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SYSTEMATIC REVIEW

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A systematic literature review of economic evaluations of pneumococcal conjugate vaccines in east and southeast Asia (2006-2019)

Bruce Cm Wang[a], Nathorn Chaiyakunapruk [b], Shuiqing Zhu[c], Joseph B. Babigumira[d], Wesley Furnback[a], Ramaa Chitale[e], Amgad Gamil[f], Kun Zhao[g] and Matt Wasserman [e]

[a]Health Economics and Real World Evidence , Elysia Group, LLC, New York, NY, USA; [b]Department of Pharmacotherapy, University of Utah, Salt Lake City, UT, USA; [c]Health Economics and Outcomes Research, Pfizer Investment Co. Ltd, Shanghai, China; [d]Department of Global Health, University of Washington, Seattle, WA, USA; [e]Health Economics and Outcomes Research, Pfizer Inc, New York, NY, USA; [f]Medical and Scientific Affairs, Pfizer Inc, Singapore; [g]Health Technology Assessment, China National Health Development Research Center, National Health Commission of the People's Republic of China

ABSTRACT

Introduction: Pneumococcal infections can lead to serious invasive diseases such as meningitis, septicemia and pneumonia, as well as milder but more common illnesses such as sinusitis and otitis media. The World Health Organization (WHO) recommends the inclusion of pneumococcal conjugate vaccines (PCVs) in infant National Immunization Program (NIP) programs worldwide. Decision-makers in Asian countries planning to introduce PCVs in their respective NIP will need a comprehensive evidence of effectiveness of PCVs at the population level and economic evidence including cost-effectiveness.

Areas Covered: A systematic literature review (from 1/1/2016 to 10/11/2019) of PCVs in East and Southeast Asia to understand (1) the contributing factors to cost-effectiveness results of PCVs and (2) whether gaps in evidence exist suggesting why the region may have yet to implement full NIPs.

Expert Opinion: In East and Southeast Asia, vaccination with PCVs was found to significantly reduce the mortality and morbidity of pneumococcal diseases and was cost-effective compared to no vaccination. Study assumptions, specifically vaccine local acquisition, the inclusion or exclusion of indirect effects (serotype replacement and herd effect), cross-protection, and protection against nontypeable *haemophilus influenzae* and serotype 3, were the main drivers of cost-effectiveness.

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East and Southeast Asia; economic evaluations; national Immunization Program; pneumococcal Conjugate Vaccine; systematic Literature Review

1. Introduction

The bacterium *Streptococcus pneumoniae* (pneumococcus) causes invasive pneumococcal disease (IPD) such as meningitis, bacteremia and sepsis as well as noninvasive mucosal diseases such as otitis media (OM) and pneumonia. Pneumococcal disease is responsible for 9.2 million vaccine preventable disease cases and 318,000 deaths around the globe in children under 5 every year [1]. Compared to other World Health Organization (WHO) regions, the Southeast Asia and Western Pacific regions account for the highest (4.4 million) and third highest (1.01 million) number of cases, respectively [1].

Pneumococcal conjugate vaccines (PCVs) came into use in 2000 with the introduction of the 7-valent PCV (PCV7). Subsequently in 2009, PCV10-GSK (Synflorix™, GlaxoSmithKline) and PCV13-PFE (Prevenar13™, Pfizer) were licensed and widely introduced and both are currently licensed for use in children under 5 years of age. PCV13-PFE is also licensed for all age groups above 5 years in most countries around the world, and currently the WHO recommends the inclusion of PCVs in infant national immunization programs (NIPs) worldwide. Vaccinations similar to PCV10-GSK and PCV13-PFE have been licensed within countries in the Southeast Asia and Western Pacific regions. First, a 10-valent vaccine has been developed by Serum Institute of India (SII), containing PCV7 serotypes plus 6A and 19A, but excluding 4 and 18 C (PCV10-SII) and was granted WHO prequalification in 2019, only in a 3 + 0 schedule [2]. PCV13-PFE and PCV10-GSK are both licensed in a 3 + 1, 2 + 1 and 3 + 0 schedule to be used depending on local epidemiology and implementation. Second, a 13-valent vaccine manufactured by Walvax Biotechnology Co. Ltd. (PCV13-WX) was licensed in China in December of 2019. While both 13-valent vaccines contain the same serotypes, PCV13-WX serotypes are conjugated to a tetanus toxoid carrier protein, in contrast to PCV13-PFE where each serotypes is conjugated to a CRM_{197} carrier protein [3].

