in a subset of subjects. Adverse events and serious adverse events, local reactions and systemic events were collected in toddlers. The result showed that:

- The proportion of responders after the infant series with serotype specific antibody concentration $\geq 0.35 \mu\text{g/mL}$ ranged from 90.9% to 100.0%. The proportion of subjects with opsonophagocytic activity (OPA) titer \geq lower limit of quantitation was $\geq 60\%$ for all serotypes with the exception of serotype 9V (30.0%).
- After the toddler dose, the evaluable group 1 subjects achieved both serotype-specific IgG concentrations $\geq 0.35 \mu\text{g/mL}$ and OPA titer \geq lower limit of quantitation,
- Adverse events were typically mild, or generally consistent with common childhood illnesses.
- IgG levels following PCV13 were similar to other populations. In YKD children aged < 5 years, 52 invasive pneumococcal disease (IPD cases) (31 PCV13-serotype) occurred during 2005 to 2008 (399.0/100,000/yr) versus 9 (7 PCV13-serotype) during January 2009 to August 2011 (106.7/100,000/yr; $P < 0.001$).
- PCV13-serotype IPD incidence declined significantly after PCV13 introduction. Although non-PCV13-serotype IPD also declined significantly, absence of PCV13-serotype IPD in children who received PCV13 suggests a protective vaccine effect.

(The study was sponsored by the Yukon Kuskokwim Health Corporation and Wyeth).

Spijkerman J et al did a randomised control trial to assess the optimal primary vaccination schedule by comparing immunogenicity of 13-valent PCV (PCV13) [serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F] in 4 different immunization schedules.⁴⁶ Between June 30, 2010, and January 25, 2011, four hundred healthy term infants in a general community in the Netherlands were randomly assigned (1:1:1:1) to receive PCV13.

- either at ages 2, 4, and 6 months (subsequently referred to as 2-4-6);
- at ages 3 and 5 months (3-5);
- at ages 2, 3, and 4 months (2-3-4);
- or at ages 2 and 4 months (2-4). All infants received a booster dose of PCV13 at age 11.5 months

The results showed that:

- One month after the booster dose, there were no differences in IgG GMCs between the schedules except for 8 of 78 comparisons.
- The use of 4 different PCV13 immunization schedules in healthy term infants resulted in no statistically significant differences in antibody levels after the booster dose for almost all serotypes.
- The 2-4-6 schedule (10.2 $\mu\text{g/mL}$ [95%CI, 8.2-12.7]) was superior to the 2-3-4 (6.5 $\mu\text{g/mL}$ [95%CI, 5.4-7.8]) schedule for serotypes 18C
- The 2-4-6 schedule (10.9 $\mu\text{g/mL}$ [95%CI, 9.0-13.3]) was also superior to the 2-3-4 (6.5 $\mu\text{g/mL}$ [95%CI, 5.4-7.8]) schedule for 23F (7.3 $\mu\text{g/mL}$ [95%CI, 5.8-9.2]) and
- The 2-4-6 schedule (8.5 $\mu\text{g/mL}$ [95%CI, 7.1-10.2]) was superior to the 2-4 (5.1 $\mu\text{g/mL}$ [95%CI 3.8-6.7]), schedule for serotypes 6B, to the 2-4 for 18C (6.6 $\mu\text{g/mL}$ [95%CI, 5.7-7.7]), and to the 2-4 for 23F (7.2 $\mu\text{g/mL}$ [95%CI, 5.9-8.8]).
- For serotype 1, the 3-5 schedules (11.7 $\mu\text{g/mL}$ [95%CI, 9.6-14.3]) was superior to the other schedules. Geometric mean concentrations for all 13 serotypes ranged between 1.6 and 19.9 $\mu\text{g/mL}$.
- Secondary outcomes demonstrated differences 1 month after the primary series. The 2-4-6 schedule was superior compared with the 3-5, 2-3-4, and 2-4 schedules for 3, 9, and 11 serotypes, respectively. Differences between schedules persisted until the booster dose.

(This study was performed by order and for the account of the Dutch Ministry of Health by additional immunization program research funding. Pfizer kindly provided 1400 PCV13 vaccines. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication).

B) SAFETY

Huu TN et al did a phase III, open-label, randomized controlled study which was conducted between February 2011 and July 2011 in one of the largest tertiary hospitals of Ho Chi Minh City (the Children Hospital No. 2 [Nhi Dong 2]) in cooperation with the Clinical Research Unit of the Pasteur Institute of Ho Chi Minh City.⁴⁷ Study participants were recruited from the hospital vaccination clinic. Eligible participants were healthy infants aged between and including 6–12 weeks (42–90 days) at the time of the first vaccination. Study participants were randomised (2:1 treatment allocation ratio) to receive 3-dose primary vaccination at 2, 3, and 4 months of age with either 10-valent pneumococcal non-typeable Haemophilus with diphtheria, tetanus acellular pertussis, hepatitis B virus, inactivated poliovirus and H. influenzae type b vaccine DTPa-HBV-IPV/Hib (PHiD-CV = PCV10 group) or DTPa-HBV-IPV/Hib administered alone (Control). The results showed that:

- Within 31 days post-vaccination, 8.2% of overall doses in the PCV10 group and 3.0% of overall doses in the control group were followed by at least one solicited and/or unsolicited, local and/or general adverse event of grade 3 intensity.
- Pain at injection site was the most common grade 3 solicited symptoms, which was reported following 6.5% (95% CI: 4.7, 8.8) of overall doses in the PCV10 and 1.0% (95% CI: 0.2, 2.9) control groups.
- Within 4 days post vaccination, the most common solicited local and general symptoms reported with any intensity were pain 48.9% of doses in the PCV10 and 31.0% of the doses in control groups)
- Irritability: 58.0% of doses in the PCV10 and 40.4% of doses control groups.
- Within 31 days post-vaccination, the incidence of unsolicited symptoms was comparable in both groups (following 12.3% of doses in the PCV-10 and 14.8% of doses control groups).
- Throughout the study, 13 serious adverse events (SAEs) were reported in nine infants in the PCV10 group and 11 SAEs in six infants in the control group. None of them were fatal or considered causally related to vaccination.

Overall, the vaccine safety profile of PCV13 was similar to that of PCV7 and PCV 10.^{12, 37-42, 46} Most of the local reactions in the three vaccine groups were mild in severity. No statistically significant differences between vaccine groups were observed after doses 1 and 2 of the infant series or after the toddler dose. There was no significant difference between vaccine groups in the incidence of systemic events.

C) COST/ COST EFFECTIVENESS

Rozenbaum MH et al did a study to update on the cost effectiveness estimates for the four dose (3+1) schedule of the seven valent pneumococcal conjugated vaccine (PCV7) in the Netherlands and to explore the impact on cost effectiveness of reduced dose schedules and implementation of 10 valent and 13 valent pneumococcal vaccines (PCV10 and PCV13).⁴⁸ Economic evaluation was done comparing PCV7, PCV10, and PCV13 with no vaccination using a decision tree analytic model. A cohort of 180,000 newborns was run through the decision tree once as a vaccinated cohort and once as an unvaccinated cohort. The analytic time frame was 5 years. For PCV7, the estimated current cost of €50 per dose within the Dutch national immunisation programme was used. For PCV13, the officially listed price of €68.56 was applied, with administration costs of €5.95 being added (total cost per dose €74.51). For PCV-10, no officially listed price is available in the Netherlands. Given that the pricing of PCV10 in other countries is conservative compared with PCV13, the authors assumed the total cost per dose of PCV10 at the midpoint between PCV7 and PCV13 (that is, €62.25). The results of the study showed that:

- In the base case analysis, the estimated burden of pneumococcal infection for a birth cohort followed for 5 years was 170,788 cases of otitis media and 198,358 cases of non-invasive pneumonia.
- Under base case assumptions—that is, assuming a five year protective period of the vaccine and no assumed net indirect effects (herd protection minus serotype replacement) among children aged over 5 years—vaccination with PVC7 in a four dose (3+1) schedule was estimated.
 - To prevent 71 cases of invasive pneumococcal disease, 5372 (31%) of otitis media and 406 cases

non-invasive pneumococcal disease in children aged up to 5 years. This corresponds with a total net gain of 27 and 2 QALYs respectively.

- Additionally 71 cases of invasive disease would be prevented by vaccination with PCV7 corresponding to a gain of 173 life years or 248 QALYs.
- Compared to no vaccination, PCV10 would prevent 6124 cases of otitis media, 463 cases of non-invasive pneumonia, and 258 cases of invasive pneumococcal disease, Overall these health benefits would result in a gain of 707 QALYs. Vaccination with PCV13 would prevent 6876 cases of otitis media, 520 cases of non-invasive pneumonia, and 331 cases of invasive pneumococcal disease, resulting in a total gain of 891 QALYs.
- The incremental cost effectiveness ratio of PCV7 was estimated at €113 891 (£98 300; \$145 000) per QALY, well over the ratio of €50 000 per QALY required for PCV-7 to be regarded as potentially cost effective.
- The incremental cost effectiveness ratios for the PCV10 was €52 947 per QALY while for PCV13 it was €50 042 per QALY

The current Dutch infant vaccination programme of four doses of PCV7 is not cost effective because of increases in invasive disease caused by nonvaccine serotypes, which reduces the overall direct effects of vaccination and offsets potential positive herd protection benefits in unvaccinated individuals. The 10 valent and 13 valent pneumococcal vaccines could have better net health benefits than PCV7 through less replacement disease and increased herd protection. Both these effects could substantially reduce the incremental cost effectiveness ratio to possibly acceptable levels, if total programme costs can be lowered by reduced schedules, reductions in vaccine prices, or both. (The study was funded by an unrestricted grant from Wyeth and the Netherlands Vaccine Institute, Bilthoven).

Klok RM, et al did a study to examine the public health and economic effects of paediatric national immunization programs of PCV10 and PCV13 in Denmark and Sweden.⁴⁹ Individuals entered the model with either a PCV10 or a PCV13 national immunization programme (NIP) in place. The vaccine cost per dose was 451.33 DKK (Danish kroner) for PCV10 and 451.33 DKK for PCV13 in Denmark. The vaccine cost per dose was 518.95 SEK (Swedish kronor) for PCV10 and 518.95 SEK for PCV13 in Sweden. Children aged <1 year were vaccinated either PCV10 or PCV13. Vaccinated children were assumed to receive the full primary series of the respective vaccine as indicated by the country-specific NIP and a booster dose in their second year of life. A previously published decision-analytic model was used to estimate the impact of PCV10 and PCV13 on reducing cases of invasive pneumococcal disease (IPD), pneumonia (PNE), and acute otitis media (AOM) by using country-specific incidence, serotype coverage, disease sequelae, mortality, vaccine effectiveness, indirect effects, costs, and utilities. Direct effects for PCV13- and PCV10-covered serotypes were assumed similar to PCV7. PCV13 was assumed to confer an indirect effect, similar to PCV7, whereas PCV10 was not. Assumptions were tested in sensitivity analyses. The results showed that:

- PCV13 is expected to save 280.7 million DKK (Danish kroner) in Denmark and 288.2 million SEK (Swedish kronor) in Sweden in direct costs compared with a vaccination program with PCV10.
- In both Denmark and Sweden, the results of this study indicate that, compared with PCV10, PCV13 will have a greater impact on disease in life-years gained (LYG), quality-adjusted life-years (QALYs) gained, IPD cases avoided, PNE cases avoided, AOM cases avoided, and in deaths avoided.
- For Denmark PCV13, it was estimated to result in 10,051 LYG; 9063 QALYs gained; 237 additional IPD cases avoided; 12,094 additional PNE cases avoided; 958 additional cases of AOM avoided; and 882 additional deaths avoided.
- For Sweden PCV13, it was estimated to result in 4245 LYG; 3953 QALYs gained; 379 additional IPD cases avoided; 8210 additional PNE cases avoided; 1459 additional cases of AOM avoided; and 378 additional deaths avoided.
- In all sensitivity analyses, PCV13 was less costly and more effective compared with PCV10.

According to the author, in this analysis, a national immunization program with PCV13 was found to be good value for money and estimated to prevent additional cases of disease among children and non-vaccinated individuals and save additional costs due to treatment of pneumococcal disease, when compared with PCV10 in Denmark and Sweden. (This study was performed and funded in full by Pfizer Inc. All authors are employees of Pfizer Inc. The authors have indicated that they have no other conflicts of interest to report).

Gomez JA, et al did a cost effective and cost utility analysis whereby a Markov model that simulated the disease processes in a birth cohort over a lifetime, within 1,128 month cycles was used to evaluate the cost-effectiveness of 10-valent pneumococcal NTHi protein D conjugate vaccine (PHiD-CV; PCV10) and 7- and 13-valent PCVs (PCV7 and PCV 13).⁵⁰ The analysis was done on newborn cohort of 2007 (500,700 participants) with a lifetime time horizon from the payers of the healthcare system perspective by discounting at a 3.5% for costs and health events. Vaccine prices per dose were obtained from the 2012 PAHO Revolving Fund (RF) for PCV13 (US\$ 16.34) and PHiD-CV /PCV10 (US\$ 14.24) (the first year with these two vaccines available at the PAHO RF), and from the PAHO Revolving Fund 2010 (the last year with this vaccine available at the PAHO RF) for PCV7 (US\$ 20.00). Expected quality-adjusted life years (QALYs), cost-savings and incremental cost effectiveness ratios (ICERs) were calculated. The results were as below:

- Without vaccination, pneumonia was associated with the greatest health economic burden (90% of QALYs lost and 63% of lifetime direct medical costs); while acute otitis media (AOM) was responsible for 1% of QALYs lost and 25% of direct medical costs.
- PCV13 was estimated to generate 719 more QALYs gained than PCV7 at an additional investment of US\$ 1.3 million, making it a cost-effective intervention compared to PCV7 for Peru.
- PCV10 was estimated to generate 769 more QALYs gained than PCV7 with a reduced investment (–US\$ 2.1 million); in addition, PCV10 was estimated to generate 50 more QALYs gained than PCV-13 with a reduced investment (–US\$ 3.4 million), hence suggesting PCV10 being most cost-effective (discounted data),
- Although PCV13 is predicted to save 20 more LYs than PCV10, at an incremental investment of US\$ 3.4 million (compared to PCV10), the ICER of PCV13 versus PCV10 is US\$ 170,391 per LY saved (greater than the 3 GDP per capita threshold for Peru)
- The probabilistic sensitivity analysis showed that PCV10 generated more QALYs gained at a reduced cost than PCV-13 in 84% of the simulations and less QALYs gains at a reduced cost in 16%.
- Additional scenarios using different assumptions on vaccine efficacies based on previous evidence were explored, but no significant change in the overall cost-effective results were observed.
- The results of this modeling study predict that PCVs are likely to be a cost-effective strategy to help relieve the epidemiological and economic burden associated with pediatric pneumococcal and NTHi diseases for Peru.
- PCV10 is likely to be a dominant (better health gains at a reduced net cost) intervention compared to PCV13 or PCV7.

According to the authors, the most significant drivers for these results are the better health and economic profile of PCV10 against AOM and its reduced cost per dose available through the PAHO Revolving Fund in the LAC region. (This study was sponsored by GlaxoSmithKline Vaccines).

Ayieko P et al did an economic evaluation whereby the costs and effects of pneumococcal vaccination among infants born in Kenya in 2010 were assessed using a decision analytic model comparing PCV10 or PCV13, in turn, with no vaccination.⁵¹ A total of 1,407,000 infants born in Kenya in 2010 contributed 6,680,436 child-years of observation during the first five years of life. The authors estimated the cost-effectiveness of introducing either PCV10 or the 13-valent vaccine (PCV13) from a societal perspective (considering both medical and non-medical costs and productivity losses) and explored the incremental impact of including indirect vaccine effects. Direct vaccine effects were estimated as a reduction in the

incidence of pneumococcal meningitis, sepsis, bacteraemic pneumonia and non-bacteraemic pneumonia. Pneumococcal disease incidence was extrapolated from a population-based hospital surveillance system in Kilifi. Vaccine efficacy estimated from a trial in Gambia. Multivariable sensitivity analysis was conducted using Monte Carlo simulation that assumed a vaccine price of US\$ 3.50 per dose. The base case analysis compared the discounted (3% per year) costs and effects of universal PCV vaccination to those associated with no PCV. The results showed that:

- The annual cost of delivering PCV10 was approximately US\$14 million. The authors projected a 42.7% reduction in pneumococcal disease episodes leading to a US\$1.97 million reduction in treatment costs and a 6.1% reduction in childhood mortality annually.
- In the PCV10 base case analysis, assuming no indirect effects, a 3% discount rate and a price of US\$ 3.50 per dose, the cost effectiveness ratio for PCV10 versus status quo was US\$59 (95% CI, 26–103) per DALY averted, US\$ 300 (95% CI, 145–488) per case averted and US\$ 1,958 (95% CI, 866–3,425) per death averted .
- Working with the same assumptions, cost effectiveness of PCV13 versus status quo was US\$ 47 (95% CI, 20– 83) per DALY averted, US\$ 238 (95% CI, 110–390) per case averted and US\$ 1,558 (95% CI, 665– 2,764) per death averted,
- PCV13 introduction improved the cost-effectiveness ratios by approximately 20% and inclusion of indirect effects improved cost-effectiveness ratios by 43– 56%.
- The Kenya Government currently pays \$0.20 per dose under a co-financing arrangement with GAVI. From the Government perspective, introduction of either PCV10 or PCV13 is cost saving. The break-even prices for PCV10 and PCV13 are US\$ 0.41 and US\$ 0.51, respectively

Hence introducing either PCV10 or PCV13 in Kenya is highly cost-effective from a societal perspective. [This work was supported by the GAVI Alliance through the PneumoADIP and by the Wellcome Trust through research fellowships to JAGS (081835) and ME (076827). The KEMRI-Wellcome Trust Research Programme is supported by core funding from the Wellcome Trust (#092654/Z/10/A). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript].

Hoshi SL et al did a cost-effectiveness analysis with Markov model and calculated incremental cost effectiveness ratios (ICERs). The authors appraise the 'value for money' of replacing PCV7 with PCV13 vaccination programme in Japan.⁵² The authors set two base-cases for analyses: "Base-case A", which assumes that the prevention of AOM by PCV13 is limited to the seven serotypes of PCV7 only; and "Base-case B", which assumes that the prevention of AOM by PCV13 is straightforwardly extended to cover non-PCV7 serotypes. The base-case analyses, which assumed both PCVs have no net indirect effect and set the cost of PCV7/PCV13 per shot at ¥10,000 (US\$125)/¥13,000 (US\$163). The authors define two vaccination programmes: current PCV7 programme and the possible replacement, i.e., PCV13 programme, with the same vaccination schedule (3 + 1). It was assumed that vaccination is fully subsidised for the uptake of 4 doses of either PCV7 or PCV13. The birth cohorts of 5 years used in the model are from Population estimates of Japan. The results showed that:

- The estimated disease cases avoided by PCV7 / PCV13 vaccination programme compared with no programme for 100,000 birth cohort in the 5-year period are as follow: 8.2/9.7 cases of meningitis, 49.4/58.4 cases of bacteraemia, 1739.4/2112.9 cases of hospitalized pneumonia, 66,188/66,188 (Base-case A) or 72,728 (Base-case B) of AOM, and 1.86/2.26 cases of death due to either meningitis, bacteraemia or pneumonia. If PCV13 replaces PCV7, the estimated incremental number of avoided cases will be: 1.49 of meningitis, 8.94 of bacteraemia, 373.5 of hospitalised pneumonia, none or 6540.2 of AOM in Base-case A or Base-case B, respectively, and 0.40 cases of death due to either meningitis, bacteraemia or pneumonia. The reduced disease cases resulting from replacing PCV7 with PCV13 would be 18.1%, 21.5%, and 9.9%, for IPD, hospitalized pneumonia, and AOM, respectively.

- The results showed that in Base-case A (assumed PCV13 has no additional protection against AOM compared to PCV7), replacing PCV7 with PCV13 will cost ¥37,722,901 (US\$471,536) or ¥35,584,455 (US\$444,850) per QALY when the caregiver's productivity loss is not included or is included, respectively.
- While in Base-case B (assumed PCV13 has additional protection against AOM compared to PCV-7), ¥343,830 (US\$4298) per QALY or more QALY is gained by saving money without or with caregiver's productivity loss, respectively.
- Also, in Base-case B if cost per PCV13 shot is equal to or less than that ¥17,000, then a PCV13 vaccination programme offered to the birth cohort in Japan is likely to be a socially acceptable option compared to the current PCV7 vaccination programme.
- Furthermore, if cost per PCV13 shot is equal to or less than ¥12,000, replacing PCV7 with PCV13 will save money and gain more QALYs. While in Base-case A, the replacement can only be socially acceptable if cost per PCV13 shot is equal to or less than ¥11,000.

(This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan).

Earnshaw SR et al did a study with the objective to examine the public health and economic impacts of a PCV10 and PCV13 paediatric national immunization programs (NIPs) in Canada.⁵³ The individuals considered were 34,108,000 individuals within Canada. About 1.4% (477,512) children < 2 years of age were considered for the vaccinated cohort. The remaining individuals comprised of the non-vaccinated cohorts, which included individuals aged 2 to <5, 5 to <18, 18 to <65, and 65+ years. A decision-analytic model was developed to examine the costs and outcomes associated with PCV10 and PCV13 pediatric national immunisation programmes (NIPs). The model followed individuals over the remainder of their lifetime. Recent disease incidence, serotype coverage, population data, percent vaccinated, costs, and utilities were obtained from the published literature. Direct and indirect effects were derived from 7-valent pneumococcal vaccine. Additional direct effect of 4% was attributed to PCV10 for moderate to severe acute otitis media to account for potential NTHi benefit. Annual number of disease cases and costs (2010 Canadian dollars) were presented. Vaccination costs were based on the acquisition cost per dose plus a direct administration fee. List price acquisition cost per dose was assumed to be \$86.26 for PCV13. Because acquisition cost of PCV10 was not available as of the writing of this article, the cost was assumed to be similar to the cost of PCV13. The outcomes of the study were as follows:

- PCV13 was found to be more cost-effective compared to PCV10: Disease prevention found more in PCV13 versus PCV10.
- 49,340 more cases of disease were prevented with PCV13 when both direct and indirect effects (Specifically, 4,084 cases of bacteraemia, 144 of meningitis, 8,760 of inpatient PNE, 6,201 of outpatient PNE, 27,001 of mild AOM, and 3,150 of moderate/severe AOM) were prevented annually when vaccinating children with PCV13.)
- As a result, the population gained 15,283 more life-years and 13,828 more QALYs when vaccinating children with PCV13 versus PCV10
- Approximately 879 deaths could be prevented annually and annual direct medical costs were reduced by \$132.8 million when vaccinating children with PCV13 compared to PCV10.
- When considering direct effects only, we observed 7,466 more cases of disease (52 more cases of bacteraemia, two of meningitis, 1,300 of inpatient PNE, 1,072 of outpatient PNE, 4,327 of mild AOM, and 713 of moderate/severe AOM) were prevented annually when vaccinating children with PCV13 versus PCV10.
- As a result, the population gained 287 more life-years and 258 more QALYs when vaccinating children with PCV13 versus PCV10.

