A review of economic evaluations of 13-valent pneumococcal conjugate vaccine (PCV13) in adults and the elderly

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The 13-valent pneumococcal conjugated vaccine (PCV13) is already recommended for some adult groups and is being considered for wider use in many countries. In order to identify the strengths and limitations of the existing economic evaluation studies of PCV13 in adults and the elderly a literature review was conducted. The majority of the studies identified (9 out of 10) found that PCV13 was cost-effective in adults and/or the elderly. However, these results were based on assumptions that could not always be informed by robust evidence. Key uncertainties included the efficacy of PCV13 against non-invasive pneumonia and the herd immunity effect of childhood vaccination programs. Emerging trial evidence on PCV13 in adults from the Netherlands offers the ability to parameterize future economic evaluations with empirical efficacy data. However, it is important that these estimates are used thoughtfully when they are transferred to other settings.

Introduction

Pneumococcal disease caused by Streptococcus pneumoniae remains a significant public health issue worldwide. Other than in infants,[1] the highest rate of invasive pneumococcal disease (IPD) is observed in the elderly,[2] who are responsible for approximately one third of all IPD and have a high case fatality rate.[3] For example, in the US, approximately 50% of deaths due to IPD occur among those aged over 65 y.[3] IPD generally results in hospitalization, requiring significant health care expenditures, however due to the large number of cases it has been estimated that non-invasive disease, in the form of non-bacteraemic pneumococcal pneumonia (NPP), is responsible for more total cost.[4]

The invasive form of pneumococcal disease (IPD) can be further clinically categorized into 3 major forms, with differing rates of associated morbidity and mortality. These forms are bactaeremic pneumonia, bacteremia without an identified focus and meningitis.[5] While IPD is typically laboratory confirmed, this is uncommon for NPP due to difficulties in specimen collection and bacteriologic diagnosis.[6] As a result the incidence of NPP is often estimated as a proportion of the overall rate of community acquired pneumonia (CAP) which is diagnosed a clinical basis only, without laboratory diagnosis of a specific causative agent.

Clinical trial evidence suggests that the pneumococcal polysaccharide vaccine (PPV), as traditionally recommended for use in adults and the elderly, is effective against IPD in these groups, however, the evidence for an impact on NPP is less clear.[7] In 2000, a 7-valent conjugated vaccine (PCV7) was licensed for use in US for children <2 years Epidemiological data in the following years suggests that use of this vaccine resulted in a decline of IPD in both vaccinated children and in the wider population via herd protection.[8]

Since PCV7 was licensed, several higher valency vaccines, have been developed, including a 13-valent vaccine (PCV13) approved for use in both children and adults. The successful implementation of conjugate vaccines in children raised the potential for use of these vaccines in the elderly.[9] Some immunological studies[10] have suggested improved immunogenicity of PCV7 over PPV23 in adults and/or the elderly.[11-15] while others have reported no significant differences.[10,16-19] In 2014 the first large clinical trial of PCV13 in the adults aged >65 y (CAPiTA trial - Community Acquired Pneumonia Immunization Trial in Adults[20]) was completed. A double-blind, randomized placebo-controlled trial conducted in the Netherlands,[20] CAPiTA has reported that PCV13 is effective against IPD and provides an estimated 45% reduction in the first episode of vaccine type NPP.[21]

No systematic review of the literature on the cost-effectiveness of PCV13 in adults or the elderly has yet been completed. The main aim of this literature review is to examine the existing research regarding the cost-effectiveness of PCV13 vaccination in these groups and identify the strengths and limitations of these studies.

Search Strategy

A literature search was performed (on the 10th of March 2014) to identify articles analyzing the cost-effectiveness of

PCV13 vaccine in adults or the elderly. The search was performed using the Scopus database with the following search terms in the abstracts, title or keywords: (pneumococc*) and (vaccin* or immun*) and (elder* or old* or adult or geriatric* or years) and (econom* or "cost-effectiveness" or "cost benefit" or "cost minimization" or "cost utility" or "economic impact")). Scopus is an abstract and citation database of literature scientific journals that covers Medline, Embase, Compendex, World textile index, Fluidex, Geobase, Biobase databases.[22]

This database search returned in total of 765 publications. Of these, 35 publications were identified as specifically focused on PCV13 and were selected for further review. We excluded 21 analyses that focused on childhood programs. A total of 14 studies on adults or the elderly were reviewed further to identify if they were full economic evaluations.[23] Finally, 10 economic evaluations of PCV13 in adults or the elderly were identified and included in the review.