Despite the large burden of pneumococcal disease, many countries in Asia have yet to implement PCVs into NIPs, in contrast to countries in North America and Europe [4]. One contributing factor to this lag in immunization coverage is that low-middle income countries (LMIC) and middle-income countries (MIC) face substantial funding constraints in expanding immunization programs [5]. However, while LMIC receive substantial financial support to expand immunization programs through Gavi, The Vaccine Alliance, MICs have not expanded immunization budgets to fund all recently licensed vaccines [5].

Given resource constraints and the rapidly changing healthcare landscape, decision-makers in Asian countries planning to introduce PCVs will need a comprehensive evidence of

CONTACT Matt Wasserman matt.wasserman@pfizer.com 235 East 42nd Street New York, NY, USA
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ARTICLE HIGHLIGHTS

- The systematic literature review identified 29 studies comparing a PCV to no vaccination and 9 studies comparing PCV10-GSK and PCV13-PFE.
- Differences in the studies, such as the inclusion and exclusion criteria, herd effect and serotype replacement, were largely driven by access to data and underlying modeling assumptions.
- In total, 86% of the analyses found the vaccination strategy to be cost-effective compared with no vaccination.
- Given no head-to-head data between PCV10-GSK and PCV13-PFE, differences in studies were driven by methodological assumptions regarding cross-protection of PCV10-GSK on serotypes 6A and 19A, the impact of PCV10-GSK on NT*Hi*, and PCV13-PFE's protection against serotype 3.

effectiveness of PCVs at the population level as well as robust economic evidence including cost-effectiveness. Though a number of economic evaluations of PCVs have been performed in Asian countries, they have differed in various ways such as the manner by which they included comparators: including comparisons to no vaccination, head to head comparisons, the incorporation of herd effect and cross-protection, and the consideration of serotype replacement.

Previous reviews of economic evaluations have focused specifically on pneumococcal OM [6], herd protection [7], modeling assumptions [8], specific countries or regions [9–11], or included all available studies [12,13]. The most comprehensive review by Wu et al (2015), was extensive but many new economic evaluations for PCVs in Asia have been published since its publication in 2015 given the broader use of PCVs in the second half of this decade [13]. Furthermore, given the widespread use of higher valent PCVs around the world, more effectiveness data is available to review the assumptions used in analysis to better understand the conclusions and interpretations of economic evaluations. This review aims to focus on studies on East and Southeast Asia and understand the contributing factors to cost-effectiveness results and whether gaps in evidence exist suggesting why the region may have yet to implement full NIPs.

2. Methods

2.1. SEARCH STRATEGY

Based on the search strategy of two prior systematic literature reviews by Wu et al (2015) [13] and Saokaew et al (2016) [14], we conducted a search of the Medline (PubMed) and EMBASE databases using the search string "pneumococc* AND conjugat* AND (vaccin* OR immun*) AND 'economic OR cost-effectiveness OR cost-benefit OR cost-utility' covering the period of 1 January 2006 to 11 October 2019.

2.2. STUDY SELECTION (*Figure 1*)

We reviewed titles and abstracts to include studies with the following criteria: (1) full economic evaluations (includes both costs and benefits for at least two interventions) of pediatric PCV7, PCV10, or PCV13 [15], (2) reported in English, (3) included children less than 12 years (i.e. were not economic evaluations focused on adult PCV use), and (4) included at least one analysis of relevant comparators in the setting of East or Southeast Asia (Fig. 1). Countries with a population of 500,000 or less were excluded from this analysis. Additionally, studies analyzing only cities or regions (with the exception of Taiwan, Macau, and Hong Kong), and not countries were excluded from the analysis.

2.3. DATA EXTRACTION

Two independent reviewers and a third reviewer deciding on any disagreement checked these inclusion criteria and extracted data using a standardized template. General study characteristics, methodology, assumptions, and results were extracted from each included study. We did not extract cost or epidemiology inputs given that these vary greatly between locales and comparison would be difficult. Therefore, we focused on modeling methods and assumptions related to PCV effectiveness and impact that can be transferable between jurisdictions. Results for comparisons between PCV7/10/13 vs. no vaccination or comparisons between PCVs were extracted.