- Approximately 14 deaths could be prevented annually and annual direct medical costs (including the cost of vaccination) were reduced by \$5.7 million when vaccinating children with PCV13 versus PCV10.
- Thus, PCV13 was found to dominate PCV10.
- Assuming a total per-dose cost of PCV10 of \$94.10 (acquisition and administration) and considering a threshold incremental cost per QALY of \$50,000, the cost per dose for PCV13 could be as high as \$737.11 to remain cost-effective, when both direct and indirect effects were considered.

According to the author, considering the epidemiology of pneumococcal disease in Canada, PCV13 is shown to be a cost-saving immunisation program because it provides substantial public health and economic benefits relative to PCV10. (This study was sponsored by Pfizer Canada, Inc.).

Blank PR and Szucs TD did a cost effectiveness analysis on PCV7 versus PCV13 using decision-analytic model structure on a hypothetical cohort of the general population in Switzerland.⁵⁴ The objective was to assess the potential health benefits and costs associated with pneumococcal vaccination strategies in Switzerland. A decision-analytic model was constructed to estimate direct medical costs and clinical effectiveness of PCV13 vaccination on invasive pneumococcal disease (IPD), pneumonia, and otitis media relative to PCV7 vaccination. The option with a one-dose catch-up vaccination in children of 15 – 59 months was also considered. Assuming 83% vaccination coverage [a total of 660,563 children would be vaccinated during a ten-year period (yearly average: 66,056).] and considering indirect effects, 1808 IPD, 5558 pneumonia and 74,136 otitis media cases could be eliminated from the entire population during a 10-year modeling period. The outcomes were as shown as below:

- Reduction in disease cases in PCV13, Avoided additional 215 IPD related fatalities
- PCV13 vaccination programme would lead to additional costs (+ € 26.2 million), but saved medical costs of – € 77.1 million due to cases averted and deaths avoided (total cost savings – € 50.9 million).
- PCV13 saved 23,242 life years and gained 18,172 QALYs over 10 year period
- If no herd protection would be considered, the cost-effectiveness ratio would increase to € 16,342 per QALY gained with costs of € 10 per child vaccinated

Hence, the study showed that PCV13 would result in cost-saving situation compared to PCV7. (This study was made possible by an unrestricted educational grant from Pfizer AG, Switzerland).

Diez- Domingo J et al did a study with the objective to estimate the potential health benefits, costs, and cost effectiveness of vaccination with PCV-13 as 2 + 1 schedule in the Community of Valencia and to generate valuable information for policy makers at regional and country levels.⁵⁵ A decision tree was designed to determine the health and economic outcomes in hypothetical cohorts of vaccinated and unvaccinated children followed over their lifetime [Ten hypothetical birth cohorts of 543,971 children (expected births in 10 years) were followed over their lifetime]. Information about disease incidence and serotype distribution were gathered from local databases and from published and unpublished local records. PCV13 effectiveness was extrapolated from PCV7 efficacy data. A 5% of herd effect and a serotype replacement of 25% were considered for the base case scenario. The total cost per dose of vaccine was estimated to be € 4708. Only direct costs were taken into account and results were expressed in terms of life-years gained (LYG) and quality adjusted life years (QALY). The outcomes showed that:

- Universal PCV13 vaccination program would decrease the number of hospital admission due to pneumonia (< 4571 cases), avoiding 310 cases of IPD, and 82,596 cases of AOM, averting 190 *S. pneumoniae* related deaths
- Total medical costs of non-vaccinating the cohort of newborns would reach up to € 403,850.859 compared to € 438,762.712 that would represent vaccinating the cohort
- The incremental cost of vaccinating the children was estimated in € 12,794 /LYG and € 10,407 /QALY

The authors suggested that a universal PCV13 vaccination program would be a cost effective intervention. (This study has been supported by an unrestricted grant by Pfizer).

Jan van Hoek A et al did a cost effectiveness analysis with the objective to investigate the cost effectiveness of the introduction of PCV13.⁵⁶ Invasive disease incidence following vaccination was projected from a dynamic infectious disease model, and combined with serotype specific disease outcomes obtained from a large hospital dataset linked to laboratory confirmation of invasive pneumococcal disease. To represent the uncertainty in outcomes of IPD estimated from this dataset, the authors took 10,000 bootstrap samples (with replacement) from the original database. The economic impact of replacing PCV-7 with PCV-13 was compared to stopping the use of pneumococcal conjugate vaccination altogether. The vaccination cost for PCV13 was about £49.60. The infectious disease model projected herd immunity and serotype replacement effects. In the base case, a discount rate of 3.5% per annum was used for costs and benefits, in conjunction with a 30 years' time horizon. The outcomes were as shown below:

- Discontinuing PCV7 would lead to an increase in invasive pneumococcal disease, costs and loss of quality of life compared to the introduction of PCV13.
- Under base case assumptions (assuming no impact on non-invasive disease, maximal competition between vaccine and non-vaccine types, time horizon of 30 years, vaccine price of £49.60, a dose + £7.50 administration costs and discounting of costs and benefits at 3.5%) the introduction of PCV-13 is only borderline cost effective compared to a scenario of discontinuing of PCV-7.
- The intervention becomes more cost-effective when projected impact of non-invasive disease is included or the discount factor for benefits is reduced to 1.5%.

(This work was supported by the UK Department of Health Policy Research Programme, grant number: 039/0031).

By A et al did a cost-effectiveness analysis with the objective to estimate the expected health outcomes, costs, and incremental cost-effectiveness ratio (ICER) of routine vaccination with the 10-valent pneumococcal vaccine (PCV10) compared to PCV13 in Sweden.⁵⁷ A Markov cohort model was used to estimate the effect of vaccination at vaccine steady state, taking a societal perspective and using a 2+1 vaccination schedule. The vaccine unit cost was based on the pharmacy retail price of SEK 518.95 per dose and assumed equal for the 2 vaccines. The result of the study showed that:

- Overall, it was estimated that with PCV13, for the cohort of 112,120 children, an additional 12.9 life years (6.0 life years discounted by 3%) would be saved over lifetime, compared with vaccination with PHiD-CV (PCV 10).
- PCV10 however, was predicted to lead to improved outcomes in terms of QALYs (taking both survival and quality of life into account), primarily because of improved quality in life due to avoided AOM cases and its complications. An additional 40.3 QALYs, or 45.3 when discounted by 3%, was estimated to be saved with PCV10 compared with PCV13.
- PCV13 would prevent 3 additional cases of invasive pneumococcal disease and 34 additional cases of pneumonia while PCV10 would avoid 3 additional cases of mastoiditis, 1010 tube insertions, and 10,420 cases of ambulatory acute otitis media compared with PCV13.
- PCV13 was estimated to save direct costs due to ID and CAP of 2.5 million SEK compared with PCV10, whereas PCV10 was estimated to save direct costs due to AOM of 37 million SEK. Including the indirect costs, an additional 33 million SEK were avoided with PCV10. Hence, the total costs saved with PCV10 compared with PCV13 were estimated at 67 million SEK, or 62 million SEK with a 3% discount rate.
- By combining morbidity and mortality benefits of all clinical outcomes, PCV10 would generate 45.3 additional QALYs compared with PCV13 and generate savings of an estimated 62 million Swedish kronors. Hence, PCV10 was the dominant vaccination alternative compared with PCV13.
- Using a threshold of £30,000 per QALY gained, introducing PCV13 is cost-effective in 100% of parameter combinations sampled if non-invasive disease outcomes are included, but only 53% if they are not.
- Replacing PCV7 with PCV13 is less cost-effective than introducing PCV13 in a situation with no pneumococcal vaccination.

The model used in this analysis showed that although PCV13 was predicted to provide somewhat higher impact on IPD and CAP, PCV10 was expected to provide a substantially greater reduction in AOM compared with PCV13. As such, the cost-effectiveness analysis suggested that, in Sweden, PCV10 provided a greater impact on overall disease burden and was cost saving compared with PCV13. (Financial support was provided by GlaxoSmithKline).

Lee KKC et al did an economic evaluation analysis with the objective to assess the health and economic impact of PCV10 compared with the current PCV13 which was recommended for Hong Kong in 2011.⁵⁸ An analytical model was used to estimate the annual economic and health outcomes of invasive pneumococcal disease (IPD), community acquired pneumonia, and acute otitis media (AOM), including nontypeable H. influenzae-related AOM for a birth cohort in Hong Kong from the payer perspective with a 10-year horizon. This model simulated in a birth cohort of 82,100 newborns the disease process of IPD (meningitis and bacteraemia), community-acquired pneumonia (CAP), and AOM caused by S. pneumoniae and NTHi within monthly cycles. The authors analysis estimated the direct impact of vaccination on children at risk (aged 0 to 9 years only) by evaluating the cost-effectiveness and assuming that steady state will be in place after 10 years. The vaccine price for PCV10 was 195 HKD while the price for PCV13 was >20% of the price of PCV10. The results of the study were as shown below:

- Model projections indicate that PCV13 and PCV10 have approximately equivalent impact on the prevention of deaths caused by IPD and pneumonia. PCV-13 is projected to prevent six additional cases of IPD, whereas PCV10 is projected to prevent 13,229 additional AOM cases and 101 additional QALYs.
- For the base case, PCV10 vaccination is estimated to save 44.6 million Hong Kong dollars (discounted by using a 5.0% discount rate). The overall savings of HKD 44.62 million were largely linked to the reduction in AOM disease burden
- Vaccination with PCV10 generated 90 (101 undiscounted) more QALYs with overall cost savings as compared with PCV13. The PCV10 vaccination program was expected to be cost saving as compared with the PCV13 vaccination program.

Hence, this study suggested that PCV10 vaccination would be potentially a cost-saving strategy and better QALYs gain compared with PCV13 vaccination. (The sponsor GlaxoSmithKline Biologicals SA was involved in all the stages of the study and development of the present manuscript).

Strutton DR et al did a cost-effectiveness analysis using decision-analytic model whereby the objective was to examine public-health and economic impacts of pneumococcal vaccine on paediatric national immunisation programs (NIPs) in Germany, Greece, and the Netherlands.⁵⁹ The total population sizes were estimated at 82,314,906 individuals in Germany, 11,149,000 in Greece; and 16,334,210 in the Netherlands. A decision-analytic model was developed to estimate the impact of PCV13, PCV7, and 10-valent pneumococcal conjugate vaccine (PCV10) on invasive pneumococcal disease (IPD), pneumonia (PNE), and acute otitis media (AOM). Using epidemiological data, the cases of IPD, PNE, and AOM, using country-specific incidence, serotype coverage, disease sequelae, mortality, vaccine effectiveness, indirect effects, costs, and utilities were calculated. The vaccination cost was €49.00 for PCV7 and PCV13, €39.90 for PCV10 in Germany; €52.40 for PCV7, €49.64 for PCV13 and €42.14 for PCV10 in Greece; €57.13 for PCV7 and PCV10, €68.56 for PCV13 in Netherlands. Direct effects for PCV13- and PCV10-covered serotypes were assumed similar to PCV7. PCV13 was assumed to confer an indirect effect, while PCV10 was not. Assumptions were tested in sensitivity analyses. The outcome of the study was:

- PCV13 was estimated to eliminate 31.7% of IPD in Germany, 46.4% in Greece and 33.8% in The Netherlands.
- Compared with PCV7 and PCV10, PCV13 was found to be cost-effective or cost saving in all cases when PCV13 indirect effects were included.
- PCV13 resulted in greater reductions in medical costs (excluding vaccine costs) to treat cases of disease in all countries.

- As a direct result of the reduction in disease, PCV13 resulted in greater reductions in medical costs (excluding vaccine costs) to treat cases of disease in all countries. When compared with PCV7, PCV13 was estimated to be a more effective and less costly strategy (i.e., cost saving) in Germany and Greece. PCV13 was estimated to be cost-effective (i.e., cost per QALY € 20, 000) in the Netherlands. When compared with PCV10, PCV13 was estimated to be cost saving in Germany, Greece, and the Netherlands.

(This study was funded in full by Wyeth Research, which was acquired by Pfizer, Inc. in October 2009).

Castañeda-Orjuela C et al did a cost-effectiveness analysis whereby the objective was to evaluate the cost-effectiveness of the introduction of pneumococcal conjugate vaccines of 7, 10, and 13 valences in the Colombian children.⁶⁰ A Markov model, which followed a cohort of children (858,137) under one year to life expectancy, was developed. Parameters of occurrence and care costs were based on data from National Health System and literature review. PCV7 is a dominated strategy. PCV10 and PCV13 were each compared to no vaccination or PCV-10 vaccination, respectively. A 2 + 1 schedule and a vaccination price of US\$ 14.00, US\$ 14.85 and US\$ 16.34 per dose were assumed in the base case for PCV7, PCV10, and PCV13 vaccines. The results showed that:

- Introduction of PCV13 rather than PCV10 increases the number of life years gained (LYG).
- From the societal perspective, in the 'competing choice' framework cost per LYG was US\$ 1837 with PCV10 and US\$ 9514 with PCV13, while PCV7 is a dominated strategy. The ICER of PCV13 is above the per capita Gross Domestic Product (GDP). Incremental cost-effectiveness ratios (ICERs) were influenced mainly by effectiveness against radiologically-confirmed pneumonia and AOM, vaccine price, and discount rate.
- In the comparison between four alternatives (no vaccination, PCV7, PCV10 and PCV13 vaccination), vaccination with PCV7 is dominated for the other alternatives. PCV13 has the highest costs and the most results achieved, although in the worst and best scenarios the ranges are overlapped with PCV10.
- The ICER of vaccination with PCV10 (compared with no vaccination) is below the Colombian willingness to pay threshold of 1 per capita GDP (US\$ 1837 per YLG, ranging from cost-saving to US\$ 22,799). In the comparison of PCV13 versus PCV10 the ICER is over 1 per capita GDP (US\$ 9516, ranging from US\$ 1184 to 43,352), but is below the 3 per capita GDP.
- PCV10 is more cost-effective with ICER below the per-capita GDP, but its inclusion requires evaluating the budget impact.
- PCV13 would prevent more disease and deaths with a higher LYG, but PCV10 would save more cost to the healthcare system due its higher impact in the prevention of AOM.

According to the author, the study showed that in the base case PCV10 is cost effective to a WTP of 1 per-capita GDP, while PCV13 ICER is above that threshold, hence the Colombian Ministry of Health will have to consider if the incremental costs of either strategies are sustainable over the longer term and consider the financial risk by budget impact analysis. (This study was possible through the financial support from the Ministry of Health of Colombia and the Colombian Expanded Program of Immunization).

Beutels P et al did a HTA report which includes a cost-effectiveness analysis to estimate the incremental effectiveness and cost-effectiveness of replacing PCV7 by either PCV10 or PCV13 in Belgium, taking into account the herd immunity and serotype replacement.⁶¹ A simulation model is developed which mimic the incidence and consequences of pneumococcal infections in cohorts of vaccinated children as well as in the general population. At the moment of study, the complete vaccination scheme with 4 injections costs over € 250 per child. The model incorporates herd immunity and serotype replacement effects, together with the extent to which PCV10 offers additional protection against AOM versus PCV13 and the extent to which PCV10 offers some protection against serotype 19A. Serotype specific vaccine efficacies against IPD were inferred indirectly from immunological data (antibodies and OPA measures), scaled from observational effectiveness data on the PCV7 vaccine. Serotype replacement was introduced in the model as a reduction in serotype coverage for IPD and as a reduction in vaccine efficacy for AOM and pneumonia (as no serotype-specific data on these conditions are available). The outcome showed that:

- Both PCV13 and PCV10 vaccines are highly likely to be cost-effective compared to PCV7
- Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision-maker either to prevent the less-frequent severe IPD cases only, or to also consider the prevention of the high burden of AOM
- Using various assumptions about the vaccine effectiveness measures, herd immunity and serotype replacement effects, the results consistently showed that both new vaccines are highly likely to be cost-saving or considered cost-effective versus PCV7, even at their current public pharmacy prices.
- Excluding the effect of herd immunity and compared to PCV7, the new PCV10 and PCV13 vaccines avoided altogether 113 to 118 IPD, 181 to 236 pneumonia, 587 to 6 317 otitis media and slightly less than 2 deaths.
- Both PCV13 and PCV10 vaccines are more cost-effective compared to PCV7. A 2+1 schedule is more desirable than a 3+1 schedule.
- The incremental cost-effectiveness ratio of PCV10 (3+1 schedule) and PCV13 (2+1 schedule) versus PCV7 ranged between dominance (i.e. the new vaccines are both more effective and less costly than PCV7), and €12 400 per quality-adjusted life-year (QALY) gained.
- PCV13 was preferable (avoids more treatment costs and gains more QALYs) to PCV10 in severe diseases only (i.e. excluding otitis media). When impact on otitis media was included, PCV10 was estimated to avoid more treatment costs than PCV13.

(This study was done by the Belgian Health Care Knowledge Centre).

Tyo RK et al did an economic evaluation using a Markov simulation model populated with Singapore-specific population parameters, vaccine costs, treatment costs, and disease incidence data.⁶² The vaccinated infant and child cohort of 226,000 was 6% of the Singapore resident population of 3.8 million. Vaccine efficacy estimates were constructed for PCV7, PCV10, and PCV13 vaccines based on their serotype coverage in Singapore and compared to 'no vaccination'.⁶² The cost of a dose of PCV7 vaccine was USD \$116 (SGD \$161), while PCV10 and PCV13 prices were USD \$123 (SGD \$170) and USD \$123 (SGD \$169) respectively. The model estimated impacts over a five-year time horizon with 3% per year discounting of costs and health effects. Costs were presented in 2010 U.S. dollars (USD) and Singapore dollars (SGD). Sensitivity analyses included varying herd immunity, serotype replacement rates, vaccine cost, and efficacy against acute otitis media. The results showed that:

➤ Reduction in disease

- Prior to vaccination, the 0 - 5 year old population of 226,000 incurred about 8,600 cases of AOM, 2,535 cases of pneumonia and 10 cases of meningitis and bacteremia yearly.
- The PCV7 vaccination program would reduce the number of AOM cases by approximately 4900 cases yearly. PCV10 estimated reducing about 5,000 AOM cases and while PCV13 estimated 5,700 AOM cases.
- The reduction of pneumonia cases in the vaccinated population varies from 135 to 158 cases with PCV13.
- In the non-vaccinated population, 12,382 pneumonia cases and 209 bacteraemia cases were predicted over the same one year period prior to vaccination.
- A similar number of cases would be avoided in the non-vaccinated population, reflecting a lower herd immunity effect and low pneumonia incidence.
- In addition, PCV7 and PCV10 would prevent 7.6 cases meningitis and bacteraemia in the vaccinated population, while PCV 13 would avert 8.8 cases.
- Furthermore, the number of bacteraemia cases avoided ranges 31 for PCV 7 to 36 for PCV13 in the non-vaccinated population.

- The estimated death due to pneumonia was 15 deaths in the vaccinated group and 2,319 deaths in the non-vaccinated group prior to vaccination.
- In addition, the estimated deaths due to IPD were 0.5 per year in the vaccinated group, while 54 deaths (due to bacteraemia) in the non-vaccinated group.
- Thus, the model estimated that one death would be avoided yearly from pneumonia and IPD in the vaccinated population.

By PCV7 and PCV10 vaccination program, 34 deaths due to pneumonia or bacteraemia would be prevented yearly in the non-vaccinated group, While PCV13 would avoid 40 deaths by herd immunity.

➤ QALYs gained

- PCV7 adds 67 QALYs in the vaccinated population and 269 QALYs through herd effects.
- PCV10 contributes 68 QALYs in direct effects and 277 QALYs through herd effects.
- PCV13 contributes 78 QALYs gained through direct effects and 397 QALYs gained in the unvaccinated population.

➤ Saving and cost-effectiveness

- PCV7 and PCV10 resulted in yearly medical savings USD 1.8M (SGD 2.5M) in the vaccinated population, and this amount of saving would increase to USD 2.1M (SGD 2.9M) for PCV 13.
- In addition, when it was projected savings due to herd immunity would total USD 1.5M (SGD 2.0M) for PCV7, USD 1.5M (SGD 2.1M) for PCV10 and USD 1.7M (SGD 2.4M) for PCV13.
- Compared to no vaccination, the estimated ICER for PCV7 was USD 43,275 (SGD 59,610) per QALYs gained, for PCV10 was USD 45,100 (SGD 62,125) per QALYs gained and PCV13 was USD 37,644 (SGD 51,854) per QALYs gained.
- Without herd effects, the estimated ICER for PCV13 was USD 204,535 (SGD 281,743) QALYs gained

Hence the authors estimated that infant vaccination against pneumococcal disease in Singapore was moderately cost-effective compared to WHO thresholds. The different findings from the 2008 and 2011 analyses by the authors suggested that the dynamic issue of serotype replacement should be monitored post-licensure and, as changes occur, vaccine effectiveness and cost-effectiveness analyses should be re-evaluated. (This work was supported by the Ministry of Health of Singapore and the Heller School at Brandeis).

