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Pneumococcal Disease: A Systematic Review of Health Utilities, Resource Use, Costs, and Economic Evaluations of Interventions

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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 summarize 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 studies in English on pneumococcal disease that reported health utilities using direct or indirect valuation methods, resource use, costs, or cost-effectiveness of intervention programs, and summarized 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 programs. 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. Hospitalization was shortest for otitis media (range: 0.1–5 days) and longest for sepsis/septicemia (6–48). The main categories of costs reported were drugs, hospitalization, and household or employer costs. Resource use was reported in hospital length of stay and number of contacts with general practitioners. Costs and resource use significantly varied among population ages, disease conditions, and settings. Current vaccination programs for both adults and children, antibiotic use and outreach programs to promote vaccination, early disease detection, and educational programs 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 programs.

Keywords: cost-effectiveness, costs, health utilities, pneumococcal disease, resource use.

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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 septicemia, pneumonia, and meningitis that often result in hospitalization, 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 pediatric 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 World Health Organization 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 programs. Nevertheless, the vaccination schedule, coverage, and specific details of their implementation vary among countries.⁹ In addition, the different vaccines differ in efficacy and levels of protection, as well as price. One of the hallmarks of pediatric vaccinations is the generation of indirect effects by the vaccines.¹⁰

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Pneumococcal vaccines have led to significant reduction in disease and carriage owing 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 modeling studies have been conducted to evaluate the cost-effectiveness of pneumococcal vaccination and treatment programs, and these are important in helping policymakers 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. Nevertheless, previous reviews on the impact of pneumococcal disease on health-related quality of life have only focused on a small number of pneumococcal infections, such as otitis media¹³ and sepsis.¹⁴ Hospitalization and long-term sequelae caused by pneumococcal diseases have economic consequences at various levels, including the individual, household, government, and overall society. Nevertheless, 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 pediatric pneumococcal vaccination programs. These reviews focused on parameters and assumptions that influenced modeling results,¹⁵ strengths and limitations of contributing studies,¹⁶ results of cost-effectiveness studies,^{17,18} their main methodological features,¹⁹ or economic profiles of vaccines in adults in costs and benefits,²⁰ or provided a summary of evidence and key drivers of results in low- and middle income countries.²¹ Nevertheless, other features, such as modeling methods, input parameters, and assumptions, can affect the generalizability 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 programs, is critical. To our knowledge, there have been no previous systematic reviews of economic evaluations of pneumococcal disease treatment and other intervention programs.

We therefore conducted a broad systematic review with the goal of identifying and summarizing 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 programs. 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 Appendix A in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>) for peer-reviewed studies published between January 1, 1990 (a decade before any national programs with conjugate vaccine) and November 31, 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 that includes meningitis, septicemia or bacteremia, and empyema or noninvasive pneumococcal disease

that includes community-acquired pneumonia (CAP), sinusitis, and otitis media; studies that reported on resource utilization 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 2-stage process. Initially, 2 independent reviewers performed title and abstract screening to exclude irrelevant studies and, finally, 2 independent reviewers screened full texts to identify relevant articles. Two reviewers independently extracted data using standardized data extraction forms from the eligible full-text studies, and specific details about the extracted data by study type are given in Appendix A in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>. 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 USD 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 Coordination Centre cost converter.²² When the costing year was not available, it was assumed to be the year before 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 program, or treatment or other intervention program. Data were not meta-analyzed owing to heterogeneities in study designs, outcomes, and intervention types and 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 checklist,²³ and no quality appraisal was conducted for studies reporting health utilities, resource consequences, or costs.