3. RESULTS

3.1. OVERVIEW OF SELECTED STUDIES

There were 172 economic evaluations published between 1 January 2006, and 11 October 2019. One hundred forty studies (81.4%) were excluded from this review for several reasons, including being non-economic evaluations (n = 18), reviews (n = 8), non-Asia-Pacific (n = 109), adult vaccination (n = 3), and evaluating nonspecific PCV (n = 2). Thus, a total of 32 publications were included in this review [16–47]. Characteristics for each of the 32 included studies are shown in Table 1. All studies included at least one analysis within East and Southeast Asia. There were three (9.38%) studies examining multiple settings [16–18], with analyses both globally and in the East and Southeast Asia region. Within the remaining 29 studies [19–47] focusing only on East and Southeast Asia, settings included China (n = 7) [19–25], Malaysia (n = 4) [26–-26–29], Japan (n = 3) [30–32], Hong Kong (n = 3) [29,33,34], Korea (n = 2) [35,36], India (n = 2) [37,38], Taiwan (n = 2) [39,40], Thailand (n = 2) [41,42], Philippines (n = 2) [43,44], Singapore (n = 1) [45], Mongolia (n = 1) [46], and Bhutan (n = 1) [47].

The majority of the included studies utilized a Markov model (n = 16) [22,25,27-31-33,36,41–45,47] or a decision tree (n = 13) [16,17,19–21,23,24,26,34,35,37,40,46]. Two studies utilized alternative modeling techniques including an agent-based simulation (n = 1) [38] and a dynamic transmission model (n = 1) [39]. The most common type of studies were cost-utility analysis (n = 24) [16–25,27–30,32,36,37,41–47], cost-effectiveness analysis (n = 5) [26,34,35,39,40], both cost-effectiveness and cost-utility (n = 2) [31,33], and extended cost-effectiveness analysis (n = 1) [38]. Half of the studies utilized a lifetime time horizon [16–19,21-25,27,41–44,46,47], 15 studies used a time horizon between five and ten years [20,26,28–37,39,40,45], and one study used a time horizon of

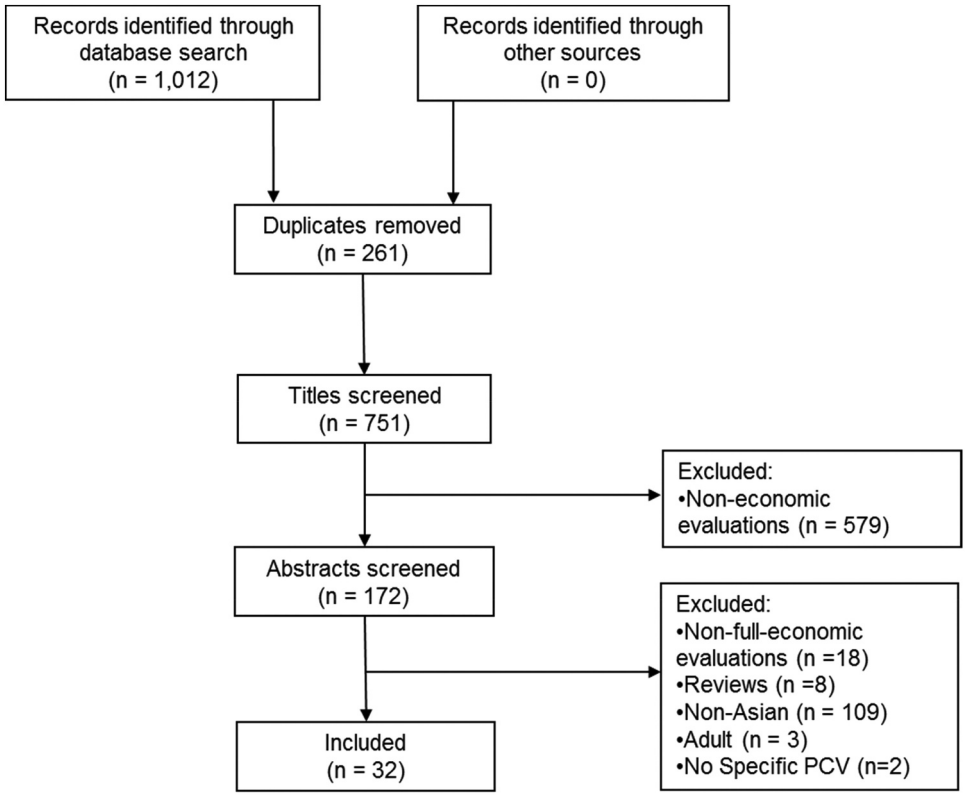

Figure 1. Study Selection Abbreviations: PCV=Pneumococcal Conjugate Vaccine

twenty years [38]. The majority of the studies (59.4%) were not industry funded [16–19,22,23,25,30,31,35,37–40,42,43,45–47].