Bocalini S et al did a study on the resident population in the province of Florence, Italy in 2010 whereby the purpose of the study was to perform a clinical/economic evaluation of the administration of a dose of PCV13 in a catch up programme for children under five years of age, who had already received three doses of PCV7.⁶³ A mathematical model of the clinical/economic impact of the adoption of 4 catch-up strategies with PCV13 (children up to 24, 36, 48 and 60 months old) was set up, with a vaccination coverage of 80%, versus immunisation with three doses of PCV7 without the catch-up programme. The time span covered by the simulation was 5.5 years. The results were later related to a reference population of 100,000 individuals. In this study, the authors assumed a vaccine price of 42.58 Euros (cost of purchasing a PCV13 dose for the National Health Service). The following clinical outcomes of infection were evaluated: hospitalized meningitis/sepsis, hospitalised bacteraemic pneumonias (complicated and uncomplicated), hospitalized non-bacteraemic pneumonias, and non-hospitalised pneumonias. The results of the study were:

➤ Reduction in disease

- Following the adoption of catch-up programme with PCV 13, 2.5 deaths / 100 000 from *S. pneumoniae* infection would be avoided for children up to 24 months and 6.6deaths/100 000 would be avoided for children up to 60 months of age.
- Thus, it is estimated 191, 322 , 423 and 483 life-years saved for children up to 24, 36, 48 and 60 months of age, respectively

➤ Costs

- The mathematical model estimated a saving of more € 1 million for children up to 24 months as following the catch-up vaccination programme due to a result of the reduction of expected cases and respective treatment costs.
 - Thus, it forecasts about a saving of almost € 3 million for children up to 60 months of age.
 - The cost of a catch-up vaccination programme was € 3 406 400 (per 100 000) for children up to 24 months with PCV 13.
- The mean cost per event avoided were €1674 Euros, € 1926 , € 2195 and € 2522 with catch-up programme until 24, 36, 48 and 60 months of age, respectively.
- The cost per year life saved, the amounts were € 12 250, € 15 176, € 18,150 and € 22,093 when vaccination children up to 24, 36, 48 and 60 months of age, respectively.

The results of this study showed that from the clinical and economic point of view, the recommendation of the Italian Ministry of Health to vaccinate children up to 24 months of life in a catch-up programme, as well as the administration of PCV13 children up to 36 months and under 60 months of age, already used in some Italian regions was justified. (This work was supported by a grant from Pfizer Italia S.r.l., Rome, Italy).

Kim SY, et al did a cost effective analysis to assess the potential impact of PCVs of different valence in Gambia.⁶⁴ The authors synthesized the best available epidemiological and cost data using a state-transition model to simulate the natural histories of various pneumococcal diseases. The authors applied the model to a hypothetical Gambian birth cohort (N = 60,000) and estimated the clinical and economic consequences of a PCV intervention over the first 5 years of life. The vaccine price (per dose) for this study was USD 3.5. For the base-case, the authors estimated incremental cost (in 2005 US dollars) per disability-adjusted life year (DALY) averted under routine vaccination using PCV9 compared to no vaccination. The authors extended the base-case results for PCV9 to estimate the cost-effectiveness of PCV7, PCV10, and PCV13, each compared to no vaccination. The estimated health outcomes averted into disability-adjusted life years (DALYs). Total costs accounted medical costs treatment and non-direct medical costs. The results were as shown:

- Vaccinating PCV9 for a cohort of 60 000 infants would be expected to prevent about 1400 (~28%) cases of primary endpoint pneumonia and 13% cases of meningitis and sepsis compared to no vaccination. Thus, it estimated the PCV 13 would prevent about 1650 cases of primary endpoint pneumonia, while 1,400 cases and 1,040 cases would prevent by PCV10 and PCV 7, respectively when compared to no vaccination.
- The average program cost for vaccinating with PCV9 (3 doses) would be \$1.02. If \$3.5 per dose, the vaccination programme cost for birth cohort would be about \$685,000. The total cost for PCV9 would be \$902,040 with vaccination and \$233,100 without vaccination. Therefore, the estimated total costs for PCV7 would be \$906,240, PCV10 would be \$902,040 and PCV13 would be \$899,280.
- Combining the primary health and economic outcome measures, the estimated costs of PCV9 vaccination per DALYs averted was \$670, compared with no vaccination.
- The numbers of averted DALYs were 740 for PCV7, 1,000 for PCV10 and 1,180 for PCV13.
- The incremental cost-effectiveness ratios (ICER) of the PCV's decreased as the valence of the vaccines increased with results of \$910 for per DALY averted for PCV7, \$670 per DALY averted for PCV10 and \$570 per DALY averted for PCV 13.
- If assume the vaccine efficacy decreased by 15% over a five year time horizon, the incremental costs per DALYs averted increased to \$940 (PCV7), \$690 (PCV9 and PCV10) and \$590 (PCV13).

According to the author, based on the information available now, infant PCV vaccination would be expected to reduce pneumococcal diseases caused by *S. pneumoniae* in The Gambia. Assuming a cost-effectiveness threshold of three times GDP per capita, all PCVs examined would be cost-effective at the tentative Advance Market Commitment (AMC) price of \$3.5 per dose. Because the cost-effectiveness of a PCV program could be affected by potential serotype replacement or herd immunity effects that may not be known until after a large scale introduction, typespecific surveillance and iterative evaluation will be critical. (The authors were funded in part by the Bill and Melinda Gates Foundation. The authors acknowledge the support from the Foundation. The funding source did not have any involvement in designing and conducting the study or in deciding to submit the manuscript for publication).

Robberstad B et al did a study to estimate the incremental costs, health effects and cost-effectiveness of the pneumococcal conjugate vaccines PCV7, PCV10 and PCV13 in Norway.⁶⁵ The authors used a Markov model to estimate costs and epidemiological burden of pneumococcal- and NTHi-related diseases (invasive pneumococcal disease (IPD), Community Acquired Pneumonia (CAP) and acute otitis media (AOM)) for a specific birth cohort. The vaccine cost per dose was NOK 304. Using the most relevant evidence and assumptions for a Norwegian setting, the authors calculated incremental costs, health effects and cost-effectiveness for different vaccination strategies. In addition, the authors performed sensitivity analyses for key parameters, tested key assumptions in scenario analyses and explored overall model uncertainty using probabilistic sensitivity analysis. The results were as follows:

➤ Health outcomes

- Compared to no vaccination, PCV7 reduced 23 cases of pneumococcal meningitis and 299 cases of pneumococcal bacteraemia, representing about one quarter of IPD cases and 80 deaths averted per birth cohort.
- PCV13 reduced 15 fewer IPD cases per birth cohort over a lifetime and 6 fewer cases of hospitalized pneumonia compared to PCV10
- However, PCV10 reduced approximately 12 000 fewer AOM cases compared to PCV13 and a reduction about 16 000 cases compared to PCV7.
- PCV13 saves 8 more life years than PCV10 but PCV10 has a QALY gain of 50 per cohort compared to PCV13.

➤ Costs and cost-effectiveness

- The administration costs of PCVs vaccination approximately NOK 67 million per birth cohort.
- When PCVs add vaccination, they reduce the cost of disease treatment by NOK 44 million (PCV7), NOK 53 million (PCV13) and 73 million (PCV10), while indirect costs reduced by NOK 38 million (PCV7), NOK 49 million (PCV13) and NOK 59 million (PCV10).
- PCV13 is slightly more effective in reducing mortality compared to PCV10, but the additional life years each come at a cost of approximately NOK 3.1 million (~ € 0.4 million).

➤ However, one way sensitive analyses indicate that the base case finding that PCV10 dominates over PCV13 (cost-saving and more effective) is insensitive to changes in model parameters.

Hence, the model predicts that both PCV13 and PCV10 provide more health gains at a lower cost than PCV7. Differences in health gains between the two second generation vaccines are small for invasive pneumococcal disease but larger for acute otitis media and myringotomy procedures. Consequently, PCV10 saves more disease treatment costs and indirect costs than PCV13. According to the authors, this study predicts that, compared to PVC 13, PCV10 entails lower costs and greater benefits if the latter is measured in terms of quality adjusted life years. PVC 13 entails more life years gained than PCV10, but those come at a cost of NOK 3.1 million per life year. The results indicate that PCV10 is cost-effective compared to PCV13 in the Norwegian setting. (This study was supported by the University of Bergen and partially sponsored by GlaxoSmithKline).

Rubin J. et al did a study to assess the public health and economic impact of a PCV13 routine vaccination program including several alternative catch-up strategies.⁶⁶ A decision-analytic model was constructed to evaluate the impact of infant vaccination with PCV13 versus PCV7 on pneumococcal disease incidence and mortality as well as the incremental benefit of a serotype catch-up program. The average price for a single dose of PCV7 in 2008 was assumed to be USD73 and for PCV13 it was USD100. PCV13 effectiveness was extrapolated from observed PCV7 data, using assumptions regarding serotype prevalence and PCV13 protection against additional serotypes. The model time horizon was 10 years. The base-case cost of PCV13 for this modelling effort was estimated to be \$100. The results were as shown:

- If PCV13 used for vaccinating 39.5 million infants would cost approximately 14.1 billion dollars during the first 10 years, while, if PCV7 was used for vaccinating the same numbers of infants would cost 10.7 billion dollars.
- Under base-case effectiveness assumption, the model predicts that PCV13 vaccination would save over \$11.4 billion in medical-care costs.
- It also would avoid approximately 106,000 cases of IPD, 948,000 cases of hospitalized pneumonia, 1.93 million cases of non-hospitalized pneumonia and 40,500 deaths over the 10-year period.
- About 14.6 million cases of simple and 1.72 million cases of complex AOM are avoided over 10-year period.
- If the vaccination is associated with \$3.61 billion in non-medical costs saving leading to net savings of \$11.6 billion over the 10-year period.
- Threshold analyses determined that PCV13 is cost-saving from the societal perspective at all prices below \$192 when compared to PCV7.
- If a catch-up program vaccinating children aged 16 - 23 months costs \$3 399 per QALYs gained, aged 16 - 35 months costs \$25 052 per QALY gained and aged 16-59 costs \$73,564 per QALY gained.

Hence, the model predicts that PCV13 is more effective and cost saving compared with PCV7, preventing 106,000 invasive pneumococcal disease (IPD) cases and 2.9 million pneumonia cases, and saving \$11.6 billion over a 10-year period. The serotype catch-up program would prevent an additional 12,600 IPD cases and 404,000 pneumonia cases, and save an additional \$737 million compared with no catch-up program. (This research was funded by Wyeth Research, which was acquired by Pfizer in October 2009).

Giglio N et al did a study by reviewing the articles published on economic evaluation relating to pneumococcal conjugate vaccines in Latin America.⁶⁷ For this review, the PubMed database and the Lylacs Latin American database were searched from the dates they were created to 30 April 2011. A total of 207 abstracts were found on PubMed and two articles from the Lylacs Latin American databases. Eight articles were selected for the cost evaluation studies. The results were as follows:

- The cost per dose for PCV10 was USD16 and for PCV13 was USD19.
- The cost/DALY for PCV10 was USD 8326.7 per year of life gained and for PCV 13 were 1,133.6 per year of life gained.
- In relation to the number of events avoided, the results varied between 0.1 and 14.8 per 1000 children under age 5 for meningitis, between 6.6 and 25.6 for pneumonia, between 0.05 and 1.18 per 1000 for bacteremia/sepsis and 57.3 and 121.7 per 1000 for otitis media.
- In terms of deaths avoided, the number of events varied between 0.22 and 6.53.
- Assuming similar costs and effectiveness for PCV10 and PCV13 with no herd effect, and bearing in mind the serotype coverage for both, without considering the cross-immunity of the serotypes, the number of IPD avoided per 1000 children vaccinated would be 1.9 for PCV10 and 2.2 for PCV13 and deaths avoided per 1,000 children vaccinated would be 0.42 for PCV10 and 0.47 for PCV13.

(Norberto D. Giglio has received an unrestricted educational grant from Wyeth for the economic valuation of CRM-based 7- valent pneumococcal conjugated vaccine (PCV7) in 2009).

Newall AT et al did a study to evaluate the cost-effectiveness of PCVs programs. It used a static deterministic state-transition model that describes transitions between a set of health states for the population over time.⁶⁸ The perspective for costs included those to the government and healthcare system. The completed vaccination schedule cost for PCV7 and PCV10 was set at Australian dollar \$291. When compared to current practice (PCV7) both vaccines offered potential benefits, with those estimated for PCV10 due primarily to prevention of otitis media and PCV13 due to a further reduction in invasive disease in Australia. Costs (Australian dollars, A\$) and health effects (quality-adjusted life years, QALYs) are attached to health states, discounted (exponentially) at 5% per annum. The population was stratified into single year age categories, initially distributed according to Australian population estimates (2009), with birth rates (2009 birth cohort = 300,639) and mortality rates (2008) from the Australian Bureau of Statistics (ABS). Birth rates remained constant for future cohorts. Vaccine programs were run over 100 years to account for long-term outcomes, including death and disability. When vaccine strategies were cost-saving, results are reported for a 5 year vaccine program with 100 years of follow-up for long-term outcomes.

- PCV13 was estimated to increase protection against IPS, preventing additional cases ~132 IPD cases in the 5th year program compared to PCV7 vaccination.
- PCV10 was estimated to increase protection against otitis media, preventing an additional ~35 000 outpatient otitis media (~1300 hospitalised) in the same program compared to PCV7 vaccination.
- In base-case, PCV10 and PCV13 were both cost-saving compared to PCV7.
- If assumed an increase in total cost to vaccinate an infant of \$100, the discounted ICERs for both vaccines were > 142 000 per QALY saved under base-case assumptions and were > 62 000 per QALY saved with incremental herd protection when compared to no vaccination.
- If assumed equivalent vaccination cost (set at \$291 for a complete schedule), the discounted ICERs were estimated at ~\$64,900 (PCV7), ~ \$50,200 (PCV10) and ~\$64,900 (PCV13) per QALY saved when compared to no vaccination

According to the authors the high proportion of current invasive disease caused by serotype 19A (as included in PCV13) may be a decisive factor in determining vaccine policy in Australia. (This project was funded by GlaxoSmithKline Pty Ltd.).

LIMITATIONS

Our study has several limitations. Although we only included RCTs for effectiveness, we also included cross sectional studies for adverse events and surveillance findings. Our study also lacks local surveillance data as well as local economic evaluation studies. Although there was no restriction in language during the search but only English full text articles were included in the report. Most published articles included in this HTA involved PCV 13. There was lack of retrievable full text published articles on PCV 10 and studies on PCV 10 retrieved were mostly presented during conference.

DISCUSSION

For efficacy/effectiveness, fourteen articles were included, whereby thirteen studies involved PCV13 as the main intervention, with only one study involving PCV 10 as the main intervention and only two studies directly comparing PCV13 and PCV10. For safety, nine articles were included, out of which eight studies had PCV 13 as the main intervention, with only one study that involved PCV 10 as the main intervention and only one study directly comparing PCV13 and PCV10. For cost effectiveness, twenty articles were included with twelve studies that included PCV 13 as the main intervention, six studies that involved PCV 10 as the main intervention while six studies were directly comparing PCV13 and PCV10. Generally the above review showed that PCV13 was more cost effective than PCV10 and PCV7.

Most of the studies were sponsored by the pharmaceutical industries except for studies by Azzri ert al³⁵,

Hoshi SL et al⁵², Jan van Hoek A et al⁵⁶, Beutels P et al⁶¹ and Tyo RK et al⁶². Azzari et al suggested that the introduction of PCV13 could have a significant added benefit in reducing the burden of pneumococcal disease in Italian children below 2 years as well in older children. Hoshi SL et al suggested that if the cost per PCV13 shot is equal to or less than ¥12,000, replacing PCV7 with PCV13 will save money and gain more QALYs. Jan van Hoek A et al however suggested that the introduction of PCV-13 was only borderline cost effective compared to a scenario of discontinuing of PCV-7. Beutels P et al in their Health Technology Assessment report mentioned that choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision-maker either to prevent the less-frequent severe IPD cases only, or to also consider the prevention of the high burden of AOM.

A report by the Centers for Disease Control and Prevention in 2010 summarizes recommendations approved by the Advisory Committee on Immunization Practices (ACIP) on February 24, 2010, for the use of PCV13 to prevent pneumococcal disease in infants and young children aged <6 years. Recommendations include 1) routine vaccination of all children aged 2–59 months, 2) vaccination of children aged 60–71 months with underlying medical conditions, and 3) vaccination of children who received ≥ 1 dose of PCV7 previously.⁶⁹ The ACIP recommendation for routine vaccination with PCV13 and the immunization schedules for children aged ≤ 59 months who have not received any previous PCV7 or PCV13 doses are the same as those published previously for PCV7^{70,71} with PCV13 replacing PCV7 for all doses. For routine immunization of infants, PCV13 is recommended as a 4-dose series at ages 2, 4, 6, and 12–15 months. Infants and children who have received ≥ 1 dose of PCV7 should complete the immunization series with PCV13. A single supplemental dose of PCV13 is recommended for all children aged 14–59 months who have received 4 doses of PCV7 or another age-appropriate, complete PCV7 schedule. For children who have underlying medical conditions, a supplemental PCV13 dose is recommended through age 71 months. Children aged 2–18 years with underlying medical conditions also should receive PPSV23 after completing all recommended doses of PCV13.

A study by Jan van Hoek A showed that in a linked dataset that contained 23,688 cases with information on diagnosis, mortality, and serotype, there were significant differences between serotypes in the propensity to cause meningitis, death, and QALY loss in each of the investigated age groups. As a result, vaccines' coverage of disease burden differed by endpoint. For example, in children under 5 years in 2009/10, PCV10 covered 39% of meningitis, 19% of deaths and 28% of the QALY loss of attributable to IPD, whereas the respective percentages for PCV13 were 65%, 67%, and 66%. The highest QALY loss per serotype in this age group was for 6A. Non-PCV serotypes causing the highest QALY loss were 22F and 33F in 5 year olds and 31 in older individuals. Marked differences exist between serotypes in clinical presentation and outcome, and the authors suggest these should be considered when evaluating the potential impact of higher valency vaccines on overall disease burden and associated QALY loss.⁷² This finding was similar to the above review whereby choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker either to prevent the severe IPD cases only, or prevention of AOM.^{49,50,53,54,55,56,57,58,61,68} PCV13 was predicted to provide a higher impact on IPD and CAP, while PCV10 was expected to provide a substantially greater reduction in AOM.^{49,50,53,54,55,56,57,58,61,68}

Rohani MY et al. conducted a study from January 2008 to December 2009 to determine the serotype distribution and susceptibility pattern of *S. pneumoniae* isolated in selected hospitals in Malaysia, after the introduction of PCV7.⁷³ The data may represent the baseline serotypes before the implementation of PCV10 and PCV13. 433 *Streptococcus pneumoniae* strains were examined to determine the serotype distribution and susceptibility to selected antibiotics.⁷³ About 50% of them were invasive isolates. The strains were isolated from patients of all age groups and 33.55% were isolated from children below 5 years. The majority was isolated from blood (48.53%) and other sterile specimens (6.30%). Community acquired pneumonia (41.70%) is the most common diagnosis followed by sepsis (9.54%). Ten most common serotypes were 19F (15.02%), 6B (10.62%), 19A (6.93%), 14 (6.70%), 1 (5.08%), 6A (5.08%), 23F (4.85%), 18C (3.93%), 3 (2.08%) and 5 (1.85%). The majority of penicillin less-susceptible strains belonged to serotype 19F followed by 19A and 6B. Based on the serotypes distribution 22 (44.00%), 28 (56.00%) and 39 (78.00%) of the invasive isolates from children ≤ 2 years were belonged to serotypes included in the PCV7, PCV10 and PCV13, respectively. This study documents marked increased in serotype 6A, 19F, and 19A and reduction in serotype 1 compare to previous data.

The high prevalence of serotype 19A and 6A contributed to reduction in diseases caused by PCV7 serotypes and increased in diseases caused by non-PCV7 serotypes. The proportion of serotype 19A isolates increased from 0.5% in 1995 and 0.3% during 2002–2004 to 6.93% in this study. There are some changes in the serotypes distribution in the last 10 years. However, because 6A and 19A are among the most significant serotypes, the PCV10 and PCV13 may provide significant protection to the Malaysian children ≤ 2 years, with 56.00% and 78.00% coverage, respectively. Regular surveillance is necessary since changes in serotypes may occur naturally with time as reported by Normark et al.⁷⁴ and serotypes replacement by nonvaccine serotypes in response to vaccine pressure. Normark et al. observed fluctuations in the serotype distribution among pneumococci causing bacteraemia in Sweden over 10 years period from 1987 to 1997. The surveillance data is required to determine the usefulness of available pneumococcal vaccines and the need for new vaccine. The study by Tyo RK et al also showed that the different findings from the 2008 and 2011 analyses by the authors suggested that the dynamic issue of serotype replacement should be monitored post-licensure and, as changes occur, vaccine effectiveness and cost-effectiveness analyses should be re-evaluated.⁶²

CONCLUSION

There was fair to good level of evidence to show that PCV7 is no longer cost effective because of increases in uinvasive diseases caused by nonvaccine serotypes, which reduces the overall direct effects of vaccination. The 10-valent and 13-valent pneumococcal vaccines showed better net health benefits than PCV7. Total programme costs can be lowered by reduction in vaccine prices.

A national immunization program with PCV10 or PCV13 was found to be good value for money and estimated to prevent additional cases of disease among children and save additional costs due to treatment of acute otitis media (AOM) and pneumococcal diseases. Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker either to prevent the severe invasive pneumococcal diseases (IPD) cases only, or prevention of AOM. There was fair to good level of evidence to show that PCV13 was predicted to provide a higher impact on IPD and CAP, while PCV10 was expected to provide a substantially greater reduction in AOM.

RECOMMENDATION

Based on the above review, it is recommended that regular surveillance is conducted since changes in serotypes may occur naturally with time and serotypes replacement by nonvaccine serotypes in response to vaccine pressure. The surveillance data is required to determine the usefulness of available pneumococcal vaccines and the need for new vaccine. It is also recommended that local economic evaluation and research should be conducted considering our healthcare systems as well as local costing that will further provide more evidence to support the above strategies.

Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker / policy maker either to prevent the severe IPD cases only, or prevention of AOM. PCV13 was predicted to provide a higher impact on severe invasive pneumococcal diseases (IPD) and community acquired pneumonia (CAP), while PCV10 was expected to provide a substantially greater reduction in acute otitis media (AOM). PCV13 may be the choice to prevent death due to pneumococcal diseases in order to achieve Millenium Development Goal 4 (MDG4). Cost of PCV10 and PCV13 are expensive and our low less than 5 mortality need also to be considered before embarking on the national pneumococcal conjugate vaccination programme. Affordability and sustainability is also an important issue for any national programme. Hence, taking into account our Malaysian scenario, PCV13 should be given for high risk group first before considering giving it for all children below 5 years old.