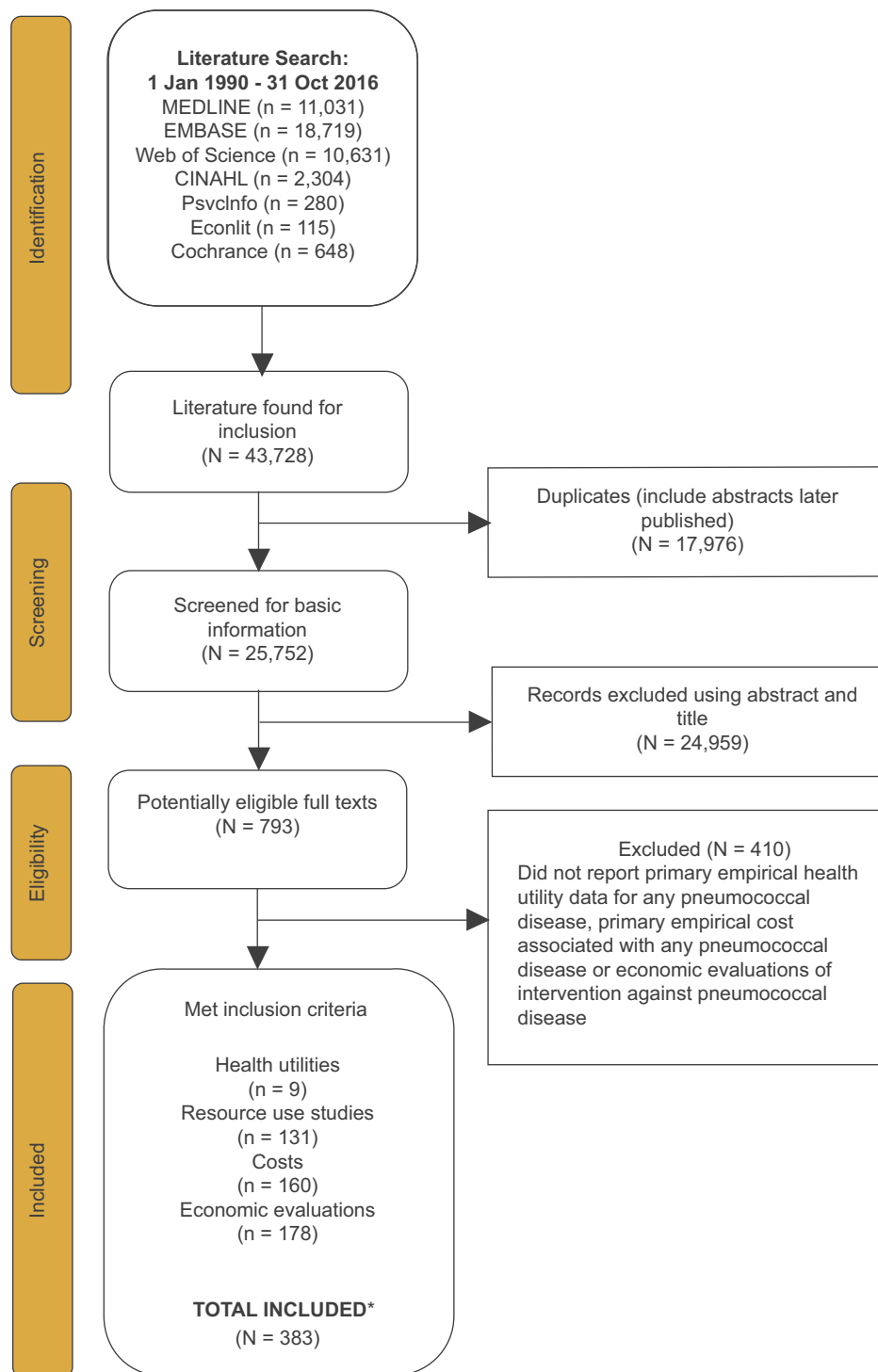
Results

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 Fig. 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. A total of 178 articles reported on economic evaluations of pneumococcal intervention programs. Of these, 50 articles reported on adult vaccination, 90 on childhood vaccination, 26 on antibiotic treatment, and 12 on other intervention programs.

Healthy Utility Studies

Nine studies assessed utility values for meningitis, otitis media, pneumonia, and sepsis/bacteremia (Table 1²⁴⁻³²; Appendix Table 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>). These studies were from United States, Thailand, Argentina, Chile, the United Kingdom, and Canada. The results are reported by disease as follows.

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



Meningitis

Two articles reported on health utility values for meningitis health states using direct valuation methods, and 5 reported health utility values for meningitis health states using indirect valuation methods (Table 1).²⁴⁻³⁰ The health utility values²⁴⁻²⁸

ranged from 0.0177 for a health state equivalent to death in the United States to 0.9971 for an outcome where blood is drawn (United States).²⁷ One study, using the time tradeoff (TTO) method, reported that parents were willing to trade up to 3 years of their own lives to prevent their child from spending any time in

Table 1. Summary of utility values in pneumococcal infected children and adults.

