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## **Abstract**

### **Background**

Pneumococcal diseases cause substantial mortality, morbidity and economic burden. Evidence on data inputs for economic evaluations of interventions targeting pneumococcal disease is critical.

### **Objectives**

To summarise evidence on resource use, costs, health utilities and cost-effectiveness for pneumococcal disease and associated interventions to inform future economic analyses.

### **Methods**

We searched MEDLINE, Embase, Web of Science, CINAHL, PsycInfo, Econlit and Cochrane databases for peer-reviewed in English studies on pneumococcal disease that reported health utilities using direct or indirect valuation methods, resource use, costs or cost-effectiveness of intervention programmes, and summarised the evidence descriptively.

### **Results**

We included 383 studies: 9 reporting health utilities, 131 resource use, 160 economic costs of pneumococcal disease, 95 both resource use and costs, and 178 economic evaluations of pneumococcal intervention programmes. Health state utility values ranged from 0 to 1 for both meningitis and otitis media, and from 0.3 to 0.7 for both pneumonia and sepsis. Hospitalisation was shortest for otitis media (range: 0.1 to 5 days) and longest for sepsis/septicaemia (6 to 48). The main categories of costs reported were drugs, hospitalisation and household or employer costs. Resource use was reported in terms of hospital length of stay and number of contacts with general practitioners. Costs and resource use significantly varied between population ages,

disease conditions and settings. Current vaccination programmes for both adults and children, antibiotic use and outreach programmes to promote vaccination, early disease detection and educational programmes are cost-effective in most countries.

## **Conclusion**

This study has generated a comprehensive repository of health economic evidence on pneumococcal disease that can be used to inform future economic evaluations of pneumococcal disease intervention programmes.

## **Introduction**

Pneumococcal diseases cause significant morbidity, mortality and economic burden (1-3). Infection by pneumococcus is often harmless, but in some individuals the bacterium can evade the mucosal surfaces into major organs such as the blood, joints and lungs, leading to serious illnesses such as septicaemia, pneumonia and meningitis that often result in hospitalisation, complications with long term sequelae, multisystem organ failure or death (4, 5). Other common but less serious manifestations include otitis media, sinusitis and bronchitis (6). The control of pneumococcal diseases has involved treating infected individuals with antibiotics, and infection prevention through the use of paediatric and adult pneumococcal vaccines (7).

Three pneumococcal vaccines are currently being used and these have prevented significant disease burden by reducing transmission of the pneumococcus in the population (8). The WHO recommends a 23-valent polysaccharide pneumococcal vaccine (PPV23) for adults and at-risk groups >2 years, and the 13-valent (PCV13) and 10-valent (PCV10) formulations for infants. In 2010, childhood formulations of PCV10 and PCV13 replaced PCV7, which was introduced in 2000. Many countries have now introduced pneumococcal vaccination programmes. However, the vaccination schedule, coverage and specific details of their implementation vary between countries (9). In addition, the different vaccines differ in efficacy and levels of protection, as well as price. One of the hallmarks of paediatric vaccinations is the generation of indirect effects by the vaccines (10). Pneumococcal vaccines have led to significant reduction in disease and carriage due to serotypes covered by the vaccines in unvaccinated populations (herd protection) and also significant replacement in carriage and disease due to serotypes not covered by the vaccines (serotype replacement) (11, 12).

A number of economic modelling studies have been conducted to evaluate the cost-effectiveness of pneumococcal vaccination and treatment programmes, and these are important in helping policy makers make decisions about resource allocation. Preference-based health-related quality of life outcomes (health utilities) and estimates of economic costs associated with pneumococcal diseases and their sequelae are key input parameters to these economic models. However, previous reviews on the impact of pneumococcal disease on health-related quality of life have only focussed on a small number of pneumococcal infections, such as otitis media (13) and sepsis (14). Hospitalisation and long-term sequelae caused by pneumococcal diseases have economic consequences at various levels including the individual, household, government and overall society. However, no previous systematic review of the global economic costs of pneumococcal diseases has been conducted.

Previous systematic reviews of economic evaluations have assessed cost-effectiveness models of adult and paediatric pneumococcal vaccination programmes. These reviews focused on parameters and assumptions that influenced modelling results (15), strengths and limitations of contributing studies (16), results of cost-effectiveness studies (17, 18), their main methodological features (19), economic profiles of vaccines in adults in terms of costs and benefits (20), or provided a summary of evidence and key drivers of results in low-and middle income countries (21). However, other features, such as modelling methods, input parameters and assumptions can affect the generalisability of results. As such, an understanding of individual input parameters such as health utility values and economic costs associated with pneumococcal disease, as well as key assumptions incorporated into cost-effectiveness analyses of preventive and treatment programmes, is critical. To our knowledge, there have been no previous systematic reviews of economic evaluations of pneumococcal disease treatment and other intervention programmes.

We therefore conducted a broad systematic review with the goal of identifying and summarising current evidence on health utilities, resource use and economic costs associated with pneumococcal disease, and the cost-effectiveness of pneumococcal disease control approaches, pneumococcal vaccination and treatment programmes. The findings should be influential in informing future economic evaluations in this area.

## **Methods**

### *Search strategy*

We searched MEDLINE, Embase, Web of Science, CINAHL, PsycInfo, Econlit and Cochrane using tailored search strategies (see Supplementary Appendix A) for peer-reviewed studies published between 1 January 1990 (a decade before any national programmes with conjugate vaccine) and 31 November 2016.

### *Selection criteria and data extraction*

We included studies that reported research on health utilities or other measures of benefit valued using economic methods associated with any aspect of pneumococcal disease: invasive pneumococcal disease (IPD) that includes meningitis, septicaemia/bacteremia and empyema or non-invasive pneumococcal disease that includes community acquired pneumonia, sinusitis and otitis media; studies that reported on resource utilisation or costs associated with any aspect of pneumococcal disease; and studies reporting an economic evaluation of a preventive or treatment intervention for any aspect of pneumococcal disease. Studies reported in languages other than English, conference abstracts with no full publication, letters, commentaries and systematic reviews were excluded, although the latter were reviewed for potential missed studies.