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HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

1. BACKGROUND INFORMATION

The human nasopharynx is the reservoir of *Streptococcus pneumoniae*, which is usually carried asymptomatically, and is transmitted to other individuals by respiratory droplets. The carriage rate is highest in young children, who most likely carry pneumococci in the nasopharynx at least one time, and are the primary source for its spread within a community. In the host, pneumococci can spread locally from the nasopharynx to cause otitis media or sinusitis, or to the lungs to cause pneumonia. Pneumococci can also cause invasive infections with high mortality. Pneumonia with empyema or bacteraemia, septicaemia and meningitis are invasive pneumococcal diseases (IPD). In Europe and the US, the risk of infection is greatest in children younger than two years old.¹⁻⁵

Pneumococcal conjugate vaccines (PCVs) containing polysaccharide antigens connected to carrier proteins have been found to be effective in developing an immune response and in reducing nasopharyngeal carriage of vaccine-type pneumococci in infants and children.⁶

The 10- and 13-valent pneumococcal conjugate vaccines (PCV-10 and PCV-13 respectively) are used to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children. Recently the indication for protecting against pneumonia among children was added for PCV 13. PCV-10 provides coverage against pneumococci and the non-typeable H. influenzae (NTHi) protein may provide protection against otitis media. The vaccine include serotypes contained in PCV 7 (4,6B,9V,14,18C,19F,23F) plus serotypes 1,5,7F.7 PCV-13 includes the serotypes contained in PCV 10 plus serotypes 3,6A,19A.⁷

In Malaysia, the overall under 5 death incident rates in 2006 was 0.6 per thousand age specific population and 3.5 per thousand live birth.⁸ Meanwhile it was reported in 2010 that there were 6 deaths per 1000 live births.⁹ Crude birth rate in 2010 was 17.5.¹⁰⁻¹¹

In 2011, the majority of pediatricians from public and private sectors have come to an agreement to introduce PCV 13 into the National Childhood Immunization programme due to its high efficacy. However, the Committee for Vaccine Use and Cost has suggested that the introduction of PCV 13 into the National Immunization Programme should be further studied in terms of cost-effectiveness. The information on the cost-effectiveness of two pneumococcal vaccines in the market (PCV10 & PCV13) with different antigenic composition and comparable efficacy is needed.

Therefore this HTA is conducted to review the evidences on the efficacy, safety, effectiveness, cost effectiveness and organizational aspects of PCV10 & PCV 13 before introducing them into the National Childhood Immunization programme.

2. POLICY QUESTION

Should pneumococcal conjugate vaccine be recommended into the National Childhood Immunization programme?

Research Question

- Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in effectiveness and in reducing in the development of IPD, pneumonia and otitis media in infants and children?
- Are the adverse events of 10-valent and 13-valent pneumococcal conjugate vaccine comparable?
- Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in cost-effectiveness?

3. OBJECTIVE

1. To undertake a systematic review on the effectiveness or efficacy of using 10-valent and 13-valent pneumococcal conjugate vaccine.
2. To assess the safety and cost effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccines.

4. METHODOLOGY

4.1 Search Strategy

Electronic database will be searched for published literatures pertaining to 10- and 13-valent pneumococcal conjugate vaccines (PCV-10 and PCV-13). The following sources will be searched:

- i. Databases as follows: MEDLINE, Pubmed, EBM Reviews – Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA Database EBM Reviews – NHS Economic Evaluation Database, EBM Full Text- Cochrane DSR, ACP journal Club and DARE.
- ii. Other database ;EMBASE, CINAHL
- iii. Additional articles will be identified from reviewing the bibliographies of retrieved articles.

4.2 Inclusion and exclusion criteria

Inclusion criteria

- i. Study design:
 - Systematic reviews, randomized control trials. Additional studies such as cohort, case control, cross sectional will also be taken into consideration.
- ii. Population:
 - infants and children below 2 5 years.
- iii. Intervention:
 - 10-valent or 13-valent pneumococcal conjugate vaccine
- iv. Comparators:
 - a. 7-valent pneumococcal conjugate vaccine
 - b. No vaccination
- v. Outcomes:
 - Efficacy and effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccine protect against
 - i. Invasive pneumococcal disease (IPD)
 - ii. Pneumonia
 - iii. Acute otitis media
 - Adverse events of 10-valent and 13-valent pneumococcal conjugate vaccine
 - Cost-effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccine
 - annual economic and health outcomes of invasive pneumococcal disease(IPD), community- acquired pneumonia and acute otitis media(AOM),
 - cost-utility of the newly available 10-valent and 13-valent conjugated pneumococcal vaccines cost- saving strategy using PCV-13 vaccination / PCV -10 vaccination
 - higher QALY gained with PCV-10 / PCV-13
- vi. Articles from year 2000

Exclusion criteria

- i. Study design – laboratory study, narrative, animal studies, case reports, case series

Based on these inclusion criteria, study selection will be carried out independently by two reviewers. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persists after discussion.

4.3 Data extraction strategy

The following data will be extracted:

- Details of methods and study population characteristics
- Details of intervention and comparator
- Details of individual outcomes for effectiveness, safety, cost effectiveness
- Details of organizational and legal implications related to the use of 10-valent and 13-valent pneumococcal conjugate vaccine

Data will be extracted from included studies by a reviewer using a pre-defined data extraction form and checked by another reviewer. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persists after discussion.

4.4 Quality assessment strategy

The methodological quality of all relevant articles will be assessed by using Critical Appraisal Skills Programme (CASP) depending on the type of study design. Quality assessment will be conducted by a reviewer and checked by a second reviewer.

4.5 Methods of analysis / synthesis

Data on clinical effectiveness, safety, and cost effectiveness will be presented in tabulated format with narrative summaries. A decision on whether to pool efficacy, safety and accuracy outcomes will be taken following the updated search and based on clinical and statistical heterogeneity and the range of outcome measures reported. Data will be pooled using fixed model unless statistical heterogeneity between studies is found, in which case random effect model will be used.

5. REPORT WRITING

References

1. Weil-Olivier C, Van Der Linden M, De Schutter I et al. Prevention of pneumococcal diseases in the post-seven valent vaccine era: A European perspective. *BMC Infectious Diseases* 2012, 12:207 <http://www.biomedcentral.com/1471-2334/12/207>
2. Melegaro A, Edmunds WJ, Pebody R, Miller E, George R: The current burden of pneumococcal disease in England and Wales. *J Infect* 2006, 52:37–48.
3. Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, Damaske B, Stefonek K, Barnes B, Patterson J, Zell ER, Schuchat A, Whitney CG: Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network. Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995–1998: Opportunities for prevention in the conjugate vaccine era. *JAMA* 2001, 285(13):1729–1735.
4. Von Kries R, Siedler A, Schmitt HJ, Reinert RR: Proportion of invasive pneumococcal infections in German children preventable by pneumococcal conjugate vaccines. *Clin Infect Dis* 2000, 31(2):482–487.
5. Eskola J, Takala AK, Kela E, Pekkanen E, Kalliokoski R, Leinonen M: Epidemiology of invasive pneumococcal infections in children in Finland. *JAMA* 1992, 16(268):3323–3327
6. Tyo KR, Rosen MM, Zeng W et al. Cost-effectiveness of conjugate pneumococcal vaccination in Singapore: Comparing estimates for 7-valent, 10-valent and 13-valent vaccines. *Vaccine* 2011;29:6686-6694.
7. Pneumococcal Disease. Available at: www.health.govt.nz/.../immunisationhandbook2011-v3.pdf Assessed on 12th March 2013.
8. A Study on Under Five Deaths in Malaysia In the year 2006. Available at: http://www.crc.gov.my/documents/report/ Study on Under 5 Deaths in Msia_2006.pdf. Assessed on 13th April 2013.
9. UNdata record review under-five mortality rate. Available at: data.un.org/Data.aspx?d=SOWC&f=inID%3A17. Assessed on 13th April 2013.
10. Malaysia@ a glance; Available at: http://www.statistics.gov.my/portal/index.php?option=com_content&view=article&id=472&Itemid=156&lang=en. Assessed on 13th April 2013.
11. Health Facts 2012. Available at: http://www.moh.gov.my/images/gallery/stats/heal_fact/ health_fact_2012_page_by_page.pdf. Assessed on 15th April 2013

Appendix 2

Electronic bibliographic databases searched

1. Medline
2. Science direct
3. Springer Link
4. Embase
5. Cochrane Central Database of Controlled Trials (CENTRAL)
6. Cochrane Database of Systematic Reviews (CDSR)
7. NHS Database of Abstracts of Reviews of Effectiveness (DARE)
8. NHS Economic Evaluation Database (NHS EED)
9. NHS Health Technology Assessment (HTA) Database
10. Pubmed

Appendix 3

Other source consulted

1. Wolters Kluwer, Lippincott
2. EBM Reviews
3. Canadian Agency for Drugs and Technologies in Health (CADTH)
4. National Institutes for Health and Clinical Excellence (NICE)
5. International Network of Agencies for Health Technology Assessment (INAHTA)
6. World Health Organisation (WHO)
7. Google Scholar
8. EuroSCAN
9. Australia and New Zealand Horizon Scanning Network
10. Guidelines International Network (G-I-N)
11. ClinicalTrials.gov
12. International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Appendix 4

SEARCH STRATEGIES USED IN THE MAJOR ELECTRONIC BIBLIOGRAPHIC DATABASES

Medline (Pubmed)

Ovid Medline (R) in-Process & other Non-Indexed citations and Ovid Medline (R) 1948 to present.

1. Pneumococcal Infections/ (10073)
2. pneumoniae infection* streptococcus.tw. (1)
3. (streptococcus pneumoniae adj1 infection*).tw. (454)
4. Pneumonia, Pneumococcal/ (4017)
5. (pneumococcal adj1 infection*).tw. (2144)
6. (pneumococcal adj1 pneumonia*).tw. (1623)
7. Meningitis, Pneumococcal/ (2835)
8. (pneumococcal adj1 meningitis).tw. (1412)
9. (streptococcus pneumoniae adj1 meningitis).tw. (173)
10. Bacteremia/ (17201)
11. bacteremia*.tw. (16799)
12. bacteraemia*.tw. (4336)
13. Otitis Media/ (15086)
14. (middle ear adj1 inflammation).tw. (173)
15. otitis media.tw. (16260)
16. pneumococcal septicaemia.tw. (74)
17. pneumococcal septicemia.tw. (102)
18. invasive pneumococcal disease*.tw. (1386)
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (67057)
20. Pneumococcal Vaccines/ (4575)
21. 13-valent Pneumococcal conjugate vaccine.tw. (156)
22. PCV13.tw. (250)
23. 10-valent pneumococcal conjugate vaccine.tw. (26)
24. PCV10.tw. (76)
25. (pneumococcal adj1 vaccin*).tw. (3475)
26. pneumococcal conjugate vaccine*.tw. (1881)
27. PCV.tw. (3817)
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (10143)
29. 19 and 28 (4394)
30. limit 29 to (english language and humans and ("infant (1 to 23 months)" or "preschool child (2 to 5 years)") and last 14 years) (1564)

Others Database

EBM Reviews - Cochrane Central Register of Controlled Trials	} Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
National Horizon Scanning unit	
Australia and New Zealand Horizon Scanning Network	
INAHTA	
FDA	

Appendix 5

DESIGNATION OF LEVELS OF EVIDENCE

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 6

EVIDENCE TABLES

This appendix contains the evidence tables with data extracted from the 37 studies included in this HTA report.

The evidence tables are arranged according to the effectiveness, immunogenicity, safety and cost effectiveness for 10-Valent and 13-Valent Pneumococcal Conjugate Vaccine.

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	1. Singleton R, Wenger J, Klejka JA et al. The 13-Valent Pneumococcal Conjugate Vaccine for Invasive Pneumococcal Disease in Alaska Native Children: Results of a Clinical Trial. <i>Pediatr Infect Dis J</i> 2013;32: 257–263
Study Type / Methods	open-label clinical trial: PCV13 impact was assessed using existing Alaska-wide IPD surveillance. Serotype-specific anti-pneumococcal IgG levels were measured postinfant series and posttoddler dose in a subset of subjects. Adverse events and serious adverse events were collected in all; local reactions and systemic events were collected in toddlers.
LE	1
Number of Patients and Characteristics	In 2009 Three hundred seventy-two eligible Yukon Kuskokwim Delta (YKD) children aged <5 years were offered PCV13 and received ≥1 dose of PCV13 during the study between January 30, 2009, and March 25, 2010.
Intervention	PCV 13
Comparison	
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> The proportion of responders after the infant series with serotypespecific antibody concentration ≥0.35 µg/mL ranged from 90.9% to 100.0%. The proportion of subjects with OPA titer ≥ lower limit of quantitation was ≥60% for all serotypes with the exception of serotype 9V (30.0%). After the toddler dose, the evaluable group 1 subjects achieved both serotype-specific IgG concentrations ≥0.35 µg/ mL and OPA titer ≥ lower limit of quantitation, Adverse events were typically mild, or generally consistent with common childhood illnesses. IgG levels following PCV13 were similar to other populations. In YKD children aged <5 years, 52 invasive pneumococcal disease [IPD cases] (31 of PCV13-serotype) occurred during 2005 to 2008 (399.0/100,000/yr) versus 9 7 PCV13-serotype) during January 2009 to August 2011 (106.7/100,000/ yr; P < 0.001). No PCV13-serotype cases occurred among PCV13 recipients (3680 person follow-up years). PCV13-serotype IPD incidence declined significantly after PCV13 introduction. Although non-PCV13-serotype IPD also declined significantly, absence of PCV13-serotype IPD in children who received PCV13 suggests a protective vaccine effect.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	2. Spijkerman J, Veenhoven RH, Wijmenga-Monsuur AJ, et al. Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine Administered According to 4 Different Primary Immunization Schedules in Infants A Randomized Clinical Trial. JAMA. 2013;310(9):930-937. doi:10.1001/jama.2013.228052
Study Type / Methods	RCT: To assess the optimal primary vaccination schedule by comparing immunogenicity of 13-valent PCV (PCV13)[serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.] in 4 different immunization schedules. randomly assigned (1:1:1:1) to receive PCV13 either at ages 2, 4, and 6 months (subsequently referred to as 2-4-6); at ages 3 and 5 months (3-5); at ages 2, 3, and 4 months (2-3-4); or at ages 2 and 4 months (2-4). All infants received a booster dose of PCV13 at age 11.5 months.
LE	1
Number of Patients and Characteristics	Healthy term infants in a general community in the Netherlands conducted between June 30, 2010, and January 25, 2011, with 99% follow-up until age 12 months
Intervention	Infants (N = 400) were randomly assigned (1:1:1:1) to receive PCV13 either at ages 2, 4, and 6 months (2-4-6); at ages 3 and 5 months (3-5); at ages 2, 3, and 4 months (2-3-4); or at ages 2 and 4 months (2-4), with a booster dose at age 11.5 months
Comparison	
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • One month after the booster dose, there were no differences in IgG GMCs between the schedules except for 8 of 78 comparisons. • The use of 4 different PCV13 immunization schedules in healthy term infants resulted in no statistically significant differences in antibody levels after the booster dose for almost all serotypes. • The 2-4-6 schedule was superior to the 2-3-4 schedule for serotypes 18C (10.2 µg/mL [95%CI, 8.2-12.7] vs 6.5 µg/mL [95%CI, 5.4-7.8]) and 23F (10.9 µg/mL [95%CI, 9.0-13.3] vs 7.3 µg/mL [95%CI, 5.8-9.2]) and superior to the 2-4 schedule for serotypes 6B (8.5 µg/mL [95%CI, 7.1-10.2] vs 5.1 µg/mL [95%CI 3.8-6.7]), 18C (6.6 µg/mL [95%CI, 5.7-7.7]), and 23F (7.2 µg/mL [95%CI, 5.9-8.8]). • For serotype 1, the 3-5 schedule (11.7 µg/mL [95%CI, 9.6-14.3]) was superior to the other schedules. Geometric mean concentrations for all 13 serotypes ranged between 1.6 and 19.9 µg/mL. • Secondary outcomes demonstrated differences 1 month after the primary series. The 2-4-6 schedule was superior compared with the 3-5, 2-3-4, and 2-4 schedules for 3, 9, and 11 serotypes, respectively. Differences between schedules persisted until the booster dose.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	3. Cohen R, Levy C, Bingen E, Koskas M, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. The Pediatric Infectious Disease Journal 2012 31(3) 297-301
Study Type / Methods	<p>Cross sectional study among young children in France</p> <p>The objective was to assess the effect of the implementation of PCV13 on pneumococcal nasopharyngeal (PNP) carriage in young children with AOM (acute otitis media).</p> <p>To assess the effect of PCV13 vaccine, 2 groups of patients;</p> <ol style="list-style-type: none"> adequately PCV13 vaccinated for the age if they had received 2 doses before 12 months or at least 1 dose after this age partially PCV13 vaccinated if they had received 1 dose of PCV13. The group of children vaccinated only with PCV7 served as the reference group.
LE	II-3
Number of Patients and Characteristics	<p>943 children (6 to 24 months of age) enrolled</p> <p>Mean age, 13.4 ± 5.0 months</p>
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	5 months (October 2010 - March 2011)
Outcome Measures / Effect Size	<p>Outcomes:</p> <p>In comparing PCV13-vaccinated children versus children exclusively vaccinated with PCV7,</p> <ul style="list-style-type: none"> overall pneumococcal nasopharyngeal (PNP) carriage was 53.9% for PCV13-vaccinated children versus 64.6% for children exclusively vaccinated with PCV7, P<0.002) carriage of serotypes not in PCV7 was 9.5% for PCV13-vaccinated children versus 20.7%, for children exclusively vaccinated with PCV7 P< 0.0001) <p>The carriage rates were also significantly lower in PCV13-vaccinated patients than in patients</p> <ul style="list-style-type: none"> only vaccinated by PCV7: serotypes 19A (7.5% for PCV13-vaccinated children versus 15.4%, for children exclusively vaccinated with PCV7 P< 0.001) serotype 7F (0.5% for PCV13-vaccinated children versus 2.8% for children exclusively vaccinated with PCV7, P<0.002) serotype 6C (3.7% for PCV13-vaccinated children versus 8.4% for children exclusively vaccinated with PCV7, P< 0.003) This study suggested that in young children (less 2 years) with AOM, PCV13 has an impact on overall PNP carriage, as well as on serotypes 19A, 7F, and 6C.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	4. Azzari C, Cortimiglia MMM, Valleriani C et al. Potential serotype coverage of three pneumococcal conjugate vaccines against invasive pneumococcal infection in Italian children. <i>Vaccine</i> . 2012; 30: 2701-2705
Study Type / Methods	<p>Cross sectional study involving 83 participating centers</p> <p>The objective was to assess the potential serotype coverage of three pneumococcal conjugate vaccines (7-, 10- and 13-valent) against bacteremic pneumococcal pneumonia and meningitis/sepsis in Italian children</p> <p>Inclusion: all children 0–16 years with a confirmed diagnosis of meningitis/sepsis (the most severe IPD) or bacteremic pneumonia (the most common IPD), admitted to Paediatric Hospitals or Paediatric wards of general hospitals in Italy during study period</p>
LE	II-3
Number of Patients and Characteristics	<p>A total of 144 patients</p> <p>Age (median 4.1 years; interquartile range 1.8–5.6) with pneumococcal meningitis/sepsis (n = 43) or pneumonia (n = 101)</p>
Intervention	PCV13
Comparison	PCV10,PCV7
Length of Follow Up	Between April 2008 and March 2011
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> 83 participating centers located in 19 of 20 Italian regions were serotyped. The 10 most prevalent serotypes were 1 (29.9%), 3 (16.0%), 19A (13.2%), 7F (8.3%), 5 (4.2%), 14 (4.2%), 6A (3.5%), 6B (3.5%), 18C (3.5%), 19F (3.5%). Serotype coverage for PCV7 was 19.4%, PCV10 was 61.8% and PCV13 was 94.4% and with no statistical difference between pneumonia and meningitis/sepsis. Hence,PCV10 would provide potential coverage for about 62% of the serotypes identified, while PCV13 would provide coverage of more than 94% (86% for meningitis/sepsis and nearly 100% for pneumonia). The author suggested that the Introduction of PCV13 could have a significant added benefit in reducing the burden of pneumococcal disease in Italian children below 2 years as well in older children.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	5. Hortal M, Estevan M, Laurani H et al. Hospitalised children with pneumonia in Uruguay: pre and post introduction of 7 and 13-valent pneumococcal conjugated vaccine into the National Immunisation Program. <i>Vaccine</i> . 2012; 30: 4934-4938
Study Type / Methods	<p>Pre and post vaccination using population-based surveillance in Uruguay, from January 1st 2009 to June 30th 2011</p> <p>The objective was to compare the incidence of consolidated pneumonia hospitalization in children less than five years of age before and after pneumococcal conjugate vaccine implementation.</p> <p>The surveillance was carried out at the same four hospitals in previous pre vaccination study</p> <p>A pediatric radiologist blinded to the clinical diagnosis interpreted the digital images according WHO definitions. Bacterial etiology was investigated in blood or in pleural fluid</p> <p>Eligible for enrollment were patients aged 0–59 months with acute lower respiratory tract infections for whom a chest X-ray was performed on admission to confirm a clinical suspected pneumonia</p> <p>Exclusion: Hospital-acquired pneumonias, bronchiolitis, asthma/bronchial hypersensitivity for whom no X-ray was ordered</p>
LE	II-2
Number of Patients and Characteristics	<p>1542 hospitalised patients under five years of age were enrolled.</p> <p>Mean age was 18.1 ± 15.6 months, 52% were males, 89% of families lived in urban areas but in area with dwelling and poverty condition</p> <p>40% of patients had been hospitalized previously with acute respiratory diseases</p>
Intervention	PCV13
Comparison	<p>PCV7</p> <p>PCV7 was included into the National Immunization Program (NIP) in March 2008 using a 2 + 1 dosing schedule</p> <p>In March 2010, PCV13 replaced PCV7.</p>
Length of Follow Up	Duration of study: 30 months
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> • 1224 were hospitalized with pneumonia (430 consolidated Pneumonias and 794 non consolidated pneumonias). In 48 consolidated pneumonias, <i>S.pneumoniae</i> etiology was recognized. • A significant reduction (44.9%) of incidence rate of consolidated pneumonia in post vaccinated patients aged 12–23 months was observed with PCV -7 vaccinations. • Pleural effusion was recorded in 89 patients. • In March 2010, PCV13 replaced PCV7. Compliance of PCV7/13 globally was 92% but the vaccination status varied among the surveyed patients because two catch-ups were carried out in addition to the routine cohort vaccination. From 2009 1st semester to 2011, 1st semester incidence rates decline reached 59%. • According to the author, to date, the ongoing surveillance documented a significant decline on incidence of hospitalizations for consolidated pneumonia in children younger than 24 months of age, suggesting the success of the 2 + 1 vaccination schedule.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	6. Esposito S, Tansey S, Thompson A et al. Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine Compared to Those of a 7-Valent Pneumococcal Conjugate Vaccine Given as a Three-Dose Series with Routine Vaccines in Healthy Infants and Toddlers, <i>Clinical And Vaccine Immunology</i> , 2010, p. 1017–1026 Vol. 17, No. 6 1556-6811/10/\$12.00 doi:10.1128/CVI.00062-10
Study Type / Methods	RCT: This study compared the safety and immunogenicity of PCV13 with those of PCV7 when given as part of the pediatric vaccination schedule recommended in Italy.
LE	1
Number of Patients and Characteristics	A total of 606 subjects were randomly assigned to receive either PCV13 or PCV7 at 3, 5, and 11 months of age; all subjects concomitantly received diphtheria-tetanus-acellular pertussis/hepatitis B-inactivated polio- <i>Haemophilus influenzae</i> type B (DTaP-HBV-IPV/Hib) vaccine
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Overall, the safety profile of PCV13 was similar to that of PCV7. Most of the local reactions in the two vaccine groups were mild in severity and lasted 1 or 2 days. No statistically significant differences between vaccine groups were observed after doses 1 and 2 of the infant series or after the toddler dose. There were no significant differences between vaccine groups in the incidence of systemic events The response to DTaP-HBV-IPV/Hib antigens was substantially the same with both PCV13 and PCV7. PCV13 elicited antipneumococcal capsular IgG antibodies to all 13 vaccine serotypes, with notable increases in concentrations seen after the toddler dose. For concomitant antigens, 95% CIs for the proportion of responders and for the difference in proportions (PCV13 – PCV7 reference) were calculated, with noninferiority declared if the lower bound of the two-sided 95% CI for the difference in proportions was greater than -10%. All of the 95% CI lower limits for the differences between PCV13 and PCV7 responses exceeded -10%, indicating that the responses to concomitant vaccine antigens when given with PCV13 vaccination were not inferior to those when given with PCV7 after both the infant series and the toddler dose. Despite a lower immunogenicity for serotypes 6B and 23F after the primary series of PCV13, responses to the seven common serotypes were comparable between the PCV13 and PCV7 groups when measured after the toddler dose. PCV13 also elicited substantial levels of OPA activity against all 13 serotypes following both the infant series and the toddler dose. PCV13 appeared comparable to PCV7 in safety profile and immunogenicity for common serotypes, demonstrated functional OPA responses for all 13 serotypes, and did not interfere with immune responses to concomitantly administered DTaP-HBV-IPV/Hib vaccine.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	7. Bryant KA, Block SL, Baker SA et al. Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine. <i>Pediatrics</i> 2010; 125; 866. DOI: 10.1542/peds.2009-1405
Study Type / Methods	RCT: The safety and immunogenicity of PCV7 were compared with those of 13-valent PCV (PCV13), which contains saccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to CRM
LE	1
Number of Patients and Characteristics	Infants were randomly assigned to receive PCV13 or PCV7 at ages 2, 4, and 6 months with other vaccines. Post-third-dose antibodies to each pneumococcal polysaccharide were measured by immunoglobulin G enzyme-linked immunosorbent assay. Antibacterial functional antibodies were measured by opsonophagocytic assay (OPA).
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Subjects received PCV13 (n= 122) or PCV7 (n = 127). For the 7 common serotypes included in PCV13 and PCV7, 88.3% to 99.1% of vaccinated infants in both groups achieved antibody concentrations of $\geq 0.35\mu\text{g/mL}$ 1 month after the third dose, and there were no significant differences between treatment groups For the 6 additional serotypes only in PCV13, 97% to 100% of PCV13-vaccinated infants achieved similar levels of pneumococcal antipolysaccharide IgG concentrations 1 month after the third dose. Geometric mean antibody concentration for PCV13 recipients ranged from 1.32 $\mu\text{g/mL}$ (serotype 23F) to 4.26$\mu\text{g/mL}$ (serotype 14). The ratio of OPA geometric mean titers for the 7 shared serotypes (PCV13:PCV7) ranged from 0.6 to 1.4, suggesting no clinically meaningful differences. For PCV13-only serotypes, OPA geometric mean titers were significantly higher in the PCV13 group than in the PCV7 group. Local reactions and systemic events were similar between groups. PCV13 was well tolerated and immunogenic, with most infants developing antipolysaccharide antibody concentrations of $\geq 0.35\mu\text{g/mL}$, as well as OPA responses, to each of the 13 serotypes
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:

Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?

Bibliographic Citation	8. Kim DS, Shin SH, Lee HJ, et al. Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine Given to Korean Children Receiving Routine Pediatric Vaccines. <i>Pediatr Infect Dis J</i> 2013;32: 266–273
Study Type / Methods	RCT: The immunogenicity and safety of 13-valent and 7-valent pneumococcal conjugate vaccines (PCV13 and PCV7) were compared when administered with routine vaccines at 6 sites in Korea
LE	1
Number of Patients and Characteristics	Healthy infants (n = 180) were randomly assigned (1:1) to receive PCV13 or PCV7 at 2, 4, 6 (infant series) and 12 months (toddler dose). Immune responses 1 month after the infant series and toddler dose were measured by enzyme-linked immunosorbent assay and opsonophagocytic activity (OPA) assay. IgG antibody geometric mean concentrations and OPA functional antibody geometric mean titers were calculated. Safety was assessed.
Intervention	PCV13
Comparison	PCV10
Length of Follow Up	
Outcome Measures / Effect Size	<p>Immune Responses After the Infant Series</p> <ul style="list-style-type: none"> For each of the 7 common serotypes, the proportion of subjects achieving IgG concentrations ≥ 0.35 $\mu\text{g/mL}$ (ie, the proportion of responders) was similar and $\geq 97.6\%$ in both the PCV13 and PCV7 vaccine groups; $\geq 92.3\%$ achieved LLOQs, except for serotype 19F which was lower (78.6%). IgG GMCs and OPA GMTs were generally similar across groups, but there was a trend toward lower responses in the PCV13 group for some serotypes. For the 6 additional serotypes unique to PCV13, the proportion of responders in the PCV13 group was 100% for all serotypes except serotype 6A (97.6%); $\geq 96.0\%$ achieved LLOQs. IgG GMCs and OPA GMTs were notably higher in the PCV13 group than in the PCV7 group. Although PCV7 elicited IgG responses to nonvaccine serotypes 5 and 19A, OPA functional antibody responses were minimal (GMTs: 4 and 7, respectively). In contrast, PCV7 elicited both IgG and OPA functional responses (GMT 492) to serotype 6A; however, the OPA responses were 4.5-fold less than those in response to PCV13 For the 7 common serotypes, PCV13 generally resulted in an increase in immune responses after the toddler dose. For serotype 14, however, which showed the highest IgG response after the infant series (GMC 14.83 $\mu\text{g/mL}$), the posttoddler response (GMC 11.51 $\mu\text{g/mL}$) was less than that after the infant series; in contrast, the OPA GMTs were higher after the toddler dose (GMT increase from 1236 to 1542). For 5 of the 6 additional serotypes, the toddler dose of PCV13 resulted in increases in IgG GMCs; the exception was serotype 3, which showed similar IgG GMCs postinfant series (1.60 $\mu\text{g/mL}$) and posttoddler dose (1.65 $\mu\text{g/mL}$). However, OPA GMTs for serotype 3 showed a notable increase from after the infant series to after the toddler dose (GMT increase from 153 to 256). These observations are consistent with at least some protection by PCV7 against 6A-mediated invasive pneumococcal disease, but no cross-protection for serotypes 5 and 19A. The toddler dose elicited higher IgG and OPA responses than postinfant series responses for most serotypes; however, for serotypes 3 and 14 only OPA responses were increased posttoddler dose. Vaccine safety profiles were similar. Incidence of systemic events was generally similar in both groups (. Fever was mostly mild, and there were no cases of severe fever.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	9. Silfverdal SA , Flodmark CE,Rombo L et al. 13-Valent pneumococcal conjugate vaccine (PCV13) in children partially immunized with 7-valent pneumococcal conjugate vaccine (PCV7): A phase 3, open-label trial. Vaccine 31 (2013) 1284– 1292
Study Type / Methods	Phase 3 open label study: evaluated immunogenicity and safety of PCV13 in Swedish infants and toddlers previously given 1 or 2 doses of PCV7 during infancy.
LE	1
Number of Patients and Characteristics	Healthy infants previously given PCV7 at ages 3 months (group 1; n = 118) or 3 and 5 months (group 2; n = 116) received PCV13 at ages 5 (group 1) and 12 months (both groups). IgG responses were assessed 1 month after each PCV13 dose and before the 12-month dose. Local reactions and systemic events were collected for 7 days postvaccination. Other adverse events were also collected.
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • One month after the 5-month dose, serotype-specific IgG GMCs were 1.56–4.70 µg/ml for PCV7 serotypes except for serotypes 6B (0.40 µg/ml) and 23F (0.57 µg/ml) (Table 1). For the 6 additional serotypes, GMCs were 0.72–1.88 µg/ml except for serotype 6A (0.28 µg/ml). • For PCV7 serotypes, the proportions of subjects with pneumococcal serotype-specific IgG concentrations $\geq 0.35\mu\text{g/ml}$ were 92.2–99.1%, except for serotypes 6B (53.0%) and 23F (62.6%). Proportions for the 6 additional serotypes were 80.9–100.0%, except for serotype 6A (36.8%). • Post-12-month dose, IgG GMCs for the PCV7 serotypes were 2.93–9.63 µg/ml (group 1) and 3.33–9.30µg/ml (group 2); and for the 6 additional serotypes, 1.85–14.65µg/ml (group 1) and 1.34–13.16 µg/ml (group 2). • GMCs increased by >4-fold in both groups from pre- to post-12-month dose. Proportions of subjects in group 1 with pneumococcal serotype-specific IgG concentrations $\geq 0.35 \text{ }\mu\text{g/ml}$ (WHO-designated postprimary reference antibody level) post-5-month dose were 92.2–99.1% for most PCV7 serotypes except 6B (53.0%) and 23F (62.6%) and 80.9–100.0% for most of the 6 additional serotypes except 6A (36.8%). • Local reactions and fever were mostly mild or moderate. • From the study it was found that PCV13 was immunogenic and safe in infants and toddlers previously partially immunized with PCV7. Even a single dose in an infant or toddler induces an immune response to the 6 additional serotypes.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	<p>10. Weckx LY, Thompson A, Berezin EN et al.</p> <p>A phase 3, randomized, double-blind trial comparing the safety and immunogenicity of the 7-valent and 13-valent pneumococcal conjugate vaccines, given with routine pediatric vaccinations, in healthy infants in Brazil.</p> <p>Vaccine.2012;30: 7566– 7572</p>
Study Type / Methods	<p>Phase III, randomized, multicenter, double-blind study in Brazil</p> <p>Immunogenicity objectives:</p> <p><i>Primary objective</i></p> <p>to compare pneumococcal immune responses induced by PCV13 with those induced by PCV7, measured 1 month after the infant series</p> <p><i>Secondary objective</i></p> <p>to compare pneumococcal immune responses induced by PCV13 with those induced by PCV7, measured 1 month post toddler dose, when PCV7 or PCV13 given concomitantly with vaccines in National program</p> <p><i>Co-primary objectives</i></p> <p>Immune responses induced by pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN]) in diphtheria, tetanus, whole-cell pertussis (DTwP) vaccine combined with Hib (DTwP-Hib)</p> <p>Safety objectives:</p> <p>Incidence rates of local reactions, systemic events, and unsolicited adverse events (AEs) after PCV13 vaccination relative those after PCV7</p> <p>Subjects were randomly assigned in a 1:1 ratio to receive either PCV13 or PCV7.</p> <p>Blood samples were collected 27–56 days after both the infant series (1 month after dose 3 of PCV7 or PCV13), and toddler dose (age 13 months).</p>
LE	1
Number of Patients and Characteristics	<p>354 enrolled (177 in each group)</p> <p>Healthy infants aged 1 month (28–54 days)</p>
Intervention	PCV13
Comparison	PCV7

<p>Length of Follow Up</p>	<p>Duration of study was 18 months.</p> <p>Follow-up at 7 months old (post infant series) and at 13 months old (post toddler dose)</p> <p>157 in PCV 13 and 159 in PCV 7 completed the infant series</p> <p>156 in PCV 13 and 156 in PCV 7 completed the toddler dose</p>
<p>Outcome Measures / Effect Size</p>	<p>Outcomes</p> <p>Immune responses to the common serotypes 1 month after the infant series</p> <ul style="list-style-type: none"> The proportion of subjects with serotype-specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$ was comparable in the PCV13 ($\geq 94.2\%$) and PCV7 ($\geq 93.0\%$) groups IgG Geometric mean concentration (GMC)s were comparable in the PCV13 and PCV7 groups <p>Immune responses to the additional serotypes after the infant series</p> <ul style="list-style-type: none"> For the 6 additional serotypes, the proportion of responders ranged from 1.3% (serotype 7F) to 98.7% (serotype 19A) in the PCV7 group For serotypes 1, 3, 5, 6A, and 7F, the response rates in the PCV13 group were significant compared with the PCV7 group. For serotype 19A, response rates were comparable in both PCV13 (99.4%) and PCV7 (98.7%) groups. IgG GMCs for the 6 additional serotypes were higher in the PCV13 group than the PCV7 group <p>Immune responses to the common serotypes after the toddler</p> <ul style="list-style-type: none"> Dose IgG GMCs were comparable in both groups for the 7 common serotypes after the toddler dose, with exception of serotype 19F <p>Immune responses to the additional serotypes after the toddler dose</p> <ul style="list-style-type: none"> IgG GMCs for the 6 additional serotypes were higher in the PCV13 group <p>Concomitant vaccine immunogenicity</p> <ul style="list-style-type: none"> The proportion of subjects achieving PT, FHA, and PRN antibody levels of ≥ 5 EU/mL and pertussis antigens 1 month after the infant series and toddler dose were similar between the PCV13 and PCV7 groups Reported local reactions and systemic events were similar in both groups <p>The study showed that PCV13 provide comparable protection for the 7 common serotypes and added protection against the 6 additional serotypes</p>
<p>Comments</p>	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:

Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?

Bibliographic Citation	11. Huang LM, Lin TY, Juergens C. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccines in Taiwan. <i>Vaccine</i> . 2012; 30: 2054– 2059
Study Type / Methods	<p>Randomized, multicenter, double-blind in Taiwan</p> <p>The objective was to evaluate immunogenicity and safety of PCV13 compared to PCV7</p> <p>Subjects were randomly assigned in a 1:1 ratio to receive PCV13 or PCV7 at 2, 4 and 6 months (infant series), and 15 months (toddler dose)</p> <p>Concomitant study vaccines were diphtheria, tetanus, acellular pertussis (DTaP), inactivated poliovirus (IPV) and Haemophilus influenzae type b (Hib), administered at 2 and 4 months; and DTaP-IPV-Hib combined with hepatitis B virus (HBV) administered at 6 months.</p> <p>Blood samples were obtained 28–42 days after the infant series and toddler dose.</p>
LE	1
Number of Patients and Characteristics	<p>168 enrolled (84 in each group)</p> <p>Day 42-98 healthy infant</p> <p>Demographic characteristics were similar at enrollment between groups with respect to race and ethnicity, mean age and mean weight. Male subjects (52.4%) were more common in the PCV13 than in the PCV7 group (44.0%).</p>
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	<p>Followup :</p> <p>Duration of study was 15 months.</p> <p>Received doses at 2, 4, 6 and 15 months.</p> <p>80 in PCV 13 and 84 in PCV 7 completed the infant series.</p> <p>80 in PCV 13 and 84 in PCV 7 completed the toddler dose.</p>
Outcome Measures / Effect Size	<p>Outcomes:</p> <p>Immune responses to the common serotypes after the infant series</p> <ul style="list-style-type: none"> The proportion of subjects with serotype-specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$ was similar in both groups ($\geq 95\%$) e.g IgG GMCs were high in both groups, generally lower in PCV13 <p>Immune responses to the additional serotypes after the infant series</p> <ul style="list-style-type: none"> For the 6 additional serotypes, the proportion of responders higher in PCV13 group (exception 19A) IgG GMCs higher in PCV13 than PCV7 <p>PCV 13: IgG GMC level for infant series</p> <ul style="list-style-type: none"> 2.89 $\mu\text{g/mL}$ (95% CI; 2.45 $\mu\text{g/mL}$, 3.42 $\mu\text{g/mL}$) for serotype 4 4.37 $\mu\text{g/mL}$ (95% CI; 3.58 $\mu\text{g/mL}$, 5.33 $\mu\text{g/mL}$) for serotype 6B 1.97 $\mu\text{g/mL}$ (95% CI; 1.70 $\mu\text{g/mL}$, 2.27 $\mu\text{g/mL}$) for serotype 9V 9.76 $\mu\text{g/mL}$ (95% CI; 8.34 $\mu\text{g/mL}$, 11.43 $\mu\text{g/mL}$) for serotype 14 2.39 $\mu\text{g/mL}$ (95% CI; 2.04 $\mu\text{g/mL}$, 2.82 $\mu\text{g/mL}$) for serotype 18C 3.60 $\mu\text{g/mL}$ (95% CI; 3.00 $\mu\text{g/mL}$, 4.32 $\mu\text{g/mL}$) for serotype 19F 1.93 $\mu\text{g/mL}$ (95% CI; 1.56 $\mu\text{g/mL}$, 2.37 $\mu\text{g/mL}$) for serotype 23F 4.14 $\mu\text{g/mL}$ (95% CI 3.45 $\mu\text{g/mL}$, 4.96 $\mu\text{g/mL}$) for serotype 1 1.20 $\mu\text{g/mL}$ (95% CI 1.00 $\mu\text{g/mL}$, 1.45 $\mu\text{g/mL}$) for serotype 3 2.47 $\mu\text{g/mL}$ (95% CI 2.09 $\mu\text{g/mL}$, 2.92 $\mu\text{g/mL}$) for serotype 5 4.57 $\mu\text{g/mL}$ (95% CI 3.92 $\mu\text{g/mL}$, 5.34 $\mu\text{g/mL}$) for serotype 6A 3.67 $\mu\text{g/mL}$ (95% CI 3.14 $\mu\text{g/mL}$, 4.29 $\mu\text{g/mL}$) for serotype 7F 3.69 $\mu\text{g/mL}$ (95% CI 3.20 $\mu\text{g/mL}$, 4.24 $\mu\text{g/mL}$) for serotype 19A

PCV7: IgG GMC level for infant series

- 4.64 µg/mL (95% CI; 4.00 µg/mL, 5.37 µg/mL) for serotype 4
- 4.82 µg/mL (95% CI; 4.09 µg/mL, 5.67 µg/mL) for serotype 6B
- 2.92 µg/mL (95% CI; 2.55 µg/mL, 3.34 µg/mL) for serotype 9V
- 11.59 µg/mL (95% CI; 9.79 µg/mL, 13.71 µg/mL) for serotype 14
- 3.07 µg/mL (95% CI; 2.64 µg/mL, 3.56 µg/mL) for serotype 18C
- 4.77 µg/mL (95% CI; 4.17 µg/mL, 5.47 µg/mL) for serotype 19F
- 3.25 µg/mL (95% CI; 2.78 µg/mL, 3.80 µg/mL) for serotype 23F
- 0.02 µg/mL (95% CI; 0.02 µg/mL, 0.02 µg/mL) for serotype 1
- 0.05 µg/mL (95% CI; 0.04 µg/mL, 0.06 µg/mL) for serotype 3
- 0.43 µg/mL (95% CI; 0.35 µg/mL, 0.53 µg/mL) for serotype 5
- 0.79 µg/mL (95% CI; 0.63 µg/mL, 0.99 µg/mL) for serotype 6A
- 0.04 µg/mL (95% CI; 0.03 µg/mL, 0.05 µg/mL) for serotype 7F
- 2.46 µg/mL (95% CI; 2.13 µg/mL, 2.84 µg/mL) for serotype 19A

Immune responses to the common serotypes after the toddler

- PCV13 higher immune response for all serotypes than postinfant series
- PCV7 showed booster responses

PCV 13: IgG GMC level for toddler dose

- 4.06 µg/mL (95% CI; 3.34 µg/mL, 4.93 µg/mL) for serotype 4
- 13.62 µg/mL (95% CI; 11.08 µg/mL, 16.73 µg/mL) for serotype 6B
- 3.18 µg/mL (95% CI; 2.66 µg/mL, 3.80 µg/mL) for serotype 9V
- 8.17 µg/mL (95% CI; 6.53 µg/mL, 10.22 µg/mL) for serotype 14
- 3.67 µg/mL (95% CI; 3.00 µg/mL, 4.49 µg/mL) for serotype 18C
- 8.07 µg/mL (95% CI; 6.58 µg/mL, 9.90 µg/mL) for serotype 19F
- 5.51 µg/mL (95% CI; 4.46 µg/mL, 6.81 µg/mL) for serotype 23F
- 7.62 µg/mL (95% CI; 6.30 µg/mL, 9.21 µg/mL) for serotype 1
- 1.29 µg/mL (95% CI; 1.09 µg/mL, 1.53 µg/mL) for serotype 3
- 4.57 µg/mL (95% CI; 3.87 µg/mL, 5.39 µg/mL) for serotype 5
- 11.55 µg/mL (95% CI; 9.66 µg/mL, 13.81 µg/mL) for serotype 6A
- 5.91 µg/mL (95% CI; 4.95 µg/mL, 7.06 µg/mL) for serotype 7F
- 8.82 µg/mL (95% CI; 7.45 µg/mL, 10.43 µg/mL) for serotype 19A

PCV7: IgG GMC level for toddler dose

- 6.34 (5.26, 7.65) for serotype 4
- 13.28 (10.87, 16.21) for serotype 6B
- 3.88 (3.27, 4.60) for serotype 9V
- 12.04 (9.90, 14.63) for serotype 14
- 4.87 (4.01, 5.90) for serotype 18C
- 7.41 (6.16, 8.92) for serotype 19F
- 7.97 (6.55, 9.68) for serotype 23F
- 0.02 (0.02, 0.02) for serotype 1
- 0.05 (0.04, 0.06) for serotype 3
- 0.43 (0.35, 0.53) for serotype 5
- 0.79 (0.63, 0.99) for serotype 6A
- 0.04 (0.03, 0.05) for serotype 7F
- 2.46 (2.13, 2.84) for serotype 19A

Local reactions and systemic events were similar in both groups. No AE, deaths or discontinuation due to AEs

The study suggested that PCV13 could offer broader serotype protection in preventing pneumococcal disease in Taiwanese children. Similar safety profile between PCV13 and PCV7

Comments

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:

Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?