Within the 32 studies, 44 analyses were comparing a PCV to no vaccination, and 9 analyses compared PCV10-GSK and PCV13-PFE. No studies currently evaluate the cost-effectiveness of PVC10-SII or PCV13-WX.

3.2. PCV7/10/13 VS. NO VACCINATION

3.2.1. Study Characteristics

There were 29 studies covering 44 different analyses of a PCV compared to no vaccination [16–31,34,35,37–47]. Three studies were multi-setting [16–18], seven studies included China [19–25], Malaysia was included in four studies [26–29], Hong Kong [29,34], India [37,38], Japan [30,31], Philippines [43,44], Taiwan [39,40], and Thailand [41,42] were included in two studies, and Bhutan [47], Korea [35], Mongolia [46], and Singapore [45] were included in one study. Overall, 34.5% of PCV7/10/13 studies were sponsored or funded by the pharmaceutical industry [20,21,24,26–28,34,41,44]. Studies evaluating PCV10-GSK vs. no vaccination were industry-sponsored in 41.7% of cases compared with 28.6% for PCV7 and 16.7% for PCV13-PFE.

3.2.2. Methodology and Assumptions

The majority (55.2%) of studies [16–19,21-25,27,41–44,46,47] utilized a lifetime time horizon when comparing a PCV to no vaccination. The remaining 13 studies [20,26,28–31,34,35,37–-31,34,35,37–40,45] used a time horizon of 20 years or less.

Overall, herd effect was considered in 72.4% [16–21,23-27,29,34,39–43,45–47] of the 29 studies comparing PCV7/10/13 to no vaccination. The consideration of herd effect was more prevalent in industry-sponsored (80.0%) than non-industry-sponsored studies (68.4%). Fewer studies included herd effect when comparing PCV7 vs. no vaccination 71.4% (n = 10) compared with the studies comparing PCV10-GSK vs. no vaccination 75.0% (n = 9), and PCV13-PFE vs. no vaccination 77.8% (n = 14). Serotype replacement was considered in 11 (37.9%) of the studies [16–18,25,27,29,38,42,44–46], and not considered (or mentioned) in the remaining 18 studies [19–-19–25,28,30,31,34,35,37–41,43,47]. Of the 12 studies evaluating PCV10-GSK vs. no vaccination, 33.3% included cross-protection or effectiveness of PCV10-GSK on non-typable *Haemophilus influenza* (NT*Hi*) [16,27,28,44].

3.2.3. Cost-Effectiveness Findings

In total, 38 (86.4%) of the 44 analyses found the vaccination strategy to be cost-effective compared with no vaccination (Table 2). The cost per additional QALY, life-year, or DALY-averted for each of the analyses is shown in Table 2. The percentage of analyses that were cost-effective increased from 78.6% with PCV7 to 83.3% with PCV10-GSK, and 94.4% with PCV13-PFE.

Industry-sponsored analyses reported vaccination was cost-effective in 91.7% of comparisons compared to 84.4% for non-