Our study selection followed a two-stage process. Initially, two independent reviewers performed title and abstract screening to exclude irrelevant studies and, finally, two independent reviewers screened full texts to identify relevant articles. Two reviewers independently extracted data using standardised data extraction forms from the eligible full text studies, and specific details about the extracted data by study type are given in the Supplementary Appendix A. At all stages, disagreements between the reviewers were resolved by consensus.

### *Analytical methods*

All cost data were adjusted to 2016 prices and subsequently converted into US dollars using purchasing power parities, with both stages of the conversion process applying the Campbell and Cochrane Economics Methods Group Evidence for Policy and Practice Information and Co-ordination Centre cost converter (22). When the costing year was not available, it was assumed to be the year prior to the publication of the article. We present disaggregated values in tabular form for health utilities, resource use and economic costs associated with each pneumococcal disease. We also present disaggregated cost-effectiveness results by type of adult and childhood vaccination programme, or treatment or other intervention programme. Data were not meta-analysed due to heterogeneities in study designs, outcomes and intervention types, as well as variations in healthcare practices and relative prices of resource inputs, but the results are instead presented in the form of a narrative synthesis.

The methodological quality of selected cost-effectiveness studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (23), and no quality appraisal was conducted for studies reporting health utilities, resource consequences or costs.

## **Results**

A total of 25,752 articles were identified by the search strategy, with 383 articles meeting the inclusion criteria after the final review stage (see Figure 1). Nine articles reported on health utilities, 131 on resource use and 160 on costs associated with pneumococcal disease, with 95 articles reporting on both resource use and costs. 178 articles reported on economic evaluations of pneumococcal intervention programmes. Of these, 50 articles reported on adult vaccination, 90 on childhood vaccination, 26 on antibiotic treatment and 12 on other intervention programmes.

### *Healthy utility studies*

Nine studies assessed utility values for meningitis, otitis media, pneumonia and sepsis/bacteraemia (Table 1 and Supplementary Table S1). These studies were from USA, Thailand, Argentina, Chile, UK, and Canada. The results are reported by disease as follows:

### *Meningitis*

Two articles reported on health utility values for meningitis health states using direct valuation methods, whilst five reported health utility values for meningitis health states using indirect valuation methods (Table 1) (24-30). The health utility values (24-28) ranged from 0.0177 for a health state equivalent to death in the USA to 0.9971 for an outcome where blood is drawn (USA) (27). One study, using the time trade-off (TTO) method, reported that parents were willing to trade up to three years of their own lives to prevent their child from spending any time in a meningitis health state and expressed a willingness to pay value of \$500 for their child to avoid spending time in the described health state (29).

### *Acute Otitis Media (OM)*

Two articles reported health utility values for otitis media health states using direct valuation methods and two articles reported health utility values for otitis media health states using indirect valuation methods (24, 29-31). The health utility values ranged from 0.073 for acute otitis media (AOM) with myringotomy in the UK (30) to an overall value of 0.97 in the USA (31). One article reported TTO generated time trade-offs ranging from 0-7 days for simple otitis media to 270-365 days for complex otitis media, both for the USA, and willingness to pay values ranging from \$100 to \$200 for AOM (29).

### *Pneumonia*

Two articles reported health utility values for pneumonia health states using direct valuation methods and two articles reported health utility values for pneumonia health states using indirect valuation methods (24, 29, 30, 32). Childhood utility values ranged from 0.44 to 0.73 in a Thai study (24). One article reported TTO values ranging from 1-180 days for moderate pneumonia to 365 days for severe pneumonia, both for the USA (29). The same study reported willingness to pay values ranging from \$200 to \$400 for pneumonia. For adults, health utility values ranged from -0.054 for hospitalised pneumonia in Chile (30) to 0.979 for usual health in Canada and the USA (32). Willingness to pay values that measured preferences for the location of pneumonia care ranged from 5% for uncomplicated pneumonia care at home to 30% of monthly household income for complicated pneumonia care at hospital in the USA (32).

### *Bacteraemia*

One article reported health utility values for sepsis or bacteraemia using direct valuation methods whilst two articles reported health utility values for these health states using indirect valuation methods (24, 29, 30). Childhood health utility values ranged from 0.33 to 0.69 in a

Thai study (24). One study reported TTO values of 90-180 days and willingness to pay values ranging from \$250 to \$300 for sepsis in the USA (29). For adults, health utility values for sepsis or bacteraemia ranged from -0.331 in Chile to -0.034 in Argentina (30).

#### *Cost and resource use studies*

A total of 160 studies reported on the costs of AOM, sinusitis, pneumonia, IPD, meningitis, empyema, and sepsis/bacteraemia (see Supplementary Appendix A for tabulated summaries of methodological characteristics, results and accompanying references). A total of 131 studies reported on resource use by patients with these disease conditions (Supplementary Appendix A). Most of the studies were from high-income settings and only 12 studies were from sub-Saharan African countries. Studies primarily reported on costs of drugs, hospitalisation and households, resources use such as hospital stays and visits, and all these varied extensively between population ages, settings and disease categories.

#### *Economic evaluations*

In total, 178 articles included in the review were economic evaluations of interventions targeted at pneumococcal infections, of which 26 focussed on the impact of antibiotic treatment on pneumococcal diseases, 12 focussed on other diagnostic/operational interventions e.g., management, treatment guidelines, standing order programmes and screening, and the largest number of studies (140) focussed on vaccinations programmes. The vaccination programmes were further stratified into adult (Table 2) and paediatric (Table 3) categories. For both adult and paediatric programmes, we report assessments of cost-effectiveness of different vaccines against no vaccination, vaccine use in different age groups, and head-to-head comparison of different vaccines.