Setting and Intervention Evaluated

Five of the selected publications considered vaccination in the US population.[24-28] two were conducted for Italy[29,30] and the remaining 3 were performed for England, the Netherlands and Spain respectively.[31-33] Of the 5 US publications, 3 were authored by Smith et al.[24,26,27] with 2 others by Weycker et al. and

Cho et al.[25,28] The publications which analyzed the cost-effectiveness in England and the Netherlands were conducted by Rozenbaum et al.[31,32]

All studies focused on evaluating the cost-effectiveness of PCV13 in adults or the elderly and excluded those aged <18 y, except for the study of Rozenbaum et al in England, where the target population was categorized as 2–15 y, 16–64 y, and ≥65 y[31] (**Table 1**). Two studies evaluated the implementation of PCV13 vaccination only in those who were in high-risk groups.[30,31] To evaluate the identified studies it is important to also understand the existing pneumococcal vaccination programs into which these new programs are being introduced.

The US and England have similar existing pneumococcal vaccination programs for the elderly with a single dose of PPV23 recommended to those aged over 65 y. For immunocompromised adults in the US, 2 PPV23 doses (5 y apart) are recommended[34] and from 2012, PCV 13 was recommended to immunocompromised patients who were previously vaccinated with PPV23.[35] The US[36] and England[37] both introduced PCV13 into their vaccination program in 2010.

In the Netherlands, PPV23 vaccine is only recommended in high risk elderly and the vaccination coverage is very low (~1%).[32] Likewise, in Italy and Spain, although the PPV23 vaccine is recommended for those ≥65 and high risk ≥2 y, the coverage rate remains low.[29,30,33] Italy and Spain (partially) have

Table 1. Summary information from the identified studies

Author/Country	Model used	Age group targeted (y)	Primary outcome	Time Horizon	Discounting rate	Potential conflict of interest
Smith et al. [24]/US	Markov model	>65 and >75	QALY[a]	Lifetime	3% both costs and outcomes	No conflict of interest reported
Weycker et al. [25]/US	Markov-type model (micro simulation)	≥50	LYG[b]	Lifetime	3% both costs and outcomes	Funded by Pfizer
Smith et al. [26]/US	Markov model	19–49, 50–59, 60–69, 70–79, 80+	QALY[a]	15 y	3% both costs and outcomes	Two of authors had research grant/s from Merck
Smith et al. [27]/US	Markov model	≥50	QALY[a]	Lifetime	3% both costs and outcomes	Two of authors had research grant/s from Merck
Cho et al. [28]/US	Markov-type model	≥19 (19–64 and ≥65)	QALY[a]	Lifetime	3% both costs and outcomes	No conflict of interest reported
Boccalini et al. [29]/Italy	Markov-type model	≥65 , ≥70 , ≥75[c]	QALY[a], LYG[b]	5 y	3% only to costs but not outcomes	One author had grant from Pfizer
Liguori et al. [30]/Italy	Markov-type model	50–79, 50–64 and 65	Case prevented	5 y	3% only to costs but not outcomes	One author had grant from Pfizer
Rozenbaum et al. [32]/ Netherlands	Decision-tree analytic	≥65	QALY[a]	5 y	Cost 4% and health outcome 1.5%	Funded by Wyeth pharmaceutical
Rozenbaum et al. [31]/ England	Markov-based model	2<group<65 and ≥65	QALY[a]	Lifetime	3% both costs and outcomes	No conflict of interest reported
Pradas et al. [33] /Spain	Dynamic transmission model (SIS[d])	≥65	Case prevented	5 y	3% only to costs but not outcomes	Funded by Pfizer and 2 authors employee of Pfizer

[a]QALY: quality adjusted life years.
[b]LYG: life years gained.
[c]Single, double (simultaneous vaccination of ≥65 and ≥70) and triple (simultaneous vaccination of ≥65 and ≥70 and ≥75) cohort were considered in this study.
[d]SIS: Susceptible-Infected-Susceptible (recovery).

also already introduced PCV13 to their vaccination programs, whereas in the Netherlands, PCV7 was introduced at 2006 and from 2011 PCV10 and PCV13 were available for infants.