Bibliographic Citation	12. Vanderkooi OG, Scheifele DW, Girgenti D, et al. Safety and immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers given with routine pediatric vaccination in Canada. <i>Vaccine</i> . 2012; 30: 2054– 2059
Study Type / Methods	<p>Phase III, randomised, multicenter, double-blind study in Canada</p> <p>The objective was to evaluate the immune and safety responses to concomitant routine childhood vaccines when given with PCV13, compared with PCV7.</p> <p>Subjects were randomized 1:1 to receive either PCV13 or PCV7 at 2,4 and 6 months (primary infant series) followed by toddler booster at 12 months</p> <p>Routine concomitant vaccines were diphtheria, tetanus, acellular pertussis, inactivated poliovirus, <i>Haemophilus influenza</i> type b at 2, 4, and 6 months; meningococcal C conjugate at 2, 6, and 12 months; and measles, mumps, and rubella and varicella vaccines at 12 months of age. Blood draws were performed at 7 and 13 months.</p> <p>Immune responses were measured against selected concomitant vaccines; meningococcal C conjugate, <i>Haemophilus influenza</i> type B and pertussis</p>
LE	1
Number of Patients and Characteristics	<p>No of patient : 603 were enrolled (300 in PCV13 group, 303 in PCV7 group)</p> <p>Patient characteristic: Healthy infant, day 42-98 at enrollment</p> <p>The baseline characteristics: 51% male, 83.7% white, 3.3% Asian, 3.0% black, 10% other race. 3.2% Hispanic or Latino ethnicity.</p> <p>There were no significant differences between treatment groups with respect to sex, race, ethnicity, age, weight, or protocol.</p>
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	<p>Follow up : Duration of study was 23 months.</p> <p>Received doses at 2,4,6 and 12 months.</p> <p>293 in PCV 13 and 291 in PCV 7 completed the infant series. 283 in PCV 13 and 282 in PCV 7 completed the toddler series.</p>
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> • There were no statistically significant differences between the groups in responses to Hib, pertussis, or menC after primary or booster vaccinations. • Response to concomitant vaccine antigens – similar in both vaccines, 2.4% lower in PCV13 (meningococcal C antigen) • specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$ were achieved for most serotypes in $\geq 90\%$ infants with the exception of serotype 3 (79.6%) and 5 (87.0%), and after the fourth dose, $\geq 98\%$ in toddler achieved serotype –specific antibody concentrations with the exception of serotype 3 (84.8%) • After the fourth dose, 98% to 100% of subjects achieved serotype-specific antibody concentrations ≥ 0.35 $\mu\text{g/mL}$, except for serotype 3 (85%). • Local reactions and systemic events were similar in both groups • No AE, deaths or discontinuation due to AEs <p>The study showed no differences between PCV7 and PCV13 on immune responses elicited by selected routine childhood vaccines concomitantly administered (measles, mumps, rubella and varicella were not assessed). The safety profile of PCV13 was similar to PCV7</p>
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	13. Scott P, Rutjes AWS, Bermetz L et al. Comparing pneumococcal conjugate vaccine schedules based on 3 and 2 primary doses: Systematic review and meta-analysis. Vaccine. 2011;29:9711 – 9721.
Study Type / Methods	Systematic review and meta analysis. Study identification. Search on 12 databases and trial registries yielded 3121 items. Excluded 3188 items. Use 29 items (8 RCTs, 1 cohort, 1 case studies) Conduct searching on 28 August 2009. Repeat searching at Embase on 17 April 2010. Screen bibliographies of selected review articles. Ask experts in the field and vaccine manufacturers. Two reviewers worked independently evaluated the articles.
LE	1
Number of Patients and Characteristics	Children up to 18 years old.
Intervention	10-valent PCV
Comparison	7-valent and 9-valent PCV
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • Seropositivity levels (antibody concentration $\geq 0.35\mu\text{g/ml}$) following 3p and 2p PCV schedules were high for most serotypes (5 RCTs). • Differences between schedules were generally small and tended to favour 3p schedules, particularly for serotypes 6B and 23F; between-study heterogeneity was high. • Seropositivity levels following 3p+1 and 2p+1 schedules were similar but small differences favouring 3p+1 schedules were seen for serotypes 6B and 23F.
Comments	

Evidence Table : 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY/EFFECTIVENESS:**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine efficacious/effective?**

Bibliographic Citation	14. Snape MD, Klinger CL, Daniels ED et al. Immunogenicity and Reactogenicity of a 13-valent Pneumococcal Conjugate Vaccine Administered at 2, 4, and 12 Months of Age – A Double-blind Randomized Active Controlled Trial. The Paediatric Infectious Disease Journal, 2010(Dec);29(12):e80-e90.
Study Type / Methods	Phase III, randomised, double blind, active-controlled study. The aim of study to assess the immunogenicity and tolerability of PCV 13 given according to this reduced dose schedule. The study was conducted from October 2006 to October 2008 and performed in the United Kingdom across nine sites. Randomisation by web-based system with a block size of four each sites separately. Blinding: participants and relevant staff during the study. Analysis by per protocol.
LE	1
Number of Patients and Characteristics	Potential participants were identified either via health computer databases or directly by general practitioners. 286 infants randomised in this study, 141 were assigned to receive PCV 13 and 145 to receive PCV 7. Health six to 14 weeks old infants were enrolled in the study. Randomisation in 1:1 ratio PCV13 to PCV 7. PCVs given at 2, 4, and 12 months of age.
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • After primary immunisation, the percentage of PCV 13 recipients with serotype-specific IgG concentration > 0.35µg/mL for the six non-PCV 7 serotypes ranged from 79.2% (serotype 6A) to 97.2% (serotype 1). • No more than 17.5% of PCV 7 recipients reached this threshold for five of these six serotypes. • At 13 months of age, >97% of PCV13 recipients had pneumococcal serotype-specific serum IgG concentrations ≥0.35µg/mL for each vaccine serotype except serotype 3 (88.2%), • Following immunisation with PCV 13 at 2 and 4 months of age, OPA titers of > 1.8 were seen in > 88% of participants for each of the 13 vaccine serotypes but four types of serotypes the percentages were below 50%. • At 5 months, 110/114 (96.5%) of PCV13 recipients and 100/102 (98.0%) of PCV7 recipients had serum anti-PRP (Hib) IgG concentration ≥0.15 µg/mL (difference, 1.5%; CI, - 7.1%, -3.7%), while 119/120 (99.2%) and 117/118 (99.2%), respectively, had MenC serum bactericidal assay titers of ≥1:8. All PCV13 recipients and 110/113 (97.3%) of PCV7 recipients had IgG concentrations against fimbrial agglutinogens of ≥2.2 EU/mL; IgG concentrations for the remaining pertussis antigens were ≥5 EU/mL for all participants. • Local reactions and systemic events were similar in the PCV13 and PCV7 groups. • A 2-, 4-, and 12-month course of PCV13 was immunogenic for all 13 vaccine serotypes and was well tolerated.
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	15. Huu TN, Toan NT, tuan HM et al. Safety and reactogenicity of primary vaccination with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine in Vietnamese infants: a randomised, controlled trial. BMC Infectious Diseases 2013, 13:95 http://www.biomedcentral.com/1471-2334/13/95
Study Type / Methods	Randomised control trial. This phase III, open-label, randomized study was conducted between February 2011 and July 2011 in one of the largest tertiary hospitals of Ho Chi Minh City (the Children Hospital No. 2 [Nhi Dong 2]) in cooperation with the Clinical Research Unit of the Pasteur Institute of Ho Chi Minh City
LE	1
Number of Patients and Characteristics	Study participants were recruited from the hospital vaccination clinic. Eligible participants were healthy infants aged between and including 6–12 weeks (42–90 days) at the time of the first vaccination. Study participants were randomised (2:1 treatment allocation ratio) to receive 3-dose primary vaccination at 2, 3, and 4 months of age with either 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine PHiD-CV coadministered with diphtheria, tetanus, acellular pertussis, hepatitis B virus, inactivated poliovirus and H. influenzae type b vaccine DTPa-HBV-IPV/Hib (PHiD-CV group) or DTPa-HBV-IPV/Hib administered alone (Control group).
Intervention	10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine PHiD-CV with diphtheria, tetanus, acellular pertussis, hepatitis B virus, inactivated poliovirus and H. influenzae type b vaccine DTPa-HBV-IPV/Hib
Comparison	diphtheria, tetanus, acellular pertussis, hepatitis B virus, inactivated poliovirus and H. influenzae type b vaccine alone
Length of Follow Up	
Outcome Measures / Effect Size	<p>Results:</p> <ul style="list-style-type: none"> • Within 31 days post-vaccination, 8.2% of overall doses in the PHiD-CV group and 3.0% of overall doses in the Control group were followed by at least one solicited and/or unsolicited, local and/or general adverse event of grade 3 intensity. • Pain at injection site was the most common grade 3 solicited symptoms, which was reported following 6.5% (95% CI: 4.7, 8.8) of overall doses in the PHiD-CV and 1.0% (95% CI: 0.2, 2.9) Control groups, respectively. • Within 4 days post vaccination, the most common solicited local and general symptoms reported with any intensity were pain 48.9% of doses in the PHiD-CV and 31.0% of the doses in Control groups) • Irritability (58.0% of doses in the PHiD-CV and 40.4% of doses Control groups). • Within 31 days post-vaccination, the incidence of unsolicited symptoms was comparable in both groups (following 12.3% of doses in the PHiD-CV and 14.8% of doses Control groups, respectively). • Throughout the study, 13 serious adverse events (SAEs) were reported in 9 infants in the PHiD-CV group and 11 SAEs in 6 infants in the Control group. None of them were fatal or considered causally related to vaccination.
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	16. Esposito S, Tansey S, Thompson A et al. Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine Compared to Those of a 7-Valent Pneumococcal Conjugate Vaccine Given as a Three-Dose Series with Routine Vaccines in Healthy Infants and Toddlers, <i>Clinical And Vaccine Immunology</i> , 2010, p. 1017–1026 Vol. 17, No. 6 1556-6811/10/\$12.00 doi:10.1128/CVI.00062-10
Study Type / Methods	RCT: This study compared the safety of PCV13 with those of PCV7 when given as part of the pediatric vaccination schedule recommended in Italy.
LE	1
Number of Patients and Characteristics	A total of 606 subjects were randomly assigned to receive either PCV13 or PCV7 at 3, 5, and 11 months of age; all subjects concomitantly received diphtheria-tetanus-acellular pertussis/hepatitis B-inactivated polio-Haemophilus influenzae type B (DTaP-HBV-IPV/Hib) vaccine
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Overall, the safety profile of PCV13 was similar to that of PCV7. Most of the local reactions in the two vaccine groups were mild in severity and lasted 1 or 2 days. No statistically significant differences between vaccine groups were observed after doses 1 and 2 of the infant series or after the toddler dose. There were no significant differences between vaccine groups in the incidence of systemic events
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	17. Bryant KA, Block SL, Baker SA et al. Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine. <i>Pediatrics</i> 2010; 125; 866. DOI: 10.1542/peds.2009-1405
Study Type / Methods	RCT: The safety of PCV7 were compared with those of 13-valent PCV (PCV13),
LE	1
Number of Patients and Characteristics	Infants were randomly assigned to receive PCV13 or PCV7 at ages 2, 4, and 6 months with other vaccines.
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Local reactions and systemic events were similar between groups. PCV13 was well tolerated
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	18. Kim DS, Shin SH, Lee HJ, et al. Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine Given to Korean Children Receiving Routine Pediatric Vaccines. <i>Pediatr Infect Dis J</i> 2013;32: 266–273
Study Type / Methods	RCT: The safety of PCV 13 and PCV 7 were compared when administered with routine vaccines at 6 sites in Korea
LE	1
Number of Patients and Characteristics	Healthy infants (n = 180) were randomly assigned (1:1) to receive PCV13 or PCV7 at 2, 4, 6 (infant series) and 12 months (toddler dose). Safety was assessed.
Intervention	PCV13
Comparison	PCV10
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Vaccine safety profiles were similar. Incidence of systemic events was generally similar in both groups (. Fever was mostly mild, and there were no cases of severe fever.
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	19. Silfverdal SA, Flodmark CE, Rombo L et al. 13-Valent pneumococcal conjugate vaccine (PCV13) in children partially immunized with 7-valent pneumococcal conjugate vaccine (PCV7): A phase 3, open-label trial. <i>Vaccine</i> 31 (2013) 1284– 1292
Study Type / Methods	Phase 3 open label study: evaluated safety of PCV13 in Swedish infants and toddlers previously given 1 or 2 doses of PCV7 during infancy.
LE	1
Number of Patients and Characteristics	Healthy infants previously given PCV7 at ages 3 months (group 1; n = 118) or 3 and 5 months (group 2; n = 116) received PCV13 at ages 5 (group 1) and 12 months (both groups). Local reactions and systemic events were collected for 7 days postvaccination. Other adverse events were also collected.
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Local reactions and fever were mostly mild or moderate. From the study it was found that PCV13 was safe in infants and toddlers previously partially immunized with PCV7.
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	20. Weckx LY, Thompson A, Berezin EN et al. A phase 3, randomized, double-blind trial comparing the safety and immunogenicity of the 7-valent and 13-valent pneumococcal conjugate vaccines, given with routine pediatric vaccinations, in healthy infants in Brazil. <i>Vaccine</i> .2012;30: 7566– 7572
Study Type / Methods	Phase III, randomized, multicenter, double-blind study in Brazil. Safety objectives: Incidence rates of local reactions, systemic events, and unsolicited adverse events (AEs) after PCV13 vaccination relative those after PCV7. Subjects were randomly assigned in a 1:1 ratio to receive either PCV13 or PCV7.
LE	1
Number of Patients and Characteristics	No. of patients: 354 enrolled (177 in each group) Healthy infants aged 1 month (28–54 days)
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	<ul style="list-style-type: none"> Duration of study was 18 months.
Outcome Measures / Effect Size	Outcomes <ul style="list-style-type: none"> Reported local reactions and systemic events were similar in both groups
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	21. Huang LM, Lin TY, Juergens C. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccines in Taiwan. <i>Vaccine</i> . 2012; 30: 2054– 2059
Study Type / Methods	Randomized, multicenter, double-blind in Taiwan. The objective was to evaluate safety of PCV13 compared to PCV7. Subjects were randomly assigned in a 1:1 ratio to receive PCV13 or PCV7 at 2, 4 and 6 months (infant series), and 15 months (toddler dose)
LE	1
Number of Patients and Characteristics	168 enrolled (84 in each group) Day 42-98 healthy infant
Intervention	PCV13
Comparison	PCV10
Length of Follow Up	Followup : Duration of study was 15 months.
Outcome Measures / Effect Size	Outcomes: <ul style="list-style-type: none"> Local reactions and systemic events were similar in both groups. No AE, deaths or discontinuation due to AEs
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	22. Vanderkooi OG, Scheifele DW, Girgenti D, et al. Safety and immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers given with routine pediatric vaccination in Canada. <i>Vaccine</i> . 2012; 30: 2054– 2059
Study Type / Methods	Phase III, randomised, multicenter, double-blind study in Canada. The objective was to evaluate the safety responses to concomitant routine childhood vaccines when given with PCV13, compared with PCV7. Subjects were randomized 1:1 to receive either PCV13 or PCV7 at 2,4 and 6 months (primary infant series) followed by toddler booster at 12 months
LE	1
Number of Patients and Characteristics	No of patient : 603 were enrolled (300 in PCV13 group, 303 in PCV7 group)
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	Follow up : Duration of study was 23 months.
Outcome Measures / Effect Size	Outcomes: <ul style="list-style-type: none"> Local reactions and systemic events were similar in both groups No AE, deaths or discontinuation due to AEs
Comments	

Evidence Table : SAFETY**Question : Is 10-valent and 13-valent pneumococcal conjugate vaccines safe?**