## *Vaccination studies*

### *Adult vaccination*

A total of 50 articles reported economic evaluations of pneumococcal vaccination in adults (Table 2 and Supplementary Table S2). Twenty-five studies were carried out in Europe, 17 in USA, 2 in Colombia and Brazil, and 1 study in Canada, Japan, China and Hong Kong. Studies were grouped by comparisons of different vaccines against no vaccination, vaccine use in different age groups and head-to-head comparison of different vaccines as follows:

#### *PPV23 versus no vaccination*

Thirty-six articles assessed the impact of PPV23 vaccination against no vaccination, with economic results varying from cost saving to a mean incremental cost-effectiveness ratio (ICER) of \$375,355 per QALY gained (33-68). The time horizon used in these analyses varied from one year to a lifetime. Some studies in the USA (34-38), UK (48), Hong Kong (52), Belgium (53), Canada (61), China (33), Brazil (63), and Turkey (67) reported that PPV23 use in the adult programme dominates in health economic terms.

#### *PCV13 versus no vaccination*

Nine studies considered the possible use of paediatric PCV13 vaccine in adult populations versus not vaccinating at all (40, 54, 58, 69-74). The economic results varied from cost saving overall to a mean ICER of \$325,021 per QALY gained. The use of PCV13 in adults over 50 years of age was cost saving in Spain (69), Colombia (70) and Finland (71).

#### *PCV13+PPV23 versus no vaccination*

Two studies from Italy and the USA assessed the cost-effectiveness of a combination or sequential use of PCV13 and PPV23 in adults against no vaccination (73, 75). The time horizon

considered varied from 5 years to 50 years. The derived mean ICERs varied between \$29,607 and \$38,384 per QALY gained.

#### *PPV23 within different age groups*

Three studies from the USA (40, 44, 76), one from Japan (77) and another study from Brazil (78) assessed the use of PPV23 within different adult age groups. In the USA, targeting 50-year olds versus all those less than 65 years with comorbidities was extendedly dominated. Vaccinating 65-year olds only versus targeting 50-year olds was dominated in health economic terms. Targeting 65 and 80 year olds versus targeting 65 year olds only was dominated, targeting three age groups (50, 65 and 80 years) versus two age groups (50 and 65 years) was extendedly dominated (44), and vaccinating at  $\geq 50$  years with PPV23 only versus influenza vaccination for all with PPV23 in adults with comorbid conditions was dominated. In Japan, vaccinating 65-80-year olds vs vaccinating 65-year olds only was dominated (77). In Brazil, universal PPV23 versus targeted PPV23 in high-risk individuals resulted in an ICER varying between \$970 and \$1,392 per life year gained (78).

#### *PCV13+PPV23 versus PPV23*

Two studies from the USA evaluated the head-to-head use of a combination of PCV13 and PPV23 against the use of PPV23 (75, 79). The models considered time horizons varying from 15 years to a lifetime. The mean ICERs derived varied between \$4,310 and \$191,822 per additional QALY.

#### *PCV13 versus PCV13+PPV23*

Two studies from the USA (40, 41) and one from France (80) assessed the cost-effectiveness of using PCV13 versus a combination of PCV13 and PPV23 in adults. The three-time horizons

considered were 5 years (France), 15 years and a lifetime (USA). In a study considering a time horizon of 15 years, PCV13 alone was dominated when used in immunocompromised adults 19-64 years of age (40) whereas in a study that considered a lifetime horizon, PCV13 was dominant when given to 50 and 65 year olds versus PCV13 at age 50 years and PPV23 at age 65 years (41). In France, there was a societal net monetary benefit of \$85,911,569 as a result of using a combination of PCV13 and PPV23 (80).

### *PCV13 versus PPV23*

Six studies estimated the cost-effectiveness of using PPV23 against PCV13 in adults in the USA (40, 41), Colombia (70), Spain (81), Germany (58) or the United Kingdom (82). The time horizon varied from 5 years to a lifetime in these models. In Colombia and the United Kingdom, PPV23 was the optimal strategy, whereas in Germany, PCV13 use in adults was the dominant strategy.

### *Paediatric vaccination*

A total of 90 articles reported the cost-effectiveness of pneumococcal vaccination in children (Table 3 and Supplementary Table S3). Thirty-nine studies were carried out in Europe, 19 in Asia, 13 in North America, 24 in South America, 3 in Australia and 7 in Africa, with some studies reporting on more than one country. Studies were grouped by analyses of different vaccines against no vaccination, vaccine use in different age groups and head-to-head comparison of different vaccines as follows:

### *PCV7 versus no vaccination*

The cost-effectiveness of the paediatric PCV7 vaccine versus no vaccination generated heterogenous results in different settings. A body of evidence suggested that PCV7 would be

cost-effective if indirect effects are included (83). In Finland, PCV7 was deemed not cost-effective (84). The ICERs ranged between \$143 per disability-adjusted life year (DALY) averted in resource-limited settings (85) to \$47,392 per DALY averted in Singapore (86), \$456 per QALY gained (87) to \$266,333 per QALY gained (88) in Canada and \$242 per life year gained (LYG) in Germany (89) to \$975,142 per LYG in Taiwan (83).

#### *PCV10 versus no vaccination*

The cost-effectiveness of PCV10 versus no vaccination was assessed in 23 countries, with analysis in Canada (90, 91), Colombia (92) and Chile (92) showing that the vaccine was highly cost-effective. The mean ICER ranged between \$65 per DALY averted in Kenya (93) and \$70,066 per DALY averted in Croatia (94), with studies in 10 countries (Argentina (95), Brazil (92), Gavi-eligible countries (96), Kenya (93), Middle-income countries (97), Malaysia (86, 98), Mexico (92), Paraguay (99, 100), Peru (92, 101, 102) and Turkey (103)) reporting that PCV10 was cost-effective (104). PCV10 use was moderately cost-effective in Singapore (86) and not cost-effective in Thailand (105).