Economic Evaluation Model

Most of the studies used a Markov (or Markov-type) model[38] to evaluate the cost-effectiveness of the PCV13 in adults except Pradas et al. who applied a dynamic model[33] (**Table 1**). Dynamic models can explicitly capture herd immunity effects, by allowing infection risks to vary proportional with the infectious prevalence and modeling population immunity.[39]

In terms of the type of economic evaluation, 7 publications were cost-utility analyses, presenting cost per Quality Adjusted Life Year (QALY) gained as the primary outcome.[24,26-29,31,32] Whereas the studies by Liguori et al.[30] and Pradas et al.[33] could be classified as cost-effectiveness analyses, calculating the cost per case of pneumococcal disease avoided as the main outcome.

Sensitivity Analyses Conducted

All of the studies performed univariate sensitivity analysis except Weycker et al. who performed probabilistic analysis. Smith et al. and Rozenbaum et al. performed probabilistic sensitivity analysis in addition to univariate sensitivity analysis.[24,26,27,31] Cho et al.[28] performed multivariate analysis.

Disease States and Outcomes

All of the studies used 2 main disease states, IPD and NPP. For invasive forms of disease, Smith et al.,[24,26,27] Rozenbaum et al. (England)[31] and Cho et al.[28] categorized IPD into meningitis and other IPD. Boccalini et al.[29] and Weycker et al.[25] used similar approaches but used bactaeremic pneumococcal pneumonia and bacteremia respectively instead of all other IPD. Rozenbaum et al. (Netherlands),[32] categorized IPD disease into meningitis, bactaeremic pneumonia, and bactaeremic without focus. Pradas et al.[33] used a similar approach, stratifying IPD into primary bacteremia, empyema, meningitis, and bactaeremic pneumonia.

For non-invasive pneumococcal disease, Smith et al. (in all 3 studies),[24,26,27] and Rozenbaum et al. (Netherlands),[32] included hospitalized NPP whereas, Weycker et al.,[25] Cho et al.,[28] Pradas et al.,[33] and Boccalini et al.,[29] included both hospitalised and non-hospitalized NPP in their analyses. Rozenbaum et al. (England)[31] did not include NPP in their (base-case) cost-effectiveness analysis. Liguori et al.[30] did not distinguish different forms of pneumococcal disease and included hospitalized CAP (invasive or not) in the analysis.

The approach to classifying consequences from IPD varied between studies. Pradas et al. included recovery from infection as an outcome but did not estimate deaths in the model.[33] Smith et al. considered recovery, mortality and IPD related disability.[24,26,27] Boccalini et al. considered recovery and mortality but not long term disability from IPD.[29] Weycker et al.[25] and Rozenbaum et al. (Netherlands)[32] considered recovery or death as the primary outcomes of pneumococcal disease in the base-case scenario. However, in their study for England[31] Rozenbaum et al. included long-term disability from IPD in base-case. Liguori et al. limited all clinical outcomes to pneumococcus related CAP hospitalization.[30]

Perspective and Costs

Five evaluations adopted a societal perspective,[24,26-28,32] 4 applied a healthcare provider perspective (considering direct health care costs only)[29-31,33] and Weycker et al. analyzed the results from both a societal and healthcare provider perspective.[25]

In the US studies the vaccination cost for PPV23 varied from $43 to $80 inclusive of administration cost and for PCV13 the price range was $125 to $149 inclusive of administration cost (**Table 2**). According to the Center for Disease Control and Prevention (updated on May 2014) the price of PPV23 and PCV13 (without administration cost) in the US were $23.31 and $85.18 respectively. Many studies did not discuss a vaccine administration cost and few separately described the cost of the vaccine and administration (**Table 2**).