Table 1. Overview of Included Studies

STUDY	SETTING	FUNDER	STUDY TYPE	PERSPECTIVE	POPULATION	VACCINE COVERAGE	TIME HORIZON	DISCOUNT RATE
Nakamura et al. 2011	Middle-Income Countries	GAVI	CUA	Societal	Under 5-year olds	Variable	Lifetime	3.0%
Tasslimi et al. 2011	Global Analysis	GAVI	CUA	Societal	Under 5-year olds	Variable	Lifetime	3.0%
Chen et al. 2019	GAVI-Eligible	WHO, GAVI, BMGF	CUA	Health systems	30 birth cohorts in 180 countries	Variable – DPT3 coverage	Lifetime (implied)	3.0%
Che et al. 2014	China	Shanghai Jiaotong University SOM	CUA	Societal	1 birth cohort	99%	100 years	3.0%
Hu et al. 2014	China	Pfizer	CUA	Payer	Birth cohort	68%, 73%, up to 83% (by implication and citation)	1 year of costs occurring 5 – 7 years into the future	5.0%
Caldwell et al. 2015	China	Pfizer	CUA	Payer	Whole Chinese population	85%	1 year for intervention, LT for costs and outcomes	3.0%
Maurer et al. 2016	China	None	CUA	Societal	Cohort of 16m Chinese infants	100%	5 years (infections) and lifetime for effects of infections	3.0%
Mo et al. 2016	China	Unclear	CUA	Societal (by report) but no indirect costs	100,000 newborns	20%	100 years	3.0%
Shen et al. 2018	China	Pfizer	CUA	Payer	One birth cohort	85%	Lifetime	3.0%
Zhou et al. 2018	China	Shanghai Health and Family Planning Commission	CUA	Payer and Societal	One birth cohort	83.27%	Lifetime	5.0%
Aljunid et al. 2011	Malaysia	Pfizer	CEA	Payer (healthcare system)	550,000 infants	90%	10 years	3.0%
Aljunid et al. 2014	Malaysia	GSK	CUA	Payer (Malaysia MOH)	Birth cohort (550,000 infants)	95%	Lifetime	5% C&O
Wang et al. 2017	Malaysia	GSK	CUA	Payer (Malaysia MOH)	Birth cohort	100%	10 years	3% (0 - 5% in SA)
Wu et al. 2016	Malaysia	Pfizer	CUA	Payer and Societal	10 successive birth cohorts	Hong Kong - 95%; Malaysia - 98-99%	10 years	0.03
Lee et al. 2013	Hong Kong	GSK	CEA/CUA	Payer	Birth cohort (82,100)	PCV-10 - 68.6% (<5), 66.7% (5 - 17), 53.3% (18 - 64), 47.0% (>65); PCV-13 - 91.4%, 73.3%, 78.3%, and 71.6%	10 years	5.0%
Lee et al. 2009	Hong Kong	Wyeth	CEA	Payer and Societal	Birth cohort (57,100 infants)	95%	10 years	5% C&O
Hoshi et al. 2012	Japan	The Ministry of Health, Labor and Welfare	CUA	Societal	Birth cohort (1,000 births)	80% (no co-pay), 65% ($13 co-pay)	5 years	3% for C&O
Hoshi et al. 2013	Japan	The Ministry of Health, Labor and Welfare	CEA/CUA	Societal	Birth cohort (1,000 births)	76.1%	5 years	3% for C&O

(*Continued*)

Table 1. (Continued).

STUDY	SETTING	FUNDER	STUDY TYPE	PERSPECTIVE	POPULATION	VACCINE COVERAGE	TIME HORIZON	DISCOUNT RATE
Shiragami et al. 2015	Japan	GSK	CUA	Healthcare provider and societal	Birth cohort (1,042,000 new-born)	100%	5 years	3% for C&O
Sohn et al. 2010	Korea	None	CEA	Societal	Birth cohort (451,514 infants)	Not Stated	5 years	5% C&O
Zhang et al. 2018	Korea	GSK	CUA	Governmental	2012 birth cohort	99%	10 years	5% C&O
Krishnamoorthy et al. 2019	India	None	CUA (/DALY averted)	Governmental	10 birth cohorts	91%, 88%, and 88% for 1st, 2nd and 3rd doses	10 years	3% for C&O
Megiddo et al. 2018	India	BMGF	ECEA	Health system	25,000 individuals/ 4300 households	77% (DPT coverage); 90% (expanded coverage)	20 years	3% (costs)
Wu et al. 2012	Taiwan	National Science Council	CEA	Healthcare & Societal	Total Population	90%	10 Years	3% for C&O
Wu et al. 2013	Taiwan	Taiwanese National Science Council	CEA	Payer and Societal	Birth cohort (191,310 infants)	90%	10 years	3% for C&O
Dilokthornsakul et al. 2019	Thailand	Pfizer	CUA	Societal	Hypothetical birth cohort of 100,000	74.1% in children < 5 years	Lifetime	0.03
Kulpeng et al. 2013	Thailand	The Thai Health Promotion Foundation	CUA	Societal	Unclear	99%	Lifetime	3% for C&O
Haasis et al. 2015	Philippines	Rockefeller Foundation, NICE International, HITAP, Dept. of Health (Philippines)	CUA	Health system	Birth cohort (2 million infants)	2 scenarios: 100% and 25%	Lifetime	3.5% C&O
Zhang et al. 2014	Philippines	GSK	CUA	Governmental	birth cohort in 2012 of 1,812,137	100% (by design)	Lifetime	5.0%
Tyo et al. 2011	Singapore	MOH	CUA	Healthcare	Infant and child cohort (226,000)	95%	5 years	3% for C&O
Sundaram et al. 2017	Mongolia	WHO/GAVI	CUA (/DALY averted)	Health system and Societal	30 birth cohorts	98.2% (1st dose), 97.9 (2nd doses), and 97.6% (3rd dose)	100 years	3% for C&O
Dorji et al. 2018	Bhutan	HITAP (Thailand Research Fund)	CUA	Governmental	1 birth cohort (2016)	97%	Lifetime	3%