#### *PCV13 versus no vaccination*

The cost-effectiveness of PCV13 was assessed in 22 countries. The ICERs varied between \$51 per DALY averted in Kenya (93) to \$71,371 per DALY averted in Croatia (94), \$3,147 per QALY gained in Philippines (106) to \$288,222 per QALY gained in England (107), and \$507 per LYG in Colombia (108) to \$42,173 per LYG in Taiwan (109). In Japan, PCV13 was cost saving (110), whereas the two analyses conducted for England (107, 111), one in Singapore (86) and another in Australia (112) showed that PCV13 was marginally cost-effective. In China (33) and Thailand (105), the analyses showed that introducing PCV13 into the national

immunisation programme was not cost-effective. In Switzerland, including a catch-up programme was cost saving compared to not including catch-up (113).

### *PCV10 versus PCV13*

A mixture of results was observed when the two vaccines were compared against each other in different settings. Comparison of the cost-effectiveness of PCV10 against PCV13 were conducted for 18 countries. In Germany (114), Greece (114), Netherlands (114), Colombia (108), Canada (115, 116), Sweden (117), Denmark (117), and Malaysia (118), PCV13 was dominant in health economic terms, whereas the analyses for Peru (102), Norway (102), UK (119), Hong Kong (120) and Turkey (121) showed PCV10 dominating PCV13.

Assumptions about herd effects and serotype replacement were highly sensitive. Incorporating herd effects increases the number of disease cases prevented and serotype replacement that still falls below pre-vaccination levels reduced the number of disease cases.

In economic evaluations of vaccination programmes, all 24 quality indicators using the CHEERS checklist were assessed, with 37 studies (74%) in adults and 61 studies (68%) in children scoring at least a 20 out of 24.

### *Treatment studies*

Twenty-six studies that estimated the cost-effectiveness of antibiotics for pneumococcal diseases CAP, otitis media, sinusitis and empyema were conducted in the USA (14 studies), two studies each in the UK and Canada, and one study each in The Netherlands, Germany, Italy, India, Malaysia, Belgium, Finland and France, Germany and the USA combined (Supplementary Table S4).

The studies that compared antibiotics for treating CAP showed that levofloxacin (122-124), ceftriaxone (125, 126), combination of moxifloxacin/co-amoxiclav (127, 128), sparfloxacin (129), gatifloxacin (130), ampicillin (131), meropenem (132), adherence to IDSA/ATS antibiotic guidelines (133), co-amoxiclav (134), azithromycin (135), seven days of home-based course of oral amoxicillin (136) and oral gemifloxacin (137) were cost saving. There were no significant cost differences between intravenous azithromycin and intravenous erythromycin (138), whilst continuous infusion cefuroxime had the same effect but cost less than intermittent infusion cefuroxime (139).

For the treatment of otitis media, the following antibiotics were found to be cost-effective: ofloxacin (140), amoxicillin (141), chemoprophylaxis (142), delayed prescription (143, 144), and the 2002 antibiotic guidelines (145).

Clinical-criteria guided antibiotic treatment versus no antibiotic treatment and radiography-guided antibiotic treatment or empirical antibiotic treatment were both cost saving when treating sinusitis (146). Computerised tomography with instillation of fibrinolytics was found to be cost-effective against percutaneous chest tube for treating empyema (147).

#### *Other interventions studies*

Twelve cost-effectiveness studies of other interventions targeting pneumococcal diseases, conducted in the USA (7 studies), Spain (2 studies), The Netherlands (2 studies) and Canada (1 study), were identified (Supplementary Table S5). Interventions such as outreach programmes to promote vaccination (148), early disease detection and treatment (149), procalcitonin protocols in CAP (150), diagnostics (151), patient management (152-155),

treatment with guidelines (156), screening (157) and educational programmes (158, 159) were found to be cost-effective.

## **Discussion**

We identified a heterogeneous body of evidence on health utility values in individuals with pneumococcal disease, resource use and economic costs associated with pneumococcal disease, and the cost-effectiveness of a range of intervention strategies targeting pneumococcal diseases including adult and childhood vaccines, use of antibiotics and other non-medical strategies. This evidence base is growing, especially in high income countries; however, we discovered several gaps in the available evidence.

Despite a large number of studies included in this review, we were constrained in our across-study and country comparisons as contributing studies differed in methodologies, as well as underpinning health care practices, relative prices of labour and capital inputs, and preference structures for health outcomes. There were relatively few studies on health utilities for individuals with pneumococcal disease; in particular, there were no studies from Sub-Saharan Africa where the burden of disease and its impact is at its greatest. A particular concern is that there is no evidence that estimates the economic burden of disease and its long-term consequences in these settings. Amongst the few studies that evaluated health utilities in individuals with pneumococcal disease, there was great variability in health utility values, ranging across the utility scale for meningitis and otitis media, whereas the utility value range for both pneumonia and sepsis was restricted to 0.3 to 0.7.

The length of hospital stay was commonly reported and was the major driver of costs in most settings. We found substantial variation in hospital stays across different clinical presentations, and costs varied significantly between countries, which seriously limits potential generalisability across settings. Reporting of cost data sources was not transparent in some cases. Our analysis provides evidence on the economic costs of a broad range of pneumococcal diseases.

Thirty-six countries assessed the impact of PPV23 against no vaccination in adults, with economic outcomes varying from cost-saving to a mean ICER of \$355,355 per QALY gained. The cost-effectiveness of PCV13 was assessed in 22 countries, with huge variations in ICER values, whilst studies in 15 countries reported that PCV13 was cost saving. Assumptions about herd effects and serotype replacement were important. Previous systematic reviews of economic evaluations have mainly focused on vaccination programmes (15-21); our comprehensive review is distinct in that it focuses on all interventions against pneumococcal disease and covers a broad range of pneumococcal disease aspects.

There were no studies from low income countries that assessed the cost-effectiveness of treatment for pneumococcal disease with antibiotics. This is a huge concern as antibiotic use has increased in low income countries and evidence on the effectiveness of various antibiotics is critical for better patient management. These studies from low-income settings should also be important as a baseline to monitor the impact on and of increasing antibiotic resistance and economic consequences going forward and any interventions against that.