The three studies[24,26,27] by Smith et al. used an estimated hospitalization cost for non-invasive pneumonia, derived from a 2006 healthcare cost and utilization project, of $16,925 per case for the age group of 65–74 years.[40] Weycker et al. used a hospitalization cost of $15,779 for non-invasive cases in the 50–64 years age group.[25] The hospitalization cost applied for non-invasive pneumonia for the Netherlands and England were €5194 ($6752.2) and £661 ($1057.6) respectively.[31,32] In the study by Cho et al. the hospitalization cost for non-invasive pneumonia ranged from $18,380 for those with HIV to $26,526 for those with end stage renal disease.[28] Boccalini et al. and Pradas et al. used €2680.85 ($3485.1) and €1983 ($2577.9) as the cost of non-invasive pneumonia hospitalization, respectively.[29,33] In the study of Liguori et al. the average cost of non-complicated and complicated pneumonia cases was €3809 ($4951.7).[30] The costs of hospitalization for IPD are summarized in **Table 2**.

Quality of Life Weights

Only those studies that applied a cost-utility framework are required to consider quality of life (utility) weights. Three different types of utility weights may be important in these studies: 1) utility weights for the acute phase of disease, 2) utility weights for those suffering from long term consequences (disabilities) from pneumococcal disease 3) utility weight changes for age or an underlying risk condition which are not related to pneumococcal disease.

Smith et al., Rozenbaum et al. and Boccalini et al.[24,26,27,29,32] considered age specific utility weights and quality of life loss during IPD episodes. Different utility weights for high and low risk individuals for each age group were also considered by Smith

Table 2. Summary of vaccination and healthcare costs in the studies[j,k]

Author/Country	Currency base	Perspective	Administration cost	Vaccination cost		IPD[a] hospitalization cost	Non-invasive hospitalization cost
				PPV23	PCV13		
Smith et al. [24]/US	2006 US $	Societal	Not reported	$43[b]	$128[b]	$20,416	$16,925
Weycker et al. [25]/US	2010 US $	Societal and Health care provider	$17	$49	$108	$26,434 $32,795[d]	$15,564
Smith et al. [26]/US	2006 US $	Societal	Not reported	$43[b]	$128[b]	$20,416	$16,925
Smith et al. [27]/US	2006 US $	Societal	Not reported	$43[b]	$128[b]	$20,416	$16,925
Cho et al. [28]/US	2009 US $	Societal	$25	$55.02	$124.37	$25,702-$79,193[e]	$18,380-$26,526[e]
Boccalini et al. [29]/Italy	2012 €	Health care provider	Not reported	€16 ($20.8)	€42.5 ($55.25)	€4068[f]-€19,114[d] ($5288.4[f]-$24848[d])	€2680.85 ($3485.1)
Liguori et al. [30]/Italy	Not reported	Health care provider	NA	Not reported	€42.5 ($55.25)	€3809 ($4951.7)	€3809 ($4951.7)
Rozenbaum et al. [32]/Netherlands	2010 €	Societal	Not reported	Not reported	€50 ($65)	€7105[g,] -€15,255[d] ($9236.5[g]-$19,831.5[d])	€5194 ($6752.2)
Rozenbaum et al. [31]/England	2012 £	Health care provider	£7.51 ($12.01)	Not reported	£56.61 ($90.576)	£825[h]-£8977[i] ($1320[h]-$14,363[i])	£661 ($1057.6)
Pradas et al. [33] /Spain	2010 €	Health care provider	Not reported	Not reported	€49.91 ($64.88) (ex-factory)	€4093[c]-€11,202[d] ($5320.9[c]-$14,562[d])	€1983 ($2577.9)

[a]IPD: Invasive pneumococcal disease.
[b]Inclusive administration cost.
[c]Cost of bacteremia.
[d]Cost of meningitis.
[e]The range for hospitalization among different immunocompromised conditions.
[f]Cost of bacteremic pneumococcal pneumonia.
[g]Cost of pneumococcal bacteremia with a focus.
[h]Cost of short hospital stay.
[i]Cost of long hospital stay.
[j]All currencies were converted to US dollar based on €1=$1.3 and £1=$1.6.
[k]Healthcare costs are in the groups targeted as shown in **Table 1**.

et al.[24,26,27] and Rozenbaum et al.[32] All of these utility weight values were obtained from a study by Sisk et al.[41] Rozenbaum et al. (England)[31] and Cho et al.[28] did not apply age specific utility weights in their studies. Rozenbaum et al.[31] applied utility weight for long-term consequences of pneumococcal disease and Cho et al.[28] applied utility weight for risk conditions, long term consequences of meningitis, and acute IPD states.