Disease area	Age group	Country	Outcome/ health state	Utility values mean (SD)	WTP values (range)	TTO-generated TTOs
Acute otitis media	Child	United States	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
	Adult	Thailand	Overall self-report	0.52-0.68 ²⁴		
			Overall proxy	0.62-0.77 ²⁴		
		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	0.44-0.73 ²⁴		
			Overall proxy	0.48-0.70 ²⁴		
	Adult	United States	Moderate pneumonia		\$200-\$300 ²⁹	1-180 days ²⁹
			Severe pneumonia		\$400 ²⁹	365 days ²⁹
		Argentina	Hospitalized pneumonia	0.309 ³⁰		
			Ambulatory pneumonia	0.628 ³⁰		
		Chile	Hospitalized pneumonia	-0.054 ³⁰		
			Ambulatory pneumonia	0.412 ³⁰		
		United Kingdom	Hospitalized pneumonia	0.035 ³⁰		
			Ambulatory pneumonia	0.508 ³⁰		
		United States and 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	0.24-0.68 ²⁴		
		Thailand	Overall proxy	0.02-0.52 ²⁴		
		UK	Overall	0.181, ²⁵ 0.774 ²⁶		
		United States	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		

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Table 1. Continued

Disease area	Age group	Country	Outcome/ health state	Utility values mean (SD)	WTP values (range)	TTO-generated TTOs
			Hospitalization	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 bacteremia	Child	Thailand	Overall self-report	0.33-0.69 ²⁴		
		Thailand	Overall proxy	0.38-0.62 ²⁴		
		United States	Overall		\$250-300 ²⁹	90-180 days ²⁹
	Adult	Argentina	Overall	−0.034 ³⁰		
		Chile	Overall	−0.331 ³⁰		
		UK	Overall	−0.295 ³⁰		

Note. Supporting references are given in parentheses. WTP indicates % of household income/amount of money an individual is willing to pay to avoid described health state.

SG indicates standard gamble; TTO, time tradeoff; WTP, willingness to pay.

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

Two articles reported health utility values for otitis media health states using direct valuation methods and 2 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 United Kingdom³⁰ to an overall value of 0.97 in the United States.³¹ One article reported TTO generated TTOs ranging from 0 to 7 days for simple otitis media to 270 to 365 days for complex otitis media, both for the United States, 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 2 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 to 180 days for moderate pneumonia to 365 days for severe pneumonia, both for the United States.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 hospitalized pneumonia in Chile³⁰ to 0.979 for usual health in Canada and the United States.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 United States.³²

Bacteremia

One article reported health utility values for sepsis or bacteremia using direct valuation methods, and 2 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 to 180 days and willingness-to-pay values ranging from \$250 to \$300 for sepsis in the United States.²⁹ For adults, health utility values for sepsis or bacteremia 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, invasive pneumococcal disease, meningitis, empyema, and sepsis/bacteremia (see Appendix A in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011> 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 (see Appendix A in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>). 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, hospitalization and households, resource use such as hospital stays and visits, and all these varied extensively among 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 focused on the impact of antibiotic treatment on pneumococcal diseases, 12 focused on other diagnostic/

Table 2. Summary of cost-effectiveness studies of pneumococcal vaccination in adults (ICERs valued in USD, 2016 prices).