Our review benefits from the inclusion of a range of studies spanning low, middle- and high-income countries, although we show that there is paucity of data on preference-based health-

related quality of life outcomes and economic costs in low income settings. Shortfalls of this study include the possibility of not finding all relevant studies, particularly given the lack of a grey literature search or searches for non-English language papers. We also did not exclude studies based on quality. There is an urgent need to conduct studies on the economic burden of pneumococcal disease and preference-based health-related quality of life outcomes in low income settings with the view to informing future research priorities. Standardisation of methods for the measurement and valuation of health utilities and economic costs, and their reporting, would enhance across-study comparisons and inform prioritisation strategies of global funders.

In conclusion, this review is the first, to our knowledge, to generate comprehensive and systematic evidence on health economic aspects of pneumococcal disease. It has generated a repository of published evidence on health utilities, resource use, costs and cost-effectiveness associated with pneumococcal disease, which should help inform future economic evaluations of intervention programmes.

### **Figure caption**

**Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature search. \*Note: 95 studies reported on both resource use and costs.**

**Table 1: Summary of utility values in pneumococcal infected children and adults. Supporting references are given in parentheses.**

<b>Disease Area</b>	<b>Age Group</b>	<b>Country</b>	<b>Outcome/health state</b>	<b>Utility values Mean (SD)</b>	<b>WTP values (range)</b>	<b>TTO generated time trade-offs</b>	
Acute Otitis Media (AOM)	Child	USA	Overall (SG approach)	0.96 (0.11)(31)			
			Overall (TTO approach)	0.97 (0.12)(31)			
			Simple otitis media		\$100(29)	0-7 days(29)	
			Complex otitis media		\$150-200(29)	270-365 days(29)	
		Thailand	Overall self-report	0.52 to 0.68(24)			
	Overall proxy		0.62 to 0.77(24)				
		Adult	Argentina	Overall	0.565(30)		
	AOM with myringotomy			0.339(30)			
			Chile	Overall	0.389(30)		
	AOM with myringotomy			0.064(30)			
	UK	Overall	0.391(30)				
AOM with myringotomy		0.073(30)					
Pneumonia	Child	Thailand	Overall self-report	0.44 to 0.73(24)			
			Overall proxy	0.48 to 0.70(24)			
		USA	Moderate pneumonia		\$200-300(29)	1-180 days(29)	
	Severe pneumonia			\$400(29)	365 days(29)		
		Adult	Argentina	Hospitalized pneumonia	0.309(30)		

			Ambulatory pneumonia	0.628(30)		
		Chile	Hospitalized pneumonia	-0.054(30)		
			Ambulatory pneumonia	0.412(30)		
		UK	Hospitalized pneumonia	0.035(30)		
			Ambulatory pneumonia	0.508(30)		
		USA & Canada	Usual health	0.79 (0.16)(32), 0.979 (0.084)(32)	Not applicable	
			Uncomplicated home	0.72 (0.18)(32), 0.994 (0.029)(32)	5% (1-20)(32)	
			Uncomplicated Hospital	0.62 (0.19)(32), 0.993 (0.032)(32)	10% (2-25)(32)	
			Delayed response home	0.56 (0.20)(32), 0.994 (0.029)(32)	10% (2-35)(32)	
			Delayed response home-hospital	0.50 (0.18)(32), 0.993 (0.032)(32)	20% (5-50)(32)	
			Delayed response hospital	0.43 (0.19)(32), 0.993 (0.032)(32)	25% (10-55)(32)	
			Complication home-hospital	0.27 (0.18)(32), 0.998 (0.053)(32)	30% (10-75)(32)	
			Complication hospital	0.28 (0.17)(32), 0.985 (0.067)(32)	30% (10-80)(32)	
Meningitis	Child	Thailand	Overall self-report	0.24 to 0.68(24)		
		Thailand	Overall proxy	0.02 to 0.52(24)		
		UK	Overall	0.181(25), 0.774(26)		
		USA	Death	0.0177 (0.07)(27)		

			Severe brain damage	0.3903 (0.37)(27)		
			Minor brain damage	0.7393 (0.29)(27)		
			Deafness	0.8611 (0.22)(27)		
			Recovery	0.9768 (0.08)(27)		
			Hospitalisation	0.9921 (0.03)(27)		
			Local infection	0.9941 (0.03)(27)		
			Blood drawn	0.9971 (0.02)(27)		
			Overall		\$500(29)	2-3 years(29)
	Adult	Argentina	Overall	-0.049(30)		
		Chile	Overall	-0.330(30)		
		UK	Overall	-0.330(30)		
	General population	UK	Family member	0.87-0.91(28)		
			Survivor	0.78-0.97(28)		
Sepsis or Bacteraemia	Child	Thailand	Overall self-report	0.33 to 0.69(24)		
		Thailand	Overall proxy	0.38 to 0.62(24)		
		USA	Overall		\$250-300(29)	90-180 days(29)
	Adult	Argentina	Overall	-0.034(30)		
		Chile	Overall	-0.331(30)		
		UK	Overall	-0.295(30)		

SG – Standard Gamble, TTO – Time trade-off

WTP – Willingness to Pay (% of household income/amount of money an individual is willing to pay to avoid described health state)

**Table 2. Summary of cost-effectiveness studies of pneumococcal vaccination in adults (ICERs valued in \$USD, 2016 prices). Supporting references are given in parentheses**