All cost-utility studies included utility weights for NPP except Rozenbaum et al. (England) who did not consider a decline in this state in base-case.[31] Cho et al. was the only study which considered utility weights for outpatient non-invasive cases.[28] The studies by Smith et al.[24,26,27] considered utility weights for long-term disability from pneumococcal disease and were the only analyses which included utility losses for potential adverse effects from vaccination.

Effectiveness of PPV23 and PVC13

Four of the publications used an expert panel (Delphi technique) to estimate the efficacy of the vaccines.[24-27,31] The other studies relied on values from publications or from their own expert opinion.[28-30,32,33] The efficacy values estimated in different publications are summarized in **Table 3**. In case of NPP, Smith et al. and Boccalini et al. only considered the effectiveness of PCV13 against hospitalized (inpatient) cases[24,26,27,29] whereas Weycker et al., Rozenbaum et al. (Netherlands) and Pradas et al.

considered the effectiveness against both inpatient and outpatient cases.[25,32,33] Rozenbaum et al. (England) assumed no effectiveness against NPP in base-case.[31]

In the main scenario of all studies, it was typically assumed that PPV23 had no efficacy against NPP cases and was less effective against IPD than PCV13. At the time that the studies were conducted, no clinical efficacy data for PCV13 against NPP was available and there was substantial variation in estimates of this important parameter between the studies (**Table 3**). In the recent CAPiTA trial the efficacy of PCV13 was estimated to be 45% against vaccine serotype caused NPP, while the estimated effect on all-cause NPP was not statistically significant.[21] Estimates of efficacy against (and incidence of) NPP from CAPiTA were generally lower than those assumed in the economic analyses reviewed and this needs to be considered when interpreting their findings.

Disease Burden Without Vaccination

The studies under review were divided into settings with very low existing PPV23 coverage (Netherlands, Spain and Italy[29,30,32,33]) and the remainder (US, England)[24,25,27,28,31] where higher coverage PPV23 programs were well established. In the low-coverage settings the studies generally used existing incidence data as the baseline, while in the high-coverage settings the burden in the absence of vaccination was calculated using the estimated effectiveness of the PPV23 program. In this method, the current IPD rates are scaled up to estimate the number of

Table 3. Summary of estimated efficacy of PPV23 and PCV13 in the studies

Author/Country	PPV23		PCV13		Age group	Source
	IPD	NPP	IPD	NPP		
Smith et al. [24]/US	80%	0%	85%	64%	65[a]	Expert panel (Delphi)
Weycker et al. [25]/US	77%	0%	85%	24%[b] (for outpatient 6%)	65–74[a]	Expert panel (Delphi) for IPD, literature and assumption for NPP
Smith et al. [26]/US	Proportion of PCV13 effectiveness	0%	50%	35%[c]	19–49,50–59, 60–69, 70–79, >80[c]	Expert panel (Delphi)
Smith et al. [27]/US	80%	0%	85%	64%	65[a]	Expert panel (Delphi)
Cho et al. [28]/US	8–25%[d]	0%	25% or 75% (in different groups)	0% or 13% (in different groups)	≥19 (19–64 and ≥65)[c]	Literature/assumptions
Boccalini et al. [29]/Italy	70%	0%	94%(meningitis) 87.5% (other IPD)	87.50%[e]	≥65 , ≥70 [a]	Literature
Liguori et al. [30]/Italy	NA	NA	87.50% [e]	87.50%[e]	50–79, 50–64 and65[a]	Literature
Rozenbaum et al. [32]/ Netherlands	NA	NA	30–90% [f]	30–90% [f]	≥65 [a]	Literature/assumptions
Rozenbaum et al. [31]/ England	NA	NA	63% (43% immunocompromised)	Not included (base-case)	≥65 [a]	Expert panel
Pradas et al. [33]/Spain	NA	NA	58%[e]	58%[e] (includes outpatient cases)	≥65 [a]	Assumption