Comparator	Setting	Results
PPV23 vs no vaccination	United States	PPV23 dominates ³³⁻³⁷
		PPV23 dominates ³⁸⁻⁴⁰
		ICER falls in NE quadrant: \$2497.94/QALY, ⁴¹ \$33 356.90/QALY, \$91 124.42/QALY, \$96 875.61/QALY, ⁴² \$4269.94/QALY, ⁴³ \$3431.43/QALY, \$1959.48/employee, ⁴⁴ \$9505.42/QALY, \$18 210.27/QALY, \$21 664.24/QALY, \$28 149.83/QALY, ⁴⁵ \$72 482.71/LYG, \$31 402.47/LYG, ⁴⁶ \$45 491.99/QALY, \$226 233.43/QALY ³⁷
	United Kingdom	PPV23 dominates ⁴⁷
		ICER falls in NE quadrant: \$375 354.91/QALY, ⁴⁸ \$14 441.17-\$73 613.17, ⁴⁹ \$19 214.83/LYG for vaccinating all high-risk adults and \$17 242.05/LYG for all 65+ year-olds, ⁵⁰ \$16 427.49/LYG ⁴⁷
	Hong Kong	PPV23 dominates ⁵¹
	Belgium	PPV23 dominates ⁵²
	the Netherlands	ICER falls in NE quadrant: \$9497.91/LYG, ⁵² \$158 334.03/QALY, \$82 533.95/QALY, \$61 194.02/QALY ⁵³
		ICER falls in NE quadrant: \$8163.48/LYG, ⁵⁴ \$66 794.34/LYG, \$29 923.87/LYG, \$12 646.40/LYG, \$5521.67/LYG, \$1959.30/LYG, \$267.18/LYG ⁵⁵
	Germany	ICER falls in NE quadrant: \$23 771.12/QALY, \$35 781.34/QALY, ⁵⁶ \$20 547.77/LYG ⁵⁷
	Europe	ICER falls in NE quadrant: \$14 275.80-\$36 554.01, ⁵⁸ \$4453.32-\$43 129.81/QALY ⁵⁹
	Canada	PPV23 dominates ⁶⁰
	Italy	ICER falls in NE quadrant: \$40 346.16/LYG ⁶¹
	China	PPV23 dominates ⁸²
	Brazil	PPV23 dominates ⁶²
	France	ICER falls in NE quadrant: \$10 010.24/LYG, \$7614.11/LYG ⁶²
		ICER falls in NE quadrant: \$28 428.20/LYS ⁶³
	Poland	ICER falls in NE quadrant: \$2102.55/QALY, \$1335.39/QALY ⁶⁴
	Colombia	ICER falls in NE quadrant: \$1691.03/LYG ⁶⁵
	Turkey	PPV23 dominates ⁶⁶
	Spain	ICER falls in NE quadrant: \$3838.65/QALY ⁶⁷
PPV23 within age groups	United States	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 ⁴³ ; use of 2 doses dominated by 1 dose in immunocompromised individuals 19-64 years ³⁹ ; 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 ⁷⁵
	Japan	ICER falls in NE quadrant: vaccinating 50 and 65 years vs 65 and 80 years (\$29 548.34/QALY); vaccinating 50, 60, 70, and 80 years vs 50, 65, and 80 years (\$85 396.23/QALY) ⁴³ ; flu and PPV23 vs CDC-influenza vaccination for all, PPV when comorbid conditions are present (\$44 076.64/QALY) ⁷⁵
		ICER falls in NW quadrant: vaccinating 65 years only dominated by vaccinating 65-80 years ⁷⁶
	Brazil	ICER falls in NE quadrant: universal program vs targeted program for high-risk persons (\$1391.66/LYG), \$969.98 ⁷⁷
PCV13 vs no vaccination	United States	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 ³⁸
	Spain	PCV13 dominates ⁶⁸
	Colombia	PCV13 dominates ⁶⁹

continued on next page

Table 2. Continued

Comparator	Setting	Results
	Finland	PCV13 dominates ⁷⁰
	Netherlands	ICER falls in NE quadrant: \$10 996.34/QALY ⁷¹
	Germany	PCV13 dominates ⁵⁷
	Italy	ICER falls in NE quadrant: \$21 602.69/QALY, \$24 530.15/QALY, \$28 116.43/QALY ⁷²
	Belgium	ICER falls in NE quadrant: \$293 478/QALY, \$134 390/QALY, \$91 643.75/QALY ⁵³
	United Kingdom	ICER falls in NE quadrant: herd immunity from infant program \$9 484.41/LYG ⁷³
PCV13 + PPV23 vs no vaccination	United States	ICER falls in NE quadrant: \$32 254.95/QALY ⁷⁴
	Italy	ICER falls in NE quadrant: \$29 606.51/QALY, \$33 669.67/QALY, \$38 384.21/QALY ⁷²
PCV13 + PPV23 vs PPV23	United States	ICER falls in NE quadrant: \$4309.89/QALY, \$8 727 087.50/QALY, \$131 356.22/QALY, \$13 813.14/QALY, \$4252.24/QALY, ⁷⁸ \$131 344.12/QALY, \$191 821.52/QALY ⁷⁴
PCV13 vs PPV23	United States	ICER falls in NE quadrant: \$33 788.19/QALY, ⁴⁰ \$82 935.40/QALY ³⁹
	Colombia	PCV13 dominates ⁶⁹
	Spain	ICER falls in NE quadrant: \$2782.26/QALY ⁸⁰
	Germany	PCV13 dominates ⁵⁷
	UK	PCV13 dominates ⁸¹
PCV13 vs PCV13 + PPV23	United States	PCV13 dominates ³⁹
		ICER falls in NE quadrant: \$52 728.29/QALY ⁴⁰
PCV13 + PPV23 vs PCV13	United States	PCV13 + PPV23 dominates ⁴⁰
		ICER falls in NE quadrant: \$579 894.28/QALY, ⁴⁰ \$159 849.73/QALY ³⁹
	France	PCV13 + PPV23 dominates ⁷⁹

Note. Supporting references are given in parentheses.