Comparator	Setting	Results
PPV23 vs no vaccination	USA	PPV23 dominates: (34), (35), (36), (37), (38)
		PPV23 dominated: (39), (40), (41)
		ICER falls in NE quadrant:\$2,497.94/QALY (42), \$33,356.90/QALY, \$91,124.42/QALY, \$96,875.61/QALY (43), \$4,269.94/QALY (44), \$3,431.43/QALY, \$1,959.48/employee (45), \$9,505.42/QALY, \$18,210.27/QALY, \$21,664.24/QALY, \$28,149.83/QALY (46), \$72,482.71/LYG, \$31,402.47/LYG (47), \$45,491.99/QALY, \$226,233.43/QALY (38)
	UK	PPV23 dominates: (48)
		ICER falls in NE quadrant:\$375,354.91/QALY (49), \$14,441.17-\$73,613.17 (50), [\$19,214.83]/LYG for vaccinating all high risk adults and \$17,242.05/LYG for all 65+ year olds (51), \$16,427.49/LYG (48)
	Hong Kong	PPV23 dominates:(52)
	Belgium	PPV23 dominates (53)
		ICER falls in NE quadrant: \$9,497.91/LYG (53), \$158,334.03/QALY, \$82,533.95/QALY, \$61,194.02/QALY (54)
	Netherlands	ICER falls in NE quadrant: \$8,163.48/LYG (55), \$66,794.34/LYG, \$29,923.87/LYG, \$12,646.40/LYG, \$5,521.67/LYG, \$1,959.30/LYG, \$267.18/LYG (56)
	Germany	ICER falls in NE quadrant: \$23,771.12/QALY, \$35,781.34/QALY (160), \$20,547.77/LYG (58)
	Europe	ICER falls in NE quadrant: \$14,275.80-\$36,554.01 (59), \$4,453.32-43,129.81/QALY (60)
	Canada	PPV23 dominates: (61)
	Italy	ICER falls in NE quadrant: \$40,346.16/LYG (62)
	China	PPV23 dominates: (33)
	Brazil	PPV23 dominates: (63)
		ICER falls in NE quadrant: \$10,010.24/LYG, \$7,614.11/LYG (63)
	France	ICER falls in NE quadrant: \$28,428.20/LYS (64)

	Poland	ICER falls in NE quadrant: \$2,102.55/QALY, \$1,335.39/QALY (65)
	Colombia	ICER falls in NE quadrant: \$1,691.03/LYG (66)
	Turkey	PPV23 dominates (67)
	Spain	ICER falls in NE quadrant: \$3,838.65/QALY (68)
PPV23 within age groups	USA	ICER falls in NW quadrant: vaccinating 50 years only dominated by vaccinating <65 years with comorbidities, vaccinating 65 years only dominated by vaccinating 50 years only, vaccinating 65 and 80 years dominated by vaccinating 65 years only, vaccinating 50, 60, 70 and 80 years dominated by vaccinating 50, 65 and 80 years (44), use of 2 doses dominated by 1 dose in immunocompromised individuals 19-64 years (40), Flu only vaccination dominated by CDC - influenza vaccination for all and PPV23 when comorbid conditions are present, PPV23 only dominated by CDC - influenza vaccination for all, PPV when comorbid conditions are present, No vaccination dominated by CDC - influenza vaccination for all+ PPV23 when comorbid conditions are present (76)
		ICER falls in NE quadrant: vaccinating 50 and 65 years vs 65 and 80 years [\$29,548.34/QALY], vaccinating 50, 60, 70 and 80yrs vs 50, 65 and 80 years [\$85,396.23/QALY] (44), Flu and PPV23 vs CDC - influenza vaccination for all, PPV when comorbid conditions are present [\$44,076.64/QALY] (76)
	Japan	ICER falls in NW quadrant: Vaccinating 65yrs only dominated by vaccinating 65-80yrs (77)
		ICER falls in NE quadrant: Vaccinating >65 years vs 65yrs only[\$50.10/QALY] (77)
	Brazil	ICER falls in NE quadrant: universal programme vs targeted programme for high risk persons [\$1,391.66/LYG], [\$969.98] (78)
PCV13 vs no vaccination	USA	ICER falls in NE quadrant: \$97,038.76/QALY, \$307,484.26/QALY, \$318,006.54/QALY, \$73,422.10/QALY, \$325,021.39/QALY, \$13,211.30/QALY (39)
	Spain	PCV13 dominates (69)
	Colombia	PCV13 dominates (70)
	Finland	PCV13 dominates (71)
	Netherlands	ICER falls in NE quadrant: \$10,996.34/QALY (72)

	Germany	PCV13 dominates (58)
	Italy	ICER falls in NE quadrant: \$21,602.69/QALY, \$24,530.15/QALY, \$28,116.43/QALY (73)
	Belgium	ICER falls in NE quadrant: \$293,478/QALY, \$134,390/QALY, \$91,643.75/QALY (54)
	UK	ICER falls in NE quadrant: herd immunity from infant programme \$9,484.41/LYG (74)
PCV13+PPV23 vs no vaccination	USA	ICER falls in NE quadrant: \$32,254.95/QALY (75)
	Italy	ICER falls in NE quadrant: \$29,606.51/QALY, \$33,669.67/QALY, \$38,384.21/QALY (73)
PCV13+PPV23 vs PPV23	USA	ICER falls in NE quadrant: \$4,309.89/QALY, \$8,727,087.50/QALY, \$131,356.22/QALY, \$13,813.14/QALY, \$4,252.24/QALY (79), \$131,344.12/QALY, \$191,821.52/QALY (75)
PCV13 vs PPV23	USA	ICER falls in NE quadrant: \$33,788.19/QALY (41), \$82,935.40/QALY (40)
	Colombia	PCV13 dominated (70)
	Spain	ICER falls in NE quadrant: \$2,782.26/QALY (81)
	Germany	PCV13 dominates (58)
	UK	PCV13 dominated (161)
PCV13 vs PCV13+PPV23	USA	PCV13 dominated (40)
		ICER falls in NE quadrant: \$52,728.29/QALY (41)
PCV13+PPV23 vs PCV13	USA	PCV13 + PPV23 dominated (41)
		ICER falls in NE quadrant: \$579,894.28/QALY (41), \$159,849.73/QALY (40)
	France	PCV13 + PPV23 dominate (80)

PCV7 – seven valent pneumococcal conjugate vaccine; PCV10 – ten valent pneumococcal conjugate vaccine; PCV13 – thirteen valent pneumococcal conjugate vaccine; PPV23 – twenty three valent pneumococcal polysaccharide vaccine; ICER – incremental cost-effectiveness ratio; NE – north east; NW – north west; QALY – quality adjusted life years; DALY – disabled adjusted life years; LYG – life years gained; CDC – Center for disease and control;

**Table 3. Summary of economic evaluations of pneumococcal vaccinations in children (ICERs valued in \$USD, 2016 prices). Supporting references are given in parentheses.**