[a]General population.
[b]Efficacy expressed against all-cause non-invasive pneumonia.
[c]Immunocompromised.
[d]25% for HIV and end stage renal disease, 8% for organ transplant and hematologic cancer.
[e]87.5% against all hospitalized CAP (invasive or non-invasive).
[f]In the base case the efficacy was studied as a range varying between 30–90% in each group.

cases that would have occurred without the PPV23 program (scaling factor 1/(1-(vaccine effectiveness x vaccine coverage))).[42] This scaling was not applied to NPP as no study assumed any impact of PPV23 on NPP incidence.

In all 3 studies by Smith et al.[24,26,27] they relied on data obtained from Active Bacterial Core Surveillance (ABC) for period of 2007–2008 to estimate the IPD incidence. Similarly, Weycker et al.[25] and Cho et al.[28] used ABC data for 2006 and 2006–2008 respectively to calculate the incidence of IPD in the no vaccination baseline. Similar data from 2009–10 were used in the evaluation in English high-risk groups[31] to obtain age and risk-group specific incidence of IPD. In the reviewed studies NPP was often assumed to represent a relatively high fraction (30–40%) of all-cause non-invasive pneumonia. The incidence rates of IPD and NPP in different studies are summarized in **Table 4**.

Herd Immunity and Serotype Replacement

Two different sources of herd immunity effects are possible when considering pneumococcal vaccination in the elderly. Firstly, there are potential impacts of childhood PCV programs, which can lead to reduced circulation of vaccine types and potentially reduced pneumococcal disease in the elderly.[43,44] Secondly, PCV13 vaccination in the elderly itself might induce a herd effect, although epidemiological evidence of this effect is yet to be observed. This latter effect was considered only by Rozenbaum et al.[31] and Pradas et al.,[33] while the influence of childhood vaccination programs was considered in the studies of Smith et al.,[24,26,27] Rozenbaum et al. (England)[31] and Weycker et al.[25] Herd immunity effects were not considered in the studies of Liguori et al.,[30] Boccalini et al.,[29] Rozenbaum et al. (Netherlands)[32] and Cho et al.[28]

Herd immunity can also lead to replacement disease, whereby an increase in disease burden from non-vaccine types can occur as the carriage of vaccine types decreases. This effect has been observed with respect to childhood conjugate vaccination[45] and was considered along with herd immunity in the studies by Smith et al.[24,26,27] and Rozenbaum et al. (England).[31]

Cost-Effectiveness and Sensitivity Analyses Results

Nine out of the 10 studies considered the vaccination of elderly with PCV13 to be cost-effective in base-case, the exception being the study of Rozenbaum et al. for England,[31] where no efficacy against CAP was included in base-case. Among these 9 studies, 2 evaluated the program to be cost saving.[30,33]

The results of the studies were often deemed to be sensitive to vaccine effectiveness.[24,26-28,31,32] The results of 4 of the studies were also found to be sensitive to herd immunity effects.[24,26,27,31] The study of Smith et al.[26] in immunocompromised patient found life expectancy to be an influential factor in sensitivity analysis. Several of the studies found that their results were robust to parameter changes in sensitivity analyses.[25,29,30,33] Two potential reasons for this robustness are the relatively high estimates of effectiveness against NNP assumed[25,29,30,33] and the relatively limited variation of base-case parameters considered in the sensitivity analyses.[29,30,33]

Based on the studies reviewed, the parameters related to the non-invasive form of pneumococcal disease seem to be an important factor in determining the cost-effectiveness of PCV13. This

Table 4. The incidence rate of IPD and NPP in the studies (rate per 100,000)