CDC indicates Centers for Disease Control and Prevention; DALY, disabled-adjusted life years; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NE, northeast; NW, northwest; 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; QALY, quality-adjusted life years.

operational interventions (for example, management, treatment guidelines, standing-order programs, and screening), and the largest number of studies (140) focused on vaccinations programs. The vaccination programs were further stratified into adult (Table 2³³⁻⁸¹) and pediatric (Table 3⁸²⁻¹⁷²) categories. For both adult and pediatric programs, 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; Appendix Table 2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>). Twenty-five studies were carried out in Europe; 17 in the United States; 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.^{33-67,82} The time horizon used in these analyses varied from 1 year to a lifetime. Some studies in the United States,³³⁻³⁷ the United Kingdom,⁴⁷ Hong Kong,⁵¹ Belgium,⁵² Canada,⁶⁰ China,⁸² Brazil,⁶² and Turkey⁶⁶ reported that PPV23 use in the adult program dominates in health economic terms.

PCV13 versus no vaccination

Nine studies considered the possible use of pediatric PCV13 vaccine in adult populations versus not vaccinating at all.^{39,53,59,68-73} 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 age 50 was cost saving in Spain,⁶⁸ Colombia,⁶⁹ and Finland.⁷⁰

PCV13 + PPV23 versus no vaccination

Two studies from Italy and the United States assessed the cost-effectiveness of a combination or sequential use of PCV13 and PPV23 in adults against no vaccination.^{72,74} 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 United States,^{39,43,75} 1 from Japan⁷⁶ and another study from Brazil⁷⁷ assessed the use of PPV23 within different adult age groups. In the United States, targeting 50-year-olds versus all those less than 65 years with comorbidities was

Table 3. Summary of economic evaluations of pneumococcal vaccinations in children (ICERs valued in USD, 2016 prices).

Comparator	Setting	Results
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 ¹²²
		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) ¹²³
	United States	PCV7 dominates ¹²⁴
		PCV7 dominated: Net benefit −\$121 835.59, −\$47 072.84, −\$20 676.43, −\$6922.48, \$42 919.35, \$16 613.94, −\$1384.50 ¹²⁵
		ICER falls in NE quadrant: \$9328.80/LYG, ¹²⁶ \$40 919.96/QALY, ¹²⁷ \$10 7000/LYG, ¹²⁸ \$204 616.52/LYG ¹²⁹
	United Kingdom	ICER falls in NE quadrant: \$63 226.75/LYG, ¹³⁰ \$61 679.34/QALY ¹³¹
	Canada	PCV7 dominates ^{90,91,132}
		ICER falls in NE quadrant: \$129 809.44/QALY, \$266 333.15/QALY, \$226 047.47/QALY, ⁸⁸ \$88 156.27/LYG, ¹³³ \$456.13/QALY ⁸⁷
	Singapore	ICER falls in NE quadrant: \$47 391.64/DALY ⁸⁶
	Turkey	ICER falls in NE quadrant: \$7627.84/LYG ¹⁰³
	Ireland	ICER falls in NE quadrant: \$310 983.05/LYG ¹³⁴
	GAVI-eligible countries	ICER falls in NE quadrant: \$196.43/DALY ⁹⁶
	South Korea	ICER falls in NE quadrant: \$197 630.41/LYG ¹³⁵
	International	ICER falls in NE quadrant: \$143.49/DALY ⁸⁵
	Latin America and the Caribbean	ICER falls in NE quadrant: \$6329.04/QALY ¹³⁶
	Sweden	PCV7 dominates: \$34 463.07/LYG ¹³⁷
		ICER falls in NE quadrant: \$3952.85/QALY, \$744.16/QALY ¹³⁸
	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
	the Netherlands	ICER falls in NE quadrant: \$21 906.11/QALY, ¹³⁹ \$36 751.26/QALY, ¹⁴⁰ \$19 995.60/QALY, ¹⁴¹ \$109 369.32/QALY ¹⁴²
	China	PCV7 dominates ¹⁴³
		ICER falls in NE quadrant: \$105 114.76/QALY, ⁸² \$12 735.68/QALY, ¹⁴⁴ \$102 275.72/QALY ¹⁴⁵
	Middle-income countries	ICER falls in NE quadrant: \$1928.12/QALY ⁹⁷
	Spain	PCV7 dominates: −\$488.15/LYG ¹⁴⁶
		ICER falls in NE quadrant: \$90 553.87/LYG, ¹⁴⁷ \$36 270.10/LYG ¹⁴⁶
	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 \$8230.82: changes in adult noninvasive pneumonia are included, ¹⁴⁸ \$138 735.75/QALY ¹⁴⁹
	Germany	PCV7 dominates: −\$833.43/QALY (healthcare), −\$6752.66/QALY (societal) ¹⁵⁰
		ICER falls in NE quadrant: \$107 648.77/LYG, ¹⁵¹ \$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 ¹⁵²
	Colombia	ICER falls in NE quadrant: \$879.19/LYG ¹⁵³
	Peru	ICER falls in NE quadrant: \$6666.58/QALY ¹⁰²
	Switzerland	ICER falls in NE quadrant: \$29 053.05/QALY ¹⁵⁴
	Argentina	ICER falls in NE quadrant: \$6376.83/QALY ¹⁵⁵
	Italy	ICER falls in NE quadrant: \$27 991.68/DALY ¹⁵⁶
	The Gambia	ICER falls in NE quadrant: \$1096.62/DALY ¹⁵⁷
	Hong Kong	ICER falls in NE quadrant: \$10 287.71/LYG, \$9441.95/LYG ¹⁵⁸
	Brazil	ICER falls in NE quadrant: \$825.91/DALY ¹⁵⁹