<b>Comparator</b>	<b>Setting</b>	<b>Results</b>
PCV7 vs no vaccination	Taiwan	ICER falls in NE quadrant: \$975,141.81/LYG, \$942,669.62/LYG, \$40,047.98/LYG, \$76,432.95/LYG (83)
	Norway	PCV7 dominates: (162)
		ICER falls in NE quadrant: \$82,683.69/QALY (\$54,630.30 if herd immunity is included), \$183,085.32/LYG (\$85,636.68/LYG if herd immunity is included) (163)
	USA	PCV7 dominates: (164)
		PCV7 dominated: Net benefit -\$121,835.59, -\$47,072.84, -\$20,676.43, -\$6,922.48, \$42,919.35, \$16,613.94, -\$1,384.50 (165)
		ICER falls in NE quadrant: \$9,328.80/LYG(166), \$40,919.96/QALY(167), \$10,7000/LYG(168), \$204,616.52/LYG(169)
	UK	ICER falls in NE quadrant: \$63,226.75/LYG(170), \$61,679.34/QALY(171)
	Canada	PCV7 dominates: (90), (172), (91)
		ICER falls in NE quadrant: \$129,809.44/QALY, \$266,333.15/QALY, \$226,047.47/QALY (88), \$88,156.27/LYG(173), \$456.13/QALY (87)
	Singapore	ICER falls in NE quadrant: \$47,391.64/DALY(86)
	Turkey	ICER falls in NE quadrant: \$7,627.84/LYG(103)
	Ireland	ICER falls in NE quadrant: \$310,983.05/LYG(174)
	GAVI-eligible countries	ICER falls in NE quadrant: \$196.43/DALY(96)
	South Korea	ICER falls in NE quadrant: \$197,630.41/LYG(175)
	International	ICER falls in NE quadrant: \$143.49/DALY(85)

	Latin America and the Caribbean	ICER falls in NE quadrant: \$6,329.04/QALY(176)
	Sweden	PCV7 dominates: \$34,463.07/LYG(177)
		ICER falls in NE quadrant: \$3,952.85/QALY, \$744.16/QALY(178)
	Finland	ICER falls in NE quadrant: \$301,658.40/LYG, \$193,174.60/LYG(84)
	Malaysia	ICER falls in NE quadrant: \$23,078.72/QALY(86)
	Netherlands	ICER falls in NE quadrant: \$21,906.11/QALY(179), \$36,751.26/QALY(180), \$19,995.60/QALY(181), \$109,369.32/QALY(182)
	China	PCV7 dominates: (183)
		ICER falls in NE quadrant: \$105,114.76/QALY(33), \$12,735.68/QALY(184), \$102,275.72/QALY(185)
	Middle-income countries	ICER falls in NE quadrant: \$1,928.12/QALY(97)
	Spain	PCV7 dominates: -\$488.15/LYG(186)
		ICER falls in NE quadrant: \$90,553.87/LYG(187), \$36,270.10/LYG(186)
	Australia	ICER falls in NE quadrant: \$50,718.33/QALY(112), (\$147,240.28: IPD-related outcomes only), (\$80,479.16-\$111,573.38: changes in non-IPD included) and \$8,230.82 : changes in adult non-invasive pneumonia are included(188), \$138,735.75/QALY(189)
	Germany	PCV7 dominates: -\$833.43/QALY (healthcare),-\$6,752.66/QALY (societal) (190)
		ICER falls in NE quadrant: ?72866/LYG(191), \$56,434.57/LYG, \$242.15/LYG, \$148,588.50/LYG(89)
	Japan	ICER falls in NE quadrant: \$16,011.63/QALY(110), \$91,368.33/QALY(192)
	Colombia	ICER falls in NE quadrant: \$879.19/LYG(193)
	Peru	ICER falls in NE quadrant: \$6,666.58/QALY(102)

	Switzerland	ICER falls in NE quadrant: \$29,053.05/QALY(194)
	Argentina	ICER falls in NE quadrant: \$6,376.83/QALY(195)
	Italy	ICER falls in NE quadrant: \$27,991.68/DALY(196)
	The Gambia	ICER falls in NE quadrant: \$1,096.62/DALY(197)
	Hong Kong	ICER falls in NE quadrant: \$10,287.71/LYG, \$9,441.95/LYG(198)
	Brazil	ICER falls in NE quadrant: \$825.91/DALY(199)
	Chile	ICER falls in NE quadrant: \$2,511.31/DALY(199)
	Uruguay	ICER falls in NE quadrant: \$1,922.98/DALY(199)
	Malaysia	ICER falls in NE quadrant: RM35,196/LYG(200)
PCV9 vs no vaccination	The Gambia	ICER falls in NE quadrant: \$36.15/DALY(201), \$807.40/DALY(197)
PCV10 vs no vaccination	Canada	PCV10 dominates: (90), (91)
	Croatia	ICER falls in NE quadrant: \$70,066.45/DALY(94)
	Brazil	ICER falls in NE quadrant: \$4,613.43/QALY (societal), \$5,279.84/DALY (healthcare) (104), \$3,725.50/QALY(92)
	Argentina	ICER falls in NE quadrant: \$9,946.66/DALY, \$9,473.33/DALY(95), \$3,298.03/QALY(92)
	Singapore	ICER falls in NE quadrant: \$49,390.25/QALY(86)
	Turkey	ICER falls in NE quadrant: \$7,279.12/LYG(103)
	GAVI-eligible countries	ICER falls in NE quadrant: \$134.97/DALY(96)
	Malaysia	ICER falls in NE quadrant: \$24,882.39/QALY(86), \$23,471.96/QALY(98)
	Netherlands	ICER falls in NE quadrant: \$24,718/QALY(180)
	Colombia	PCV10 dominates: (92)
		ICER falls in NE quadrant: \$843.24/LYG(108), \$2,036.33/LYG(202)
	Chile	PCV10 dominates : (92)
		ICER falls in NE quadrant: \$7,917.55/QALY(92)