Author/Country	Age group	IPD[a]	NPP[b] (hospitalization)	Comments
Smith et al. [24]/US	65–80+	25.9–60.1	567[c]	30% of all-cause CAP is pneumococcal
Weycker et al. [25]/US	65–75	18	491	-
Smith et al. [26]/US	60–69	58.52	868[c]	30% of all-cause CAP is pneumococcal
Smith et al. [27]/US	60–69	25.9	567[c]	30% of all-cause CAP is pneumococcal
Cho et al. [28]/US	≥65	6.8–550.6[d]	160–10330[e]	-
Boccalini et al. [29]/Italy	65–74	9.5	42.2[f]	39.8% of all-cause CAP is pneumococcal
Liguori et al. [30]/Italy	50–79	Expressed as total number/s	Expressed as total number/s	40% of all-cause CAP is pneumococcal
Rozenbaum et al. [32]/ Netherlands	65–69	47.4[g]	89	35% of all-cause CAP is pneumococcal
Rozenbaum et al. [31]/ England	≥65	43.5 (high risk group)	1210 (includes outpatient)	42% of all-cause CAP is pneumococcal
Pradas et al. [33]/Spain	>50	29.7	318.7	50% of all-cause CAP is pneumococcal

[a]IPD: Invasive pneumococcal disease.
[b]NPP: Non-bacteraemic pneumococcal pneumonia.
[c]In all studies by Smith et al. the age group for NPP hospitalization was ≥65.
[d]PCV13 serotype IPD rate 6.8–80.1 and PPV23 serotype IPD rate 43.8–550.6 dependent on immunosuppression condition.
[e]NPP rate 160–10330 dependent on immunosuppression condition.
[f]Calculated based on rate of non-invasive CAP, 31.8% of CAP hospitalized, and 39% of all cause CAP being pneumococcal.
[g]Calculated based on addition of rates of different IPD cases.

includes the efficacy of PCV13 against hospitalized NPP, inclusion of efficacy against outpatient cases of NPP and the proportion of CAP due to *S. pneumoniae*. The cost of vaccination was also influential but was often not discussed in the studies.

Discussion

At the time these studies were conducted there were several relatively uncertain parameters that influenced the cost-effectiveness of the programs, these included: the effectiveness of PCV13 against IPD and NPP, the effectiveness of PPV23 used to estimate the "no vaccination" baseline and the assumed herd immunity of PCV13 immunization in infants. The values used to inform these parameters in the reviewed studies were often not obtained directly from empirical evidence but rather from sources such as expert panels. As a result, the generally favorable results found in the cost-effectiveness analysis reviewed must be interpreted cautiously.

The CAPiTA study conducted in the Netherlands is a milestone clinical trial to measure effectiveness of PCV13 against IPD and NPP. With the publication of the CAPiTA results, the cost effectiveness of PCV13 in different countries needs to be reassessed making use of this new clinical evidence. However, when translating the result of this trial to other settings several factors need to carefully considered. The Netherlands had low existing coverage of PPV23 (~1%) and PCV7 and PCV10 (rather than PCV13) were used for vaccination in children during this period. This may create complexities when applying the results of the trial to settings which have already implemented PCV13 in children. In these settings, the herd protection from this childhood PCV13 program may reduce the disease burden available for prevention by an elderly program using the same vaccine. To help address this, sero-specific trial efficacy estimates can be applied to local sero-specific disease estimates from after the introduction of PCV13 in children. The use of PCV13 in infants can also

result in replacement effects which may increase the incidence of serotypes in the elderly which are not present in PCV13.

The second potential issue that should be considered when using the results of the CAPiTA trial from the Netherlands relates to the absence of PPV23 in the elderly in this setting. Since all serotypes (except one) of PCV13 are shared with PPV23, it may be that any existing PPV23 programs in other settings could interact with the effect of PCV13 and the incremental effect of PCV13 needs to be carefully estimated. If replacement of PPV23 with PCV13 is considered then the (gradual) impact of the cessation of the PPV23 program will also have to be modeled.

Conclusion

The majority of the studies (9 out of 10) found that PCV13 was cost-effective in adults and/or the elderly. However, these results were based on key assumptions that could not always be informed by robust evidence. The results of the CAPiTA trial offer the ability to parameterize future economic evaluations with improved empirical efficacy data. It is important that these estimates are used thoughtfully as existing vaccination schedules and coverage may differ to those in the Netherlands. The use of PCV13 in adult and elderly groups offers scope to substantially reduce disease burden but due to the costs involved rigorous economic evaluations are needed.

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