Bibliographic Citation	23. Snape MD, Klinger CL, Daniels ED et al. Immunogenicity and Reactogenicity of a 13-valent Pneumococcal Conjugate Vaccine Administered at 2, 4, and 12 Months of Age – A Double-blind Randomized Active Controlled Trial. <i>The Paediatric Infectious Disease Journal</i> , 2010(Dec);29(12):e80-e90.
Study Type / Methods	Phase III, randomised, double blind, active-controlled study. The aim of study to assess the tolerability of PCV 13 given according to this reduced dose schedule. The study was conducted from October 2006 to October 2008 and performed in the United Kingdom across nine sites.
LE	1
Number of Patients and Characteristics	Potential participants were identified either via health computer databases or directly by general practitioners. 286 infants randomised in this study, 141 were assigned to receive PCV 13 and 145 to receive PCV 7.
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Local reactions and systemic events were similar in the PCV13 and PCV7 groups.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	24. Rozenbaum MH, Sanders EAM, Jan van Hoek et al. Cost effectiveness of pneumococcal vaccination among Dutch infants: an economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines. 2010; 340:c2509 doi:10.1136/bmj.c2509
Study Type / Methods	Economic evaluation comparing PCV-7, PCV-10, and PCV-13 with no vaccination using a decision tree analytic model
LE	II-2
Number of Patients and Characteristics	A cohort of 180 000 newborns followed until 5 years of age.
Intervention	PCV 10 or PCV 13, PCV 7
Comparison	No vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<p>A cohort of 180,000 newborns was run through the decision tree once as a vaccinated cohort and once as an unvaccinated cohort. The analytic time frame was 5 years.</p> <ul style="list-style-type: none"> In the base case analysis, the estimated burden of pneumococcal infection for a birth cohort followed for 5 years was 170788 cases of otitis media and 198358 cases of non-invasive pneumonia. Under base case assumptions—that is, assuming a five year protective period of the vaccine and no assumed net indirect effects (herd protection minus serotype replacement) among children aged over 5 years—vaccination with PCV-7 in a four dose (3+1) schedule was estimated <ul style="list-style-type: none"> To prevent 71 cases of invasive pneumococcal disease, 5372 (31%) of otitis media and 406 cases non-invasive pneumococcal disease in children aged up to 5 years. This corresponds with a total net gain of 27 and 2 QALYs respectively. Additionally 71 cases of invasive disease would be prevented by vaccination with PCV-7 corresponding to a gain of 173 life years or 248 QALYs. Compared to no vaccination, PCV -10 would prevent 6124 cases of otitis media, 463 cases of non-invasive pneumonia, and 258 cases of invasive pneumococcal disease, Overall these health benefits would result in a gain of 707 QALYs. Vaccination with PCV-13 would prevent 6876 cases of otitis media, 520 cases of non-invasive pneumonia, and 331 cases of invasive pneumococcal disease, resulting in a total gain of 891 QALYs. The incremental cost effectiveness ratio of PCV-7 was estimated at €13 891 (£98 300; \$145 000) per QALY, well over the ratio of €0 000 per QALY required for PCV-7 to be regarded as potentially cost effective. The incremental cost effectiveness ratios for the PCV-10 was €2 947 per QALY while for PCV-13 it was €0 042 per QALY <p>The current Dutch infant vaccination programme of four doses of PCV-7 is not cost effective because of increases in invasive disease caused by nonvaccine serotypes, which reduces the overall direct effects of vaccination and offsets potential positive herd protection benefits in unvaccinated individuals. The 10 valent and 13 valent pneumococcal vaccines could have better net health benefits than PCV-7 through less replacement disease and increased herd protection. Both these effects could substantially reduce the incremental cost effectiveness ratio to possibly acceptable levels, if total programme costs can be lowered by reduced schedules, reductions in vaccine prices, or both.</p>
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	25. Klok RM, Lindkvist RM, Ekelund M, et al. Cost-Effectiveness of a 10- Versus 13-Valent Pneumococcal Conjugate Vaccine in Denmark and Sweden. <i>Clinical Therapeutics</i> /Volume 35, Number 2, 2013
Study Type / Methods	<p>Cost effectiveness:</p> <p>A previously published decision-analytic model was used to estimate the impact of PCV10 and PCV13 on reducing cases of invasive pneumococcal disease (IPD), pneumonia (PNE), and acute otitis media (AOM) by using country-specific incidence, serotype coverage, disease sequelae, mortality, vaccine effectiveness, indirect effects, costs, and utilities. Direct effects for PCV13- and PCV10-covered serotypes were assumed similar to PCV7. PCV13 was assumed to confer an indirect effect, similar to PCV7, whereas PCV10 was not. Assumptions were tested in sensitivity analyses.</p>
LE	II-2
Number of Patients and Characteristics	<p>Individuals</p> <p>entered the model with either a PCV10 or a PCV13 NIP in place. Children aged ≥ 1 year were vaccinated with either PCV10 or PCV13; vaccinated children were assumed to receive the full primary series of the respective vaccine as indicated by the country-specific NIP and a booster dose in their second year of life</p>
Intervention	PCV13
Comparison	PCV-10
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • PCV13 is expected to save 280.7 million DKK (Danish kroner) in Denmark and 288.2 million SEK (Swedish kronor) in Sweden in direct costs compared with a vaccination program with PCV10. • In both Denmark and Sweden, the results of this study indicate that, compared with PCV10, PCV13 will have a greater impact on disease in life-years gained (LYG), quality-adjusted life-years (QALYs) gained, IPD cases avoided, PNE cases avoided, AOM cases avoided, and in deaths avoided. • For Denmark PCV13, it was estimated to result in 10,051 LYG; 9063 QALYs gained; 237 additional IPD cases avoided; 12,094 additional PNE cases avoided; 958 additional cases of AOM avoided; and 882 additional deaths avoided. • For Sweden PCV13, it was estimated to result in 4245 LYG; 3953 QALYs gained; 379 additional IPD cases avoided; 8210 additional PNE cases avoided; 1459 additional cases of AOM avoided; and 378 additional deaths avoided. • In all sensitivity analyses, PCV13 was less costly and more effective compared with PCV10. <p>According to the author, In this analysis, a national immunization program with PCV13 was found to be good value for money and estimated to prevent additional cases of disease among children and nonvaccinated individuals and save additional costs due to treatment of pneumococcal disease, when compared with PCV10 in Denmark and Sweden.</p>
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	26. Gomez JA, Tirado JC, Rojas AAN et al. Cost-effectiveness and cost utility analysis of three pneumococcal conjugate vaccines in children of Peru. BMC Public Health 2013, 13:1025 doi: 10.1186/1471-2458-13-1025
Study Type / Methods	Cost effective and cost utility: A Markov model that simulated the disease processes in a birth cohort over a lifetime, within 1,128 month cycles was used to evaluate the cost-effectiveness of 10-valent pneumococcal NTHi protein D conjugate vaccine (PHiD-CV) and 7- and 13-valent PCVs (PCV-7 and PCV- 13). Expected quality-adjusted life years (QALYs), cost-savings and incremental cost effectiveness ratios (ICERs) were calculated. Time horizon :Lifetime, Perspective : Payers of the healthcare system Discounting: 3.5% for costs and health events
LE	II-2
Number of Patients and Characteristics	Newborn cohort of 2007 (500,700) Time horizon :Lifetime, Perspective : Payers of the healthcare system Discounting: 3.5% for costs and health events
Intervention	PCV-7, PCV-13, and 10-valent pneumococcal NTHi protein D conjugate vaccine (PHiD-CV)
Comparison	No vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> Without vaccination, pneumonia was associated with the greatest health economic burden (90% of QALYs lost and 63% of lifetime direct medical costs); while acute otitis media (AOM) was responsible for 1% of QALYs lost and 25% of direct medical costs. PCV-13 was estimated to generate 719 more QALYs gained than PCV-7 at an additional investment of US\$ 1.3 million, making it a cost-effective intervention compared to PCV-7 for Peru. PHiD-CV was estimated to generate 769 more QALYs gained than PCV-7 with a reduced investment (–US\$ 2.1 million); in addition, PHiD-CV was estimated to generate 50 more QALYs gained than PCV-13 with a reduced investment (–US\$ 3.4 million), hence suggesting PHiD-CV being most cost-effective (discounted data), Although PCV-13 is predicted to save 20 more LYs than PHiD-CV, at an incremental investment of US\$ 3.4 million (compared to PHiD-CV), the ICER of PCV-13 versus PHiD-CV is US\$ 170,391 per LY saved (greater than the 3 GDP per capita threshold for Peru) The probabilistic sensitivity analysis showed that PHiD-CV generated more QALYs gained at a reduced cost than PCV-13 in 84% of the simulations and less QALYs gains at a reduced cost in 16%. Additional scenarios using different assumptions on vaccine efficacies based on previous evidence were explored, but no significant change in the overall cost-effective results were observed. The results of this modeling study predict that PCVs are likely to be a cost-effective strategy to help relieve the epidemiological and economic burden associated with pediatric pneumococcal and NTHi diseases for Peru. PHiD-CV is likely to be a dominant (better health gains at a reduced net cost) intervention compared to PCV-13 or PCV-7. The most significant drivers for these results are the better health and economic profile of PHiD-CV against AOM and its reduced cost per dose available through the PAHO Revolving Fund in the LAC region.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	27. Ayieko P,Griffiths UK, Ndiritu M et al. Assessment of Health Benefits and Cost-Effectiveness of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccination in Kenyan Children. PLOS ONE, 2013, Volume 8, Issue 6, e67324
Study Type / Methods	<p>Estimated the cost-effectiveness of introducing either PCV10 or the13-valent vaccine (PCV13) from a societal perspective (considering both medical and non-medical costs and productivity losses) and explored the incremental impact of including indirect vaccine effects. Direct vaccine effects were estimated as a reduction in the incidence of pneumococcal meningitis, sepsis, bacteraemic pneumonia and non-bacteraemic pneumonia.</p> <p>Pneumococcal disease incidence was extrapolated from a population-based hospital surveillance system in Kilifi. Vaccine efficacy estimated from a trial in The Gambia.</p> <p>Multivariable sensitivity analysis was conducted using Monte Carlo simulation.assumed a vaccine price of US\$ 3.50 per dose. The base case analysis compared the discounted (3% per year) costs and effects of universal PCV vaccination to those associated with no PCV</p>
LE	II-2
Number of Patients and Characteristics	The costs and effects of pneumococcal vaccination among infants born in Kenya in 2010 were assessed using a decision analytic model comparing PCV10 or PCV13, in turn, with no vaccination. A total of 1,407,000 infants born in Kenya in 2010 contributed 6,680,436 child-years of observation during the first five years of life.
Intervention	PCV10 or PCV13
Comparison	no vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> The annual cost of delivering PCV10 was approximately US\$14 million. The authors projected a 42.7% reduction in pneumococcal disease episodes leading to a US\$1.97 million reduction in treatment costs and a 6.1% reduction in childhood mortality annually. In the PCV10 base case analysis, assuming no indirect effects, a 3% discount rate and a price of US\$ 3.50 per dose, the cost effectiveness ratio for PCV10 versus status quo was US\$59 (95% CI, 26–103) per DALY averted, US\$ 300 (95% CI, 145–488) per case averted and US\$ 1,958 (95% CI, 866–3,425) per death averted . Working with the same assumptions, cost effectiveness of PCV13 versus status quo was US\$ 47 (95% CI, 20– 83) per DALY averted, US\$ 238 (95% CI, 110–390) per case averted and US\$ 1,558 (95% CI, 665– 2,764) per death averted, PCV13 introduction improved the cost-effectiveness ratios by approximately 20% and inclusion of indirect effects improved cost-effectiveness ratios by 43– 56%. The Kenya Government currently pays \$0.20 per dose under a co-financing arrangement with GAVI. From the Government perspective, introduction of either PCV10 or PCV13 is cost saving. The break-even prices for PCV10 and PCV13 are US\$ 0.41 and US\$ 0.51, respectively. Hence introducing either PCV10 or PCV13 in Kenya is highly cost-effective from a societal perspective.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	28. Hosh SL, Kondo M, Okubo I. Economic evaluation of vaccination programme of 13-valent pneumococcal conjugate vaccine to the birth cohort in Japan. <i>Vaccine</i> 31 (2013) 2762– 2771. http://dx.doi.org/10.1016/j.vaccine.2013.03.052
Study Type / Methods	A cost-effectiveness analysis with Markov model and calculated incremental cost effectiveness ratios (ICERs) The author appraise the 'value for money' of replacing PCV-7 with PCV-13 vaccination programme in Japan. The authors set two base-cases for analyses: "Base-case A", which assumes that the prevention of AOM by PCV-13 is limited to the seven serotypes of PCV-7 only; and "Base-case B", which assumes that the prevention of AOM by PCV-13 is straightforwardly extended to cover non-PCV-7 serotypes.
LE	II-2
Number of Patients and Characteristics	The author define two vaccination programmes: current PCV-7 programme and the possible replacement, i.e., PCV-13 programme, with the same vaccination schedule (3 + 1). It was assumed that vaccination is fully subsidised for the uptake of 4 doses of either PCV-7 or PCV-13. The birth cohorts of 5 years used in the model are from Population estimates of Japan
Intervention	PCV 13
Comparison	No vaccination programme
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> The estimated disease cases avoided by PCV-7/PCV-13 vaccination programme compared with no programme for 100,000 birth cohort in the 5-year period are as follow: 8.2/9.7 cases of meningitis, 49.4/58.4 cases of bacteraemia, 1739.4/2112.9 cases of hospitalized pneumonia, 66,188/66,188 (Base-case A) or 72,728 (Base-case B) of AOM, and 1.86/2.26 cases of death due to either meningitis, bacteraemia or pneumonia. If PCV-13 replaces PCV-7, the estimated incremental number of avoided cases will be: 1.49 of meningitis, 8.94 of bacteraemia, 373.5 of hospitalised pneumonia, none or 6540.2 of AOM in Base-case A or Base-case B, respectively, and 0.40 cases of death due to either meningitis, bacteraemia or pneumonia. The reduced disease cases resulting from replacing PCV-7 with PCV-13 would be 18.1%, 21.5%, and 9.9%, for IPD, hospitalized pneumonia, and AOM, respectively. The results show that in Base-case A (assumed PCV-13 has no additional protection against AOM compared to PCV-7), replacing PCV-7 with PCV-13 will cost ¥37,722,901 (US\$471,536) or ¥35,584,455 (US\$444,850) per QALY when the caregiver's productivity loss is not included or is included, respectively. While in Base-case B (assumed PCV-13 has additional protection against AOM compared to PCV-7), ¥343,830 (US\$4298) per QALY or more QALY is gained by saving money without or with caregiver's productivity loss, respectively. Also, in Base-case B if cost per PCV-13 shot is equal to or less than that ¥17,000, then a PCV-13 vaccination programme offered to the birth cohort in Japan is likely to be a socially acceptable option compared to the current PCV-7 vaccination programme. Furthermore, if cost per PCV-13 shot is equal to or less than ¥12,000, replacing PCV-7 with PCV-13 will save money and gain more QALYs. While in Base-case A, the replacement can only be socially acceptable if cost per PCV-13 shot is equal to or less than ¥11,000.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	29. Earnshaw SR, McDade CL, Zanotti G et al. Cost-effectiveness of 2 + 1 dosing of 13-valent and 10-valent pneumococcal conjugate vaccines in Canada BMC Infectious Diseases 2012;12:101
Study Type / Methods	Cost effectiveness analysis using decision-analytic model The objective was to examine public health and economic impacts of a PCV10 and PCV13 pediatric national immunization programs (NIPs) in Canada.
LE	II-2
Number of Patients and Characteristics	34,108,000 individuals within Canada were considered. 1.4% (477,512) children < 2 years of age were considered for the vaccinated cohort. The remaining individuals comprised the non-vaccinated cohorts, which included individuals aged 2 to<5, 5 to <18, 18 to<65, and 65+ years.
Intervention	PCV13
Comparison	PCV10
Length of Follow Up	Followup : Duration of study was 15 months. 2 dose of primary series, followed by booster at 12 to 15 months
Outcome Measures / Effect Size	<p>Outcomes:</p> <p>PCV13 was found to be more cost-effective compared to PCV10: Disease prevention found more in PCV13 versus PCV10.</p> <ul style="list-style-type: none"> • 49,340 more cases of disease were prevented with PCV13 when both direct and indirect effects (Specifically, 4,084 cases of bacteremia, 144 of meningitis, 8,760 of inpatient PNE, 6,201 of outpatient PNE, 27,001 of mild AOM, and 3,150 of moderate/ severe AOM were prevented annually when vaccinating children with PCV13.) • As a result, the population gained 15,283 more life-years and 13,828 more QALYs when vaccinating children with PCV13 versus PCV10 • Approximately 879 deaths could be prevented annually and annual direct medical costs were reduced by \$132.8 million when vaccinating children with PCV13 versus than PCV10. • When considering direct effects only, we observed 7,466 more cases of disease (52 more cases of bacteremia, 2 of meningitis, 1,300 of inpatient PNE, 1,072 of outpatient PNE, 4,327 of mild AOM, and 713 of moderate/severe AOM) were prevented annually when vaccinating children with PCV13 versus PCV10. • As a result, the population gained 287 more life-years and 258 more QALYs when vaccinating children with PCV13 versus PCV10. • Approximately 14 deaths could be prevented annually and annual direct medical costs (including the cost of vaccination) were reduced by \$5.7 million when vaccinating children with PCV13 versus than PCV10. • Thus, PCV13 was found to dominate PCV10. • Assuming a total per-dose cost of PCV10 of \$94.10 (acquisition and administration) and considering a threshold incremental cost per QALY of \$50,000, the cost per dose for PCV13 could be as high as \$737.11 to remain cost-effective, when both direct and indirect effects were considered. <p>According to the author, Considering the epidemiology of pneumococcal disease in Canada, PCV13 is shown to be a cost-saving immunization program because it provides substantial public health and economic benefits relative to PCV10.</p>
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	30. Blank PR and Szucs TD. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine in Switzerland. <i>Vaccine</i> . 2012; 30: 4267-4275
Study Type / Methods	Cost effectiveness analysis on PCV7 vs PCV13 using decision-analytic model structure The objective was to assess the potential health benefits and costs associated with pneumococcal vaccination strategies in Switzerland
LE	II-2
Number of Patients and Characteristics	Hypothetical cohort of general population in Switzerland
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<p>A decision-analytic model was constructed to estimate direct medical costs and clinical effectiveness of PCV13 vaccination on invasive pneumococcal disease (IPD), pneumonia, and otitis media relative to PCV7 vaccination. The option with an one-dose catch-up vaccination in children of 15–59 months was also considered. Assuming 83% vaccination coverage and considering indirect effects, 1808 IPD, 5558 pneumonia and 74,136 otitis media cases could be eliminated from the entire population during a 10-year modelling period.</p> <p>Outcomes:</p> <ul style="list-style-type: none"> • Reduction in disease cases in PCV 13, Avoided additional 215 IPD related fatalities • PCV13 vaccination programme would lead to additional costs (+€26.2 Mio), but saved medical costs of –€77.1 Mio due to cases averted and deaths avoided (total cost savings –€50.9 Mio). • PCV13 saved 23,242 life years and gained 18,172 QALYs over 10 year period • If no herd protection would be considered, the cost-effectiveness ratio would increase to EUR 16,342 per QALY gained with costs of EUR 10 per child vaccinated <p>Hence, the study showed that PCV13 would result in cost-saving situation compared to PCV7.</p>
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	31. Díez- Domingo J, I Ridao-López M, Gutiérrez-Gimeno et al. Pharmacoeconomic assessment of implementing a universal PCV-13 vaccination programme in the Valencian public health system (Spain). <i>Vaccine</i> . 2011; 29: 9640– 9648
Study Type / Methods	<p>Cost-effective analysis ;</p> <p>The objective of this study was to estimate the potential health benefits and the associated costs of introducing PCV13 vaccination as 2 + 1 schedule in the Community of Valencia,Spain</p> <p>Information about disease incidence and serotype distribution were gathered from local databases and from published and unpublished local records</p> <p>PCV13 effectiveness was extrapolated from PCV7 efficacy data.</p> <p>A 5% of herd effect and a serotype replacement of 25% were considered for the base case scenario.</p> <p>Only direct costs were taken into account and results were expressed in terms of life-years gained (LYG) and quality adjusted life years (QALY)</p>
LE	II-2
Number of Patients and Characteristics	
Intervention	PCV13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> • Universal PCV13 vaccination program would decrease the number of hospital admission due to pneumonia (< 4571 cases), avoiding 310 cases of IPD, and 82,596 cases of AOM, averting 190 S. pneumoniae related deaths • Total medical costs of non-vaccinating the cohort of newborns would reach up to 403,850.859 € compared to 438,762.712 € that would represent vaccinating the cohort. • The incremental cost of vaccinating the children was estimated in 12,794 €/LYG and 10,407 €/QALY <p>Conclusion:</p> <ul style="list-style-type: none"> • A universal PCV13 vaccination program would be a cost effective intervention
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	32. Jan van Hoek A, Choi YH, Trotter C, et al. The cost effectiveness of a 13-valent pneumococcal conjugate vaccination for infants in England. <i>Vaccine</i> . 2012; 30: 7205-7213
Study Type / Methods	<p>A cost effectiveness analysis</p> <p>The objective was to investigate the cost effectiveness of the introduction of PCV13</p> <p>Using an infectious disease model which projected herd immunity and serotype replacement effects</p> <p>The economic impact of replacing PCV7 with PCV13 was compared to stopping the use of pneumococcal conjugate vaccination altogether</p> <p>In the base case, a discount rate of 3.5% per annum was used for costs and benefits, in conjunction with a 30 years time horizon</p>
LE	II-2
Number of Patients and Characteristics	
Intervention	PCV 13
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> Discontinuing PCV7 would lead to an increased in invasive pneumococcal disease, costs and loss of quality of life compared to the introduction of PCV13. Under base case assumptions (assuming no impact on non-invasive disease, maximal competition between vaccine and non-vaccine types, time horizon of 30 years, vaccine price of £49.60 a dose + £7.50 administration costs and discounting of costs and benefits at 3.5%) the introduction of PCV-13 is only borderline cost effective compared to a scenario of discontinuing of PCV-7. The intervention becomes more cost-effective when projected impact of non-invasive disease is included or the discount factor for benefits is reduced to 1.5%. Using a threshold of £30,000 per QALY gained, introducing PCV- 13 is cost-effective in 100% of parameter combinations sampled if non-invasive disease outcomes are included, but only 53% if they are not. Replacing PCV7 with PCV13 is less cost- effective than introducing PCV13 in a situation with no pneumococcal vaccination
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	33. By A, Sobocki P, Forsgren A, Silfverdal SA. Comparing Health Outcomes and Costs of General Vaccination with Pneumococcal Conjugate Vaccines in Sweden: A Markov Model Clinical Therapeutics 2012; 34(1): 177-189
Study Type / Methods	<p>Cost-effectiveness analysis</p> <p>The objective was to estimate the expected health outcomes, costs, and incremental cost-effectiveness ratio (ICER) of routine vaccination with the 10-valent pneumococcal PHiD-CV compared to PCV13 in Sweden</p> <p>A Markov cohort model was used to estimate the effect of vaccination at vaccine steady state, taking a societal perspective and using a 2+1 vaccination schedule</p>
LE	II-2
Number of Patients and Characteristics	
Intervention	PHiD-CV (PCV10)
Comparison	PCV13
Length of Follow Up	
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> The vaccine efficacy was adjusted for serotype coverage in Sweden, and the maximum effectiveness for PHiD-CV (PCV 10) and PCV13 was calculated to be 82.2% (children <2 years), 81.9% (children 2–5 years) PCV13 would prevent 3 additional cases of invasive pneumococcal disease and 34 additional cases of pneumonia PHiD-CV would avoid 3 additional cases of mastoiditis, 1010 tube insertions, and 10,420 cases of ambulatory acute otitis media compared with PCV13. PCV13 was estimated to save direct costs due to ID and CAP of 2.5 million SEK compared with PHiD-CV, whereas PHiD-CV was estimated to save direct costs due to AOM of 37 million SEK. Including the indirect costs, an additional 33 million SEK were avoided with PHiD-CV. Hence, the total costs saved with PHiD-CV compared with PCV13 were estimated at 67 million SEK, or 62 million SEK with a 3% discount rate. By combining morbidity and mortality benefits of all clinical outcomes, PHiD-CV would generate 45.3 additional QALYs compared with PCV13 and generate savings of an estimated 62 million Swedish kronors. Hence, PHiD-CV was the dominant vaccination alternative compared with PCV13.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	34. Lee KKC, Wu DBC, Topachevskiy O, et al. The Health Economic Impact of Universal Infant Vaccination with the 10-Valent Pneumococcal Nontypeable Haemophilus influenzae Protein D Conjugate Vaccine as Compared with 13-Valent Pneumococcal Conjugate Vaccine in Hong Kong. Value in Health Regional Issues 2013;2: 64-74
Study Type / Methods	<p>Economic evaluation analysis</p> <p>The objective was to assess the health and economic impact of PCV10 compared with the current PCV13</p> <p>An analytical model was used to estimate the annual economic and health outcomes of invasive pneumococcal disease (IPD), community acquired pneumonia, and acute otitis media (AOM), including nontypeable H. influenzae-related AOM</p> <p>From the payer perspective with a 10-year horizon.</p>
LE	II-2
Number of Patients and Characteristics	
Intervention	PCV10
Comparison	PCV13
Length of Follow Up	PCV10 and PCV13 given as three doses in the first 6 months of life, with a booster at age 12 to 15 months.
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> Model projections indicate that PCV-13 and PCV-10 have approximately equivalent impact on the prevention of deaths caused by IPD and pneumonia. PCV-13 is projected to prevent 6 additional cases of IPD, whereas PCV-10 is projected to prevent 13,229 additional AOM cases and 101 additional QALYs. For the base case, PCV-10 vaccination is estimated to save 44.6 million Hong Kong dollars (discounted by using a 5.0% discount rate). The overall savings of HKD 44.62 million were largely linked to the reduction in AOM disease burden Vaccination with PCV-10 generated 90 (101 undiscounted) more QALYs with overall cost savings as compared with PCV-13. The PCV-10 vaccination program was expected to be cost saving as compared with the PCV-13 vaccination program. Hence, this study suggested that PCV10 vaccination would be potentially a cost-saving strategy and better QALYs gain compared with PCV13 vaccination
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	35. Strutton DR, Farkouh RA, Earnshaw SR, et al. Cost-effectiveness of 13-valent pneumococcal conjugate vaccine: Germany, Greece and The Netherlands. Journal of Infection (2012) 64. 54-67
Study Type / Methods	Cost-effectiveness analysis using decision-analytic model The objective was to examine public-health and economic impacts of pneumococcal vaccine on paediatric national immunization programs (NIPs) in Germany, Greece, and the Netherlands
LE	II-2
Number of Patients and Characteristics	
Intervention	PCV13
Comparison	PCV10, PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> • PCV13 was estimated to eliminate 31.7% of IPD in Germany, 46.4% in Greece and 33.8% in The Netherlands. • Compared with PCV7 and PCV10, PCV13 was found to be cost-effective or cost saving in all cases when PCV13 indirect effects were included. • PCV13 resulted in greater reductions in medical costs (excluding vaccine costs) to treat cases of disease in all countries. • As a direct result of the reduction in disease, PCV13 resulted in greater reductions in medical costs (excluding vaccine costs) to treat cases of disease in all countries. When compared with PCV7, PCV13 was estimated to be a more effective and less costly strategy (i.e., cost saving) in Germany and Greece. PCV13 was estimated to be cost-effective (i.e., cost per QALY €20, 000) in the Netherlands. When compared with PCV10, PCV13 was estimated to be cost saving in Germany, Greece, and the Netherlands.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	36. Castañeda-Orjuela C, Alvis-Guzmán N, Velandia-González M, et al. Cost-effectiveness of pneumococcal conjugate vaccines of 7,10 and 13 valences in Colombian children. <i>Vaccine</i> .2012;30: 1936-1943
Study Type / Methods	Cost-effectiveness analysis The objective was to evaluate the cost-effectiveness of the introduction of pneumococcal conjugate vaccines of 7, 10, and 13 valences in the Colombian children A Markov model, which followed a cohort of children under one year to life expectancy,
LE	II-2
Number of Patients and Characteristics	A Markov model, which followed a cohort of children under one year to life expectancy, was developed. Parameters of occurrence and care costs were based on data from National Health System and literature review. PCV-7 is a dominated strategy. PCV-10 and PCV-13 were each compared to no vaccination or PCV-10 vaccination, respectively. A 2 + 1 schedule and a vaccination price of US\$ 14.00, US\$ 14.85 and US\$ 16.34 per dose were assumed in the base case for PCV-7, -10, and PCV-13 vaccines.
Intervention	PCV13
Comparison	PCV10, no vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> • Introduction of PCV-13 rather than PCV-10 increases the number of life years gained (LYG). • From the societal perspective, in the 'competing choice' framework cost per YLG was US\$ 1837 with PCV-10 and US\$ 9514 with PCV-13, while PCV-7 is a dominated strategy. The ICER of PCV-13 is above the per capita Gross Domestic Product. Incremental cost-effectiveness ratios (ICERs) were influenced mainly by effectiveness against radiologically-confirmed pneumonia and AOM, vaccine price, and discount rate. • In the comparison between four alternatives in the Table 4 (not vaccination, PCV-7, -10 and -13), vaccination with PCV-7 is dominated for the other alternatives. PCV-13 has the highest costs and the most results achieved, although in the worst and best scenarios the ranges are overlapped with PCV-10. The ICER of vaccination with PCV-10 (compared with not vaccination) is below the Colombian willingness to pay threshold of 1 per capita GDP (US\$ 1837 per YLG, ranging from cost-saving to US\$ 22,799). In the comparison of PCV-13 versus PCV-10 the ICER is over 1 per capita GDP (US\$ 9516, ranging from US\$ 1184 to 43,352), but is below the 3 per capita GDP. • PCV10 is more cost-effective with ICER below the per-capita GDP, but its inclusion requires evaluating the budget impact. • PCV-13 would prevent more disease and deaths with a higher YLG, but PCV10 would save more cost to the healthcare system due its higher impact in the prevention of AOM.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	37. Beutels P, Blommaert A, Hanquet G, et al Cost-effectiveness of 10- and 13-valent pneumococcal conjugate vaccines in childhood. Health Technology Assessment (HTA). Belgian Health Care Knowledge Centre (KCE). 2011.
Study Type / Methods	Cost-effectiveness analysis (HTA report) To estimate the incremental effectiveness and cost-effectiveness of replacing PCV7 by either PCV10 or PCV13 in Belgium, taking into account the herd immunity and serotype replacement
LE	II-2
Number of Patients and Characteristics	
Intervention	PCV13, PCV10
Comparison	PCV7
Length of Follow Up	
Outcome Measures / Effect Size	<p>Outcomes:</p> <ul style="list-style-type: none"> Both PCV13 and PCV10 vaccines are highly likely to be cost-effective compared to PCV7 Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision-maker either to prevent the less-frequent severe IPD cases only, or to also consider the prevention of the high burden of AOM Using various assumptions about the vaccine effectiveness measures, herd immunity and serotype replacement effects, the results consistently showed that both new vaccines are highly likely to be cost-saving or considered cost-effective versus PCV7, even at their current public pharmacy prices. Excluding the effect of herd immunity and compared to PCV7, the new PCV10 and PCV13 vaccines avoided altogether 113 to 118 IPD, 181 to 236 pneumonia, 587 to 6 317 otitis media and slightly less than 2 deaths. Both PCV13 and PCV10 vaccines are more cost-effective compared to PCV7. A 2+1 schedule is more desirable than a 3+1 schedule. The incremental cost-effectiveness ratio of PCV10 (3+1 schedule) and PCV13 (2+1 schedule) versus PCV7 ranged between dominance (i.e. the new vaccines are both more effective and less costly than PCV7), and €2 400 per quality-adjusted life-year (QALY) gained. PCV13 was preferable (avoids more treatment costs and gains more QALYs) to PCV10 in severe diseases only (i.e. excluding otitis media). When impact on otitis media was included, PCV10 was estimated to avoid more treatment costs than PCV13.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	38. Tyo RK, Rosen M. M, Zeng W et al. Cost-effectiveness of conjugate pneumococcal vaccination in Singapore: Comparing estimates for 7-valent, 10-valent and 13-valent vaccines. <i>Vaccine</i> . 2011;29:6686-6694.
Study Type / Methods	<p>Economic evaluation</p> <p>The aim of the study to quantitatively model the cost and public health impact of adding various pneumococcal vaccination strategies to Singapore's National Childhood Immunisation Programme.</p> <p>Use Markov stimulation model with Singapore –specific population parameters, vaccine costs, treatment costs and disease incidence data.</p> <p>The model estimated impacts over a five year horizon.</p> <p>Discounted 3% per year for costs and health effects.</p> <p>Vaccine efficacy was examine : quality adjusted life years (QALY) gained and deaths averted.</p>
LE	II-2
Number of Patients and Characteristics	<p>The impact of vaccine studied against invasive pneumonia disease (IPD) (meningitis, bacteremia), acute otitis media (AOM) and pneumonia.</p> <p>Targeted population: 0 – 5 year with TreeAge model.</p> <p>Non-vaccinated population: over five years old (divided into three groups: 6-19, 20-59, and 60 plus years)</p>
Intervention	PCV 10 and PCV 13
Comparison	PCV 7 and no vaccination
Length of Follow Up	