Abbreviations: BMGF=Bill & Malinda Gates Foundation; CEA=Cost-Effectiveness Analysis; C&O=Costs and Outcomes; CUA=Cost-Utility Analysis; DALY=Disability Adjusted Life-Years; DPT3= 3rd Dose Diphtheria, Pertussis, and Tetanus Vaccine; ECEA=Extended Cost-Effectiveness Analysis; GAVI=Gavi, The Vaccine Alliance; GSK=GlaxoSmithKline; HITAP=Health, Intervention and Technology Assessment Program; LT= lifetime; MOH=Ministry of Health; NICE=The National Institute for Healthcare Excellence; PCV=Pneumococcal Conjugate Vaccine; SA=Sensitivity Analysis; WHO=World Health Organization

Table 2. Cost-Effectiveness Results

STUDY	SETTING	COMPARISON	OUTCOME	RESULT	NIP STATUS
Nakamura et al. 2011	Middle-Income Countries	PCV7 vs. No Vaccination	$1,600 / DALY Averted	Cost-Effective	————
		PCV10-GSK vs. No Vaccination	$1,000 / DALY Averted	Cost-Effective	
		PCV13-PFE vs. No Vaccination	$900 / DALY Averted	Cost-Effective	
Tasslimi et al. 2011	Global Analysis	PCV7 vs. No Vaccination	$146 / DALY Averted	Cost-Effective	————
		PCV10-GSK vs. No Vaccination	$88 / DALY Averted	Cost-Effective	
		PCV13-PFE vs. No Vaccination	$77 / DALY Averted	Cost-Effective	
Chen et al. 2019	GAVI-Eligible	PCV13-PFE vs. No Vaccination	I$853 / DALY Averted	Cost-Effective	————
Che et al. 2014	China	PCV7 vs. No Vaccination	$530,354 / QALY (No Herd Effect)	Not Cost-Effective	None
			$95,319 / QALY (Herd Considered)	Not Cost-Effective	
Hu et al. 2014	China	PCV7 vs. No Vaccination	$6,435 / QALY	Cost-Effective	None
Caldwell et al. 2015	China	PCV7 vs. No Vaccination	$2,125 / QALY	Cost-Effective	None
Maurer et al. 2016	China	PCV7 vs. No Vaccination	$18,224 / QALY	Cost-Effective	None
		PCV10-GSK vs. No Vaccination	$16,664 / QALY	Cost-Effective	
		PCV13-PFE vs. No Vaccination	$11,436 / QALY	Cost-Effective	
Mo et al. 2016	China	PCV7 vs. No Vaccination	$104,094 / QALY	Not Cost-Effective	None
		PCV13-PFE vs. No Vaccination	$29,460 / QALY	Cost-Effective	
Shen et al. 2018	China	PCV13-PFE vs. No Vaccination	¥79,304/QALY (direct)	Cost-Effective	None
			¥76,551/QALY (direct + indirect IPD)	Cost-Effective	
			¥3,777/QALY (direct + indirect IPD and PNE)	Cost-Effective	
Zhou et al. 2018	China	PCV13-PFE vs. No Vaccination	$20,709 / QALY (Healthcare)	Cost-Effective	None
			$18,483 / QALY (Societal)	Cost-Effective	
Aljunid et al. 2011	Malaysia	PCV7 vs. No Vaccination	$10,261 / QALY	Cost-Effective	None
Aljunid et al. 2014	Malaysia	PCV10-GSK vs. No Vaccination	$9,406 / QALY	Cost-Effective	None
		PCV10-GSK vs. PCV13-PFE	Dominant	Cost-Effective	
Wang et al. 2017	Malaysia	PCV10-GSK vs. No Vaccination	$28,497 / QALY	Cost-Effective	None
		PCV10-GSK vs. PCV13-PFE	Dominant	Cost-Effective	
Wu et al. 2016	Malaysia	PCV10-GSK vs. No Vaccination	$21,438 / QALY (Payer)	Cost-Effective	None
			$20,667 / QALY (Societal)	Cost-Effective	
		PCV13-PFE vs. No Vaccination	$6,389 / QALY (Payer)	Cost-Effective	
			$4,883 / QALY (Societal)	Cost-Effective	
		PCV13-PFE vs. No Vaccination	Dominant (Payer)	Cost-Effective	
			Dominant (Societal)	Cost-Effective	
	Hong Kong	PCV10-GSK vs. No Vaccination	$46,832 / QALY (Payer)	Cost-Effective	
			$40,923 / QALY (Societal)	Cost-Effective	
		PCV13-PFE vs. No Vaccination	Dominant (Payer)	Cost-Effective	PCV13-PFE
			Dominant (Societal)	Cost-Effective	
		PCV13-PFE vs. No Vaccination	Dominant (Payer)	Cost-Effective	
			Dominant (Societal)	Cost-Effective	
Lee et al. 2013	Hong Kong	PCV10-GSK vs. PCV13-PFE	Dominant	Cost-Effective	PCV13-PFE
Lee et al. 2009	Hong Kong	PCV7 vs. No Vaccination	$6,460 / LYG (Payer)	Cost-Effective	PCV13-PFE
			$5,929 / LYG (Societal)	Cost-Effective	
Hoshi et al. 2012	Japan	PCV7 vs. No Vaccination	$93,013 / QALY (Vaccinated Alone)	Cost-Effective	PCV13-PFE
			$93,013 / QALY (Co-Vaccination)	Cost-Effective	