	Mexico	ICER falls in NE quadrant: \$4,491.51/QALY (92)
	Peru	ICER falls in NE quadrant: \$5,092.86/QALY(92), \$1,690.99/DALY(101), \$4,988.30/QALY(102)
	Middle-income countries	ICER falls in NE quadrant: \$1,205.07/DALY(97)
	Australia	ICER falls in NE quadrant: \$39,245.32/QALY(112)
	Philippines	ICER falls in NE quadrant: \$3,936.43/QALY(106)
	Paraguay	ICER falls in NE quadrant: \$4,268.87/DALY, \$2,128.34/DALY(99), \$2,770.10/DALY(100)
	The Gambia	ICER falls in NE quadrant: \$807.40/DALY(197)
	Georgia	ICER falls in NE quadrant: \$1,657.65/LYG(203)
	Thailand	ICER falls in NE quadrant: \$46,738.69/QALY(105)
	Ecuador	ICER falls in NE quadrant: \$1,619.63/DALY(100)
	Honduras	ICER falls in NE quadrant: \$2,464.13/DALY(100)
	Kenya	ICER falls in NE quadrant: \$64.61/DALY(93)
PCV13 vs no vaccination	Taiwan	ICER falls in NE quadrant: \$42,173.26/LYG, \$20,284.62/LYG(109)
	Croatia	ICER falls in NE quadrant: \$71,370.93/DALY(94)
	England	ICER falls in NE quadrant: marginally cost-effective (111), \$288,222.01/QALY(107)
	Argentina	ICER falls in NE quadrant: \$12,135.97/DALY, \$11,650.44/DALY(95)
	Singapore	ICER falls in NE quadrant: \$41,224.98/QALY(86)
	Turkey	ICER falls in NE quadrant: \$7,184.70/LYG(103)
	GAVI-eligible countries	ICER falls in NE quadrant: \$126.53/DALY(96)
	Egypt	ICER falls in NE quadrant: \$4,059.63/DALY(204)
	Malaysia	ICER falls in NE quadrant: \$20,332.14/QALY(86)
	Netherlands	ICER falls in NE quadrant: \$23,488/QALY(180)
	Colombia	ICER falls in NE quadrant: \$507.19/LYG(108)
	Peru	ICER falls in NE quadrant: \$1,373.86/DALY(101), \$5,905.03/QALY(102)

	China	ICER falls in NE quadrant: \$29,748.93/QALY(33)
	Middle-income countries	ICER falls in NE quadrant: \$1,084.57/DALY(97)
	Australia	ICER falls in NE quadrant: \$43,251.33/QALY(112)
	Japan	PCV13 dominates: (110)
	Philippines	ICER falls in NE quadrant: \$3,147.09/QALY(106)
	Paraguay	ICER falls in NE quadrant: \$5,432.81/DALY, \$4,053.82/DALY(99)
	The Gambia	ICER falls in NE quadrant: \$686.89/DALY(197)
	Thailand	ICER falls in NE quadrant: \$47,456.68/QALY(105)
	Kenya	ICER falls in NE quadrant: \$51.47/DALY(93)
	Spain	ICER falls in NE quadrant: \$15,863.02/QALY(205)
PCV7 vs PCV10	Colombia	PCV7 dominates: (202)
PCV10 vs PCV7	Canada	PCV10 dominates: (90), (91), (116)
	Peru	PCV10 dominates: (206)
	Turkey	PCV10 dominates: (121)
PCV7 vs PCV13	Japan	PCV7 dominated: (110)
	Canada	PCV7 dominated: (116)
PCV13 vs PCV7	Germany	PCV13 dominates: (114)
	Netherlands	ICER falls in NE quadrant: \$49.50/QALY(114)
	Norway	PCV13 dominates: (162)
	USA	PCV13 dominates: (207)
	Switzerland	PCV13 dominates: (113)
	Peru	ICER falls in NE quadrant: \$2,020.81/QALY(102)
	Turkey	PCV13 dominates: (121)
PCV13 vs PCV10	Germany	PCV13 dominates: (114)
	Greece	PCV13 dominates: (114)
	Netherlands	PCV13 dominates: (114)

		ICER falls in NE quadrant: \$833,665.01/QALY(208)
	Peru	PCV13 dominated: (102)
		ICER falls in NE quadrant: \$13.95/avoided hospitalisation(206), \$546.81/DALY(101)
	Argentina	ICER falls in NE quadrant: \$31,201.23/DALY, \$30,610.40/DALY(95)
	Colombia	PCV13 dominates: (108)
	Canada	PCV13 dominates: (115), (116)
	Sweden	PCV13 dominates: (117)
		PCV13 dominated: (209)
	Denmark	PCV13 dominates: (117)
	Malaysia	PCV13 dominates: (118)
		ICER falls in NE quadrant: \$5,211.38/QALY(118)
PCV10 vs PCV13	Philippines	ICER falls in NE quadrant: \$3,000.80/QALY(210), \$930.95/QALY(106)
	Norway	PCV10 dominates:(162)
	Canada	PCV10 dominates: (119)
	UK	PCV10 dominates: (119)
	Hong Kong	PCV10 dominates: (120)
	Colombia	ICER falls in NE quadrant: \$10,548.58/LYG(202)
	Malaysia	PCV10 dominates: (98)
	Turkey	PCV10 dominates: (121)
PCV13: catch-up vs no catch-up	Switzerland	Catch-up dominates: (113)
	Italy	ICER falls in NE quadrant: \$17,358.18/YLS(211)
PCV13: 2 dose vs 3 dose	USA	ICER falls in NE quadrant: \$321,895.05/QALY(212)

PCV7 – seven valent pneumococcal conjugate vaccine; PCV9 – nine valent pneumococcal conjugate vaccine; PCV10 – ten valent pneumococcal conjugate vaccine; PCV13 – thirteen valent pneumococcal conjugate vaccine;  
ICER – incremental cost-effectiveness ratio; NE – northeast; QALY – quality adjusted life years; DALY – disabled adjusted life years; LYG – life years gained; IPD – invasive pneumococcal disease

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