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Table 3. Continued

Comparator	Setting	Results
PCV9 vs no vaccination	Chile	ICER falls in NE quadrant: \$2511.31/DALY ¹⁵⁹
	Uruguay	ICER falls in NE quadrant: \$1922.98/DALY ¹⁵⁹
	Malaysia	ICER falls in NE quadrant: Malaysian ringgit 35 196/LYG ¹⁶⁰
	The Gambia	ICER falls in NE quadrant: \$36.15/DALY, ¹⁶¹ \$807.40/DALY ¹⁵⁷
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: \$4613.43/QALY (societal), \$5279.84/DALY healthcare, ¹⁰⁴ \$3725.50/QALY ⁹²
	Argentina	ICER falls in NE quadrant: \$9946.66/DALY, \$9473.33/DALY, ⁹⁵ \$3298.03/QALY ⁹²
	Singapore	ICER falls in NE quadrant: \$49 390.25/QALY ⁸⁶
	Turkey	ICER falls in NE quadrant: \$7279.12/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 ¹⁴⁰
	Colombia	PCV10 dominates ⁹²
		ICER falls in NE quadrant: \$843.24/LYG, ¹⁰⁸ \$2036.33/LYG ¹⁶⁶
	Chile	PCV10 dominates ⁹²
		ICER falls in NE quadrant: \$7917.55/QALY ⁹²
	Mexico	ICER falls in NE quadrant: \$4491.51/QALY ⁹²
	Peru	ICER falls in NE quadrant: \$5092.86/QALY, ⁹² \$1690.99/DALY, ¹⁰¹ \$4988.30/QALY ¹⁰²
	Middle-income countries	ICER falls in NE quadrant: \$1205.07/DALY ⁹⁷
	Australia	ICER falls in NE quadrant: \$39 245.32/QALY ¹¹²
	Philippines	ICER falls in NE quadrant: \$3936.43/QALY ¹⁰⁶
	Paraguay	ICER falls in NE quadrant: \$4268.87/DALY, \$2128.34/DALY, ⁹⁹ \$2770.10/DALY ¹⁰⁰
	The Gambia	ICER falls in NE quadrant: \$807.40/DALY ¹⁵⁷
PCV13 vs no vaccination	Georgia	ICER falls in NE quadrant: \$1657.65/LYG ¹⁶³
	Thailand	ICER falls in NE quadrant: \$46 738.69/QALY ¹⁰⁵
	Ecuador	ICER falls in NE quadrant: \$1619.63/DALY ¹⁰⁰
	Honduras	ICER falls in NE quadrant: \$2464.13/DALY ¹⁰⁰
	Kenya	ICER falls in NE quadrant: \$64.61/DALY ⁹³
	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: \$7184.70/LYG ¹⁰³
	GAVI-eligible countries	ICER falls in NE quadrant: \$126.53/DALY ⁹⁶
	Egypt	ICER falls in NE quadrant: \$4059.63/DALY ¹⁶⁴
	Malaysia	ICER falls in NE quadrant: \$20 332.14/QALY ⁸⁶
	Netherlands	ICER falls in NE quadrant: \$23 488/QALY ¹⁴⁰
	Colombia	ICER falls in NE quadrant: \$507.19/LYG ¹⁰⁸
	Peru	ICER falls in NE quadrant: \$1373.86/DALY, ¹⁰¹ \$5905.03/QALY ¹⁰²
	China	ICER falls in NE quadrant: \$29 748.93/QALY ⁸²
	Middle-income countries	ICER falls in NE quadrant: \$1084.57/DALY ⁹⁷