<p>Outcome Measures / Effect Size</p>	<ul style="list-style-type: none"> ➤ Reduction in disease <ul style="list-style-type: none"> • Prior to vaccination, the 0 -5 year old population of 226 000 incurred about 86 00 cases of AOM, 2535 cases of pneumonia and 10 cases of meningitis and bacteremia yearly. • The PCV 7 vaccination program would reduce the number of AOM cases by approximately 4900 cases yearly. PCV 10 estimated reducing about 5000 AOM cases and while PCV 13 estimated 5700 AOM cases. • The reduction of pneumonia cases in the vaccinated population varies from 135 to 158 cases with PCV13. • In the non-vaccinated population, 12 382 pneumonia cases and 209 bacteraemia cases were predicted over the same one year period prior to vaccination. • A similar number of cases would be avoided in the non-vaccinated population, reflecting a lower herd immunity effect and low pneumonia incidence. • In addition, PCV 7 and PCV 10 would prevent 7.6 cases meningitis and bacteraemia in the vaccinated population, while PCV 13 would avert 8.8 cases. • Furthermore, the number of bacteraemia cases avoided ranges 31 for PCV 7 to 36 for PCV 13 in the non-vaccinated population. • The estimated death due to pneumonia was 15 deaths in the vaccinated group and 2319 deaths in the non-vaccinated group prior to vaccination. • In addition, the estimated deaths due to IPD were 0.5 per year in the vaccinated group, while 54 deaths (due to bacteraemia) in the non-vaccinated group. • Thus, the model estimated that one death would be avoided yearly from pneumonia and IPD in the vaccinated population. • By PCV 7 and PCV 10 vaccination program, 34 deaths due to pneumonia or bacteraemia would be prevented yearly in the non-vaccinated group, While PCV 13 would avoid 40 deaths by herd immunity. ➤ QALYs gained <ul style="list-style-type: none"> • PCV 7 adds 67 QALYs in the vaccinated population and 269 QALYs through herd effects. • PCV 10 contributes 68 QALYs in direct effects and 277 QALYs through herd effects. • PCV 13 contributes 78 QALYs gained through direct effects and 397 QALYs gained in the unvaccinated population. ➤ Saving and cost-effectiveness <ul style="list-style-type: none"> • PCV 7 and PCV 10 resulted in yearly medical savings USD 1.8M (SGD 2.5M) in the vaccinated population, and this amount of saving would increase to USD 2.1M (SGD 2.9M) for PCV 13. • In addition, when it was projected savings due to herd immunity would total USD 1.5M (SGD 2.0M) for PCV 7, USD 1.5M (SGD 2.1M) for PCV 10 and USD 1.7M (SGD 2.4M) for PCV 13. • Compared to no vaccination, the estimated ICER for PCV 7 was USD 43 275 (SGD 59 610) per QALYs gained, for PCV 10 was USD 45 100 (SGD 62 125) per QALYs gained and PCV 13 was USD 37 644 (SGD 51 854) per QALYs gained. • Without herd effects, the estimated ICER for PCV 13 was USD 204 535 (SGD 281 743) QALYs gained
<p>Comments</p>	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	39. Bocalini S, Azzari C, Resti M et al. Economic and clinical evaluation of a catch up dose of 13-valent pneumococcal conjugate vaccine in children already immunised with three doses of the 7-valent vaccine in Italy. <i>Vaccine</i> . 2011;29:9521-9528.
Study Type / Methods	<p>Economic evaluation.</p> <p>The purpose of this study was to perform a clinical/economic evaluation of the administration of a dose of PCV 13 in a catch up programme for children under five years of age, who had already received three doses of PCV 7.</p> <p>The study used an already developed mathematical stimulation model.</p> <p>The study was performed on the resident population in the province of Florence at 1 January 2010.</p> <p>A discount rate 3% per year to medical costs.</p> <p>The outcomes were number of cases and deaths that would be avoided by the catch-up programme. In addition, cost per case avoided and cost per year of life saved were calculated.</p>
LE	II-2
Number of Patients and Characteristics	<p>Under five years of age.</p> <p>Cases of pneumonia, invasive pneumococcal disease (IPD) and acute otitis media (AOM)</p> <p>Catch-up vaccination programme for PCV 13 from PCV 7.</p>
Intervention	PCV13
Comparison	
Length of Follow Up	
Outcome Measures / Effect Size	<ol style="list-style-type: none"> Reduction in disease <ul style="list-style-type: none"> Following the adoption of catch-up programme with PCV 13, 2.5 deaths / 100 000 from <i>S. pneumonia</i> infection would be avoided for children up to 24 months and 6.6deaths/100 000 would be avoided for children up to 60 months of age. Thus, it estimated 191, 322, 423 and 483 life-years saved for children up to 24, 36, 48 and 60 months of age, respectively Costs <ul style="list-style-type: none"> The mathematical model estimated a saving of more 1 million Euros for children up to 24 months as following the catch-up vaccination programme due to a result of the reduction of expected cases and respective treatment costs. Thus, it forecasts about a saving of almost 3million Euros for children up to 60 months of age. The cost of a catch-up vaccination programme was 3 406 400 Euros (per 100 000) for children up to 24 months with PCV 13. The mean cost per event avoided were 1674 Euros, 1926 Euros, 2195 Euros and 2522 Euros with catch-up programme until 24, 36, 48 and 60 months of age, respectively. The cost per year life saved, the amounts were 12 250 Euros, 15 176 Euros, 18 150 Euros and 22 093 Euros when vaccination children up to 24, 36, 48 and 60 months of age, respectively.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	40. Kim SY, Lee G and Goldie S.J. Economic evaluation of pneumococcal conjugate vaccination in The Gambia. BMC Infectious Disease. 2010;10:260.
Study Type / Methods	Economic evaluation. The objective was to assess the potential impact of PCVs of different valence in The Gambia. The estimated health outcomes averted into disability-adjusted life years (DALYs). Discounted at 3%. Total costs accounted medical costs treatment and non-direct medical costs.
LE	II-2
Number of Patients and Characteristics	Under 60 months of age.
Intervention	PCV 9 (Adjusted the base-case vaccine impact estimates for PCV 7, PCV 10 and PCV 13)
Comparison	No vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<ol style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Vaccinating PCV9 for a cohort of 60 000 infants would be expected to prevent about 1400 (~28%) cases of primary endpoint pneumonia and 13% cases of meningitis and sepsis compared to no vaccination. Thus, it estimated the PCV 13 would prevent about 1650 cases of primary endpoint pneumonia, while 1400 cases and 1040 cases would prevent by PCV10 and PCV 7, respectively when compared to no vaccination. Costs <ul style="list-style-type: none"> The average program cost for vaccinating with PCV 9 (3 doses) would be \$1.02. If \$3.5 per dose, the vaccination programme cost for birth cohort would be about \$685 000. The total cost for PCV 9 would be \$902 040 with vaccination and \$233 100 without vaccination. Therefore, the estimated total costs for PCV 7, PCV 10 and PCV 13 would be \$906 240, \$902 040 and \$899 280, respectively. Combining the primary health and economic outcome measures, the estimated costs of PCV 9 vaccination per DALYs averted was \$670, compared with no vaccination. The numbers of averted DALYs were 740, 1000 and 1180 for PCV 7, PCV 10 and PCV 13, respectively. The incremental cost-effectiveness ratios (ICER) of the PCV's decreased as the valence of the vaccines increased with results of \$910, \$670 and \$570 per DALY averted. If assume the vaccine efficacy decreased by 15% over a five year time horizon, the incremental costs per DALYs averted increased to \$940 (PCV 7), \$690 (PCV 9 and PCV 10) and \$590 (PCV 13). Using the threshold cost-effectiveness of GDP per capita (\$360 in 2005 US\$ for 2008), none of the PCVs would be considered very cost-effective at the unit price of \$3.5, while all the vaccines would be considered cost-effective under the threshold of three times GDP per capita.
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	41. Robberstad B, Frostad C. R, Akselen P. E et al. Economic evaluation of second generation pneumococcal conjugate vaccines. <i>Vaccine</i> . 2011;29:8564-8574.
Study Type / Methods	Economic evaluation. The aim of this study was to estimate incremental costs, health effects and cost-effectiveness of the pneumococcal conjugate vaccines PCV 7, PCV 10 and PCV 13 in Norway. Use Markov model. Discounted 4%.
LE	II-2
Number of Patients and Characteristics	Infants
Intervention	PCV 7, PCV 10 and PCV 13
Comparison	No vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> ➤ Health outcomes <ul style="list-style-type: none"> • Compared to no vaccination, PCV 7 reduced 23 cases of pneumococcal meningitis and 299 cases of pneumococcal bacteraemia, representing about one quarter of IPD cases and 80 deaths averted per birth cohort. • PCV 13 reduced 15 fewer IPD cases per birth cohort over a lifetime and 6 fewer cases of hospitalized pneumonia compared to PCV 10 • However, PCV 10 reduced approximately 12 000 fewer AOM cases compared to PCV 13 and a reduction about 16 000 cases compared to PCV 7. • PCV 13 saves 8 more life years than PCV 10 but PCV 10 has a QALY gain of 50 per cohort compared to PCV 13. ➤ Costs and cost-effectiveness <ul style="list-style-type: none"> ✓ The administration costs of PCVs vaccination approximately NOK 67 million per birth cohort. ✓ When PCVs add vaccination, they reduce the cost of disease treatment by NOK 44 million (PCV 7), NOK 53 million (PCV 13) and 73 million (PCV 10), while indirect costs reduced by NOK 38 million (PCV 7), NOK 49 million (PCV 13) and NOK 59 million (PCV 10). ✓ PCV 13 is slightly more effective in reducing mortality compared to PCV 10, but the additional life years each come at a cost of approximately NOK 3.1 million (~€0.4 million). ➤ However, one way sensitive analyses indicate that the base case finding that PCV 10 dominates over PCV 13 (cost-saving and more effective) is insensitive to changes in model parameters. <p>Hence, the model predicts that both PCV13 and PHiD-CV provide more health gains at a lower cost than PCV7. Differences in health gains between the two second generation vaccines are small for invasive pneumococcal disease but larger for acute otitis media and myringotomy procedures. Consequently, PCV 10 saves more disease treatment costs and indirect costs than PCV13. This study predicts that, compared to PVC13, PCV entails lower costs and greater benefits if the latter is measured in terms of quality adjusted life years. PVC13 entails more life years gained than PCV 10, but those come at a cost of NOK 3.1 million (~D 0.4 million) per life year. The results indicate that PCV 10 is cost-effective compared to PCV13 in the Norwegian setting.</p>
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	42. Rubin J. L, Mc Garry L. J, Strutton D. R et al. Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States. <i>Vaccine</i> . 2010;28:7634-7643.
Study Type / Methods	<p>Economic evaluation.</p> <p>The aim of this study is to assess the public health and economic impact of a PCV13 routine vaccination program including several alternative catch-up strategies.</p> <p>It used a decision-analytic model with Markov (state-transition) structure.</p> <p>Outcomes were direct effects, indirect effects</p> <p>The model time horizon is 10 years.</p> <p>The base-case cost of PCV 13 for this modelling effort was estimated to be \$100.</p> <p>Calculated for QALYs and ICER.</p>
LE	II-2
Number of Patients and Characteristics	<p>Infants.</p> <p>Cases of IPD, pneumonia and AOM</p>
Intervention	PCV 13 with 4 doses at 2, 4, 6 and 12-15 months
Comparison	PCV 7(at 2, 4, 6 and 12-15 months)
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> ✓ If PCV13 used for vaccinating 39.5 million infants would cost approximately 14.1 billion dollars during the first 10 years. ✓ While, if PCV7 used for vaccinating the same numbers of infants would cost 10.7 billion dollars. ✓ Under base-case effectiveness assumption, the model predicts that PCV 13 vaccination would save over \$11.4 billion in medical-care costs. ✓ It also would avoid approximately 106 000 cases of IPD, 948 000 cases of hospitalized pneumonia, 1.93 million cases of non-hospitalized pneumonia and 40 500 deaths over the 10-year period. ✓ About 14.6 million cases of simple and 1.72 million cases of complex AOM are avoided over 10-year period. ✓ If the vaccination is associated with \$3.61 billion in non-medical costs saving leading to net savings of \$11.6 billion over the 10-year period. ✓ Threshold analyses determined that PCV 13 is cost-saving from the societal perspective at all prices below \$192 when compared to PCV 7. ✓ If a catch-up program vaccinating children aged 16-23 months costs \$3 399 per QALYs gained, aged 16-35 months costs \$25 052 per QALY gained and aged 16-59 costs \$73 564 per QALY gained. <p>Hence, the model predicts that PCV13 is more effective and cost saving compared with PCV7, preventing 106,000 invasive pneumococcal disease (IPD) cases and 2.9 million pneumonia cases, and saving \$11.6 billion over a 10-year period. The serotype catch-up program would prevent an additional 12,600 IPD cases and 404,000 pneumonia cases, and save an additional \$737 million compared with no catch-up program.</p>
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	43. Giglio N, Micone P, Gentile A et al. The pharmacoeconomic of pneumococcal conjugate vaccines in Latin America. <i>Vaccine</i> . 2011;295:C35-C42.
Study Type / Methods	<p>Economic evaluation.</p> <p>The aim of this study is to review the articles published on economic evaluation relating to pneumococcal conjugate vaccines in Latin America,</p> <p>Searched on PubMed and the Lylacs Latin American databases up to 30 April 2011.</p> <p>A total of 207 abstracts were found on PubMed and two articles from the Lylacs Latin American databases.</p> <p>Only eight articles were selected.</p> <p>It used simple decision trees for the model construction and Markov Model.</p> <p>Results: the number of events, QALYs gained and DALYs avoided.</p>
LE	II-2
Number of Patients and Characteristics	IPD, pneumonia and AOM cases.
Intervention	PCV10, PCV13, PCV7
Comparison	No vaccination.
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • The cost per dose for PCV 10 was USD 16 and for PCV 13 was USD 19. • The cost/DALY for PCV 10 was USD 8326.7 per year of life gained and for PCV 13 were 1133.6 per year of life gained. • In relation to the number of events avoided, the results varied between 0.1 and 14.8 per 1000 children under age 5 for meningitis, between 6.6 and 25.6 for pneumonia, between 0.05 and 1.18 per 1000 for bacteremia/sepsis and 57.3 and 121.7 per 1000 for otitis media. • In terms of deaths avoided, the number of events varied between 0.22 and 6.53. • Assuming similar costs and effectiveness for PCV10 and PCV13 with no herd effect, and bearing in mind the serotype coverage for both , without considering the cross-immunity of the serotypes, the number of IPD and deaths avoided per 1000 children vaccinated would be 1.9 and 2.2, respectively; and 0.42 and 0.47, respectively
Comments	

Evidence Table : COST EFFECTIVENESS**Question : Is 10-valent or 13-valent pneumococcal conjugate vaccine cost effective?**

Bibliographic Citation	44. Newall AT, Creighton P, Philip D J et al. The potential cost-effectiveness of infant pneumococcal vaccines in Australia. <i>Vaccines</i> . 2011;29:8077-8085.
Study Type / Methods	<p>Economic evaluation</p> <p>The aim of this study to evaluate the cost-effectiveness of PCVs programs.</p> <p>It used a static deterministic state-transition model (between a set of health states for population over a time).</p> <p>Discounted 5%.</p> <p>Results: QALYs</p>
LE	II-2
Number of Patients and Characteristics	Cases of IPD, otitis media and pneumonia
Intervention	PCV 10, PCV 13
Comparison	PCV 7, No vaccination
Length of Follow Up	
Outcome Measures / Effect Size	<ul style="list-style-type: none"> • PCV 13 was estimated to increase protection against IPS, preventing additional cases ~132 IPD cases in the 5th year program compared to PCV 7 vaccination. • PCV 10 was estimated to increase protection against otitis media, preventing an additional ~35 000 outpatient otitis media (~1300 hospitalised) in the same program compared to PCV 7 vaccination. • In base-case, PCV 10 and PCV 13 were both cost-saving compared to PCV 7. • If assumed an increase in total cost to vaccinate an infant of \$100, the discounted ICERs for both vaccines were > 142 000 per QALY saved under base-case assumptions and were > 62 000 per QALY saved with incremental herd protection when compared to no vaccination. • If assumed equivalent vaccination cost (set at \$291 for a complete schedule), the discounted ICERs were estimated at ~\$64 900 (PCV7), ~ \$50 200 (PCV10) and ~\$64 900 (PCV13) per QALY saved when compared to no vaccination
Comments	

LIST OF EXCLUDED STUDIES FOR EVIDENCE TABLE

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