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Table 3. Continued

Comparator	Setting	Results
	Australia	ICER falls in NE quadrant: \$43 251.33/QALY ¹¹²
	Japan	PCV13 dominates ¹¹⁰
	Philippines	ICER falls in NE quadrant: \$3147.09/QALY ¹⁰⁶
	Paraguay	ICER falls in NE quadrant: \$5432.81/DALY, \$4053.82/DALY ⁹⁹
	The Gambia	ICER falls in NE quadrant: \$686.89/DALY ¹⁵⁷
	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 ¹⁶⁵
PCV7 vs PCV10	Colombia	PCV7 dominates ¹⁶²
PCV10 vs PCV7	Canada	PCV10 dominates ^{90,91,116}
	Peru	PCV10 dominates ¹⁵⁴
	Turkey	PCV10 dominates ¹²¹
PCV7 vs PCV13	Japan	PCV7 dominates ¹¹⁰
	Canada	PCV7 dominates ¹¹⁶
PCV13 vs PCV7	Germany	PCV13 dominates ¹¹⁴
	Netherlands	ICER falls in NE quadrant: \$49.50/QALY ¹¹⁴
	Norway	PCV13 dominates ¹²²
	United States	PCV13 dominates ¹⁶⁷
	Switzerland	PCV13 dominates ¹¹³
	Peru	ICER falls in NE quadrant: \$2020.81/QALY ¹⁰²
	Turkey	PCV13 dominates ¹²¹
PCV13 vs PCV10	Germany	PCV13 dominates ¹¹⁴
	Greece	PCV13 dominates ¹¹⁴
	The Netherlands	PCV13 dominates ¹¹⁴
		ICER falls in NE quadrant: \$833 665.01/QALY ¹⁶⁸
	Peru	PCV13 dominated ¹⁰²
		ICER falls in NE quadrant: \$13.95/avoided hospitalization, ¹⁶⁶ \$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 dominates ¹⁶⁹
	Denmark	PCV13 dominates ¹¹⁷
	Malaysia	PCV13 dominates ¹¹⁸
		ICER falls in NE quadrant: \$5211.38/QALY ¹¹⁸
PCV10 vs PCV13	Philippines	ICER falls in NE quadrant: \$3000.80/QALY, ¹⁷⁰ \$930.95/QALY ¹⁰⁶
	Norway	PCV10 dominates ¹²²
	Canada	PCV10 dominates ¹¹⁹
	UK	PCV10 dominates ¹¹⁹
	Hong Kong	PCV10 dominates ¹²⁰
	Colombia	ICER falls in NE quadrant: \$10 548.58/LYG ¹⁶²
	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 ¹⁷¹
PCV13: 2 dose vs 3 dose	United States	ICER falls in NE quadrant: \$321 895.05/QALY ¹⁷²

Note. Supporting references are given in parentheses.

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

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 3 age groups (50, 65, and 80 years) versus 2 age groups (50 and 65 years) was extendedly dominated,⁴³ and vaccinating at ≥ 50 years with PPV23 only versus influenza vaccination for all with PPV23 in adults with comorbid conditions was dominated. In Japan, vaccinating 65- to 80-year-olds versus vaccinating 65-year-olds only was dominated.⁷⁶ In Brazil, universal PPV23 versus targeted PPV23 in high-risk individuals resulted in an ICER varying between \$970 and \$1392 per life year gained.⁷⁷

PCV13 + PPV23 versus PPV23

Two studies from the United States evaluated the head-to-head use of a combination of PCV13 and PPV23 against the use of PPV23.^{74,78} The models considered time horizons varying from 15 years to a lifetime. The mean ICERs derived varied between \$4310 and \$191 822 per additional QALY.

PCV13 versus PCV13 + PPV23

Two studies from the United States^{39,40} and 1 from France⁷⁹ assessed the cost-effectiveness of using PCV13 versus a combination of PCV13 and PPV23 in adults. The 3 time horizons considered were 5 years (France), 15 years, and a lifetime (United States). In a study considering a time horizon of 15 years, PCV13 alone was dominated when used in immunocompromised adults 19 to 64 years of age,³⁹ 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.⁴⁰ In France, there was a societal net monetary benefit of \$85 911 569 as a result of using a combination of PCV13 and PPV23.⁷⁹

PCV13 versus PPV23

Six studies estimated the cost-effectiveness of using PPV23 against PCV13 in adults in the United States,^{39,40} Colombia,⁶⁹ Spain,⁸⁰ Germany⁵⁷ or the United Kingdom.¹⁷³ 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.

Pediatric vaccination

A total of 90 articles reported the cost-effectiveness of pneumococcal vaccination in children (Table 3; Appendix Table 3 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>). 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 1 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 pediatric 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 settings⁸⁵ and \$47 392 per DALY averted in Singapore,⁸⁶ \$456 per QALY gained⁸⁷ and \$266 333 per QALY gained⁸⁸ in Canada, and \$242 per life year gained (LYG) in Germany⁸⁹ 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 Chile⁹² showing that the vaccine was highly cost-effective. The mean ICER ranged between \$65 per DALY averted in Kenya⁹³ 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 Turkey¹⁰³) reporting that PCV10 was cost-effective.¹⁰⁴ PCV10 use was moderately cost-effective in Singapore⁸⁶ 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 Kenya⁹³ and \$71 371 per DALY averted in Croatia,⁹⁴ \$3147 per QALY gained in Philippines¹⁰⁶ and \$288 222 per QALY gained in England,¹⁰⁷ and \$507 per LYG in Colombia¹⁰⁸ and \$42 173 per LYG in Taiwan.¹⁰⁹ In Japan, PCV13 was cost saving,¹¹⁰ whereas the 2 analyses conducted for England,^{107,111} 1 in Singapore⁸⁶ and another in Australia,¹¹² showed that PCV13 was marginally cost-effective. In China⁸² and Thailand,¹⁰⁵ the analyses showed that introducing PCV13 into the national immunization program was not cost-effective. In Switzerland, including a catch-up program was cost saving compared to not including catchup.¹¹³

PCV10 versus PCV13

A mixture of results was observed when the 2 vaccines were compared against each other in different settings. Comparison of the cost-effectiveness of PCV10 against PCV13 was conducted for 18 countries. In Germany,¹¹⁴ Greece,¹¹⁴ the 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 the United Kingdom,¹¹⁹ Hong Kong,¹²⁰ and Turkey¹²¹ 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 programs, all 24 quality indicators using the Consolidated Health Economic Evaluation Reporting Standards checklist were assessed, with 37 studies (74%) in adults and 61 studies (68%) in children scoring at least a 20 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 United States (14 studies), 2 studies each in the United Kingdom and Canada, and 1 study each in the Netherlands, Germany, Italy, India, Malaysia, Belgium, Finland and France, and Germany and the United States combined (see Appendix Table 4 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>).

The studies that compared antibiotics for treating CAP showed that levofloxacin,¹⁷⁴⁻¹⁷⁶ ceftriaxone,^{177,178} a combination of moxifloxacin and co-amoxiclav,^{179,180} sparfloxacin,¹⁸¹ gatifloxacin,¹⁸² ampicillin,¹⁸³ meropenem,¹⁸⁴ adherence to Infectious Diseases Society of America/American Thoracic Society antibiotic guidelines,¹⁸⁵ co-amoxiclav,¹⁸⁶ azithromycin,¹⁸⁷ 7 days of a home-based course of oral amoxicillin,¹⁸⁸ and oral gemifloxacin¹⁸⁹ were cost saving. There were no significant cost differences between

intravenous azithromycin and intravenous erythromycin,¹⁹⁰ whereas a continuous infusion of cefuroxime had the same effect but cost less than an intermittent infusion of cefuroxime.¹⁹¹

For the treatment of otitis media, the following antibiotics were found to be cost-effective: ofloxacin,¹⁹² amoxicillin,¹⁹³ chemoprophylaxis,¹⁹⁴ delayed prescription,^{195,196} and the 2002 antibiotic guidelines.¹⁹⁷

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.¹⁹⁸ Computerized tomography with instillation of fibrinolytics was found to be cost-effective against a percutaneous chest tube for treating empyema.¹⁹⁹

Other Interventions Studies

Twelve cost-effectiveness studies of other interventions targeting pneumococcal diseases, conducted in the United States (7 studies), Spain (2 studies), the Netherlands (2 studies), and Canada (1 study), were identified (see Appendix Table 5 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2019.06.011>). Interventions such as outreach programs to promote vaccination,²⁰⁰ early disease detection and treatment,²⁰¹ procalcitonin protocols in CAP,²⁰² diagnostics,²⁰³ patient management,²⁰⁴⁻²⁰⁷ treatment with guidelines,²⁰⁸ screening,²⁰⁹ and educational programs^{210,211} 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 because contributing studies differed in methodologies and underpinning healthcare practices, relative prices of labor 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 are 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. Among 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 among countries, which seriously limits potential generalizability 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, whereas 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 programs¹⁵⁻²¹; 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 because 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 a 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 gray 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 of informing future research priorities. Standardization of methods for the measurement and valuation of health utilities and economic costs, and their reporting, would enhance across-study comparisons and inform prioritization 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 programs.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2019.06.011>.

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