(*Continued*)

Table 2. (Continued).

STUDY	SETTING	COMPARISON	OUTCOME	RESULT	NIP STATUS
Hoshi et al. 2013	Japan	PCV7 vs. No Vaccination	¥6,352,110 (Base Case A; Payer)	Cost-Effective	PCV13-PFE
			¥6,352,110 (Base Case B; Payer)	Cost-Effective	
			¥1,588,575 (Base Case A; Societal)	Cost-Effective	
			¥1,588,575 (Base Case B; Societal)	Cost-Effective	
		PCV13-PFE vs. No Vaccination	¥9,034,940 (Base Case A; Payer)	Cost-Effective	
			¥4,368,278 (Base Case B; Payer)	Cost-Effective	
			¥4,495,903 (Base Case A; Societal)	Cost-Effective	
			Dominant (Base Case B; Societal)	Cost-Effective	
		PCV13-PFE vs. PCV7	¥37,722,901 (Base Case A; Payer)	Not Cost-Effective	
			¥343,830 (Base Case B; Payer)	Cost-Effective	
			¥35,584,455 (Base Case A; Societal)	Not Cost-Effective	
			Dominant (Base Case B; Societal)	Cost-Effective	
Shiragami et al. 2015	Japan	PCV10-GSK vs. PCV13-PFE	Dominant	Cost-Effective	PCV13-PFE
Sohn et al. 2010	Korea	PCV7 vs. No Vaccination	$115,549 (4-Dose Schedule);	Not Cost-Effective	PCV10-GSK & PCV13-PFE
			$79,955 (3-Dose Schedule)	Not Cost-Effective	
Zhang et al. 2018	Korea	PCV10-GSK vs. PCV13-PFE	Dominant	Cost-Effective	PCV10-GSK & PCV13-PFE
Krishnamoorthy et al. 2019	India	PCV13-PFE vs. No Vaccination	$467 / DALY Averted	Cost-Effective	PCV13-PFE*
Megiddo et al. 2018	India	PCV13-PFE vs. No Vaccination	$144 per YLL averted (current coverage)	Cost-Effective	PCV13-PFE*
			$127 per YLL averted (expanded coverage)	Cost-Effective	
Wu et al. 2012	Taiwan	PCV13-PFE vs. No Vaccination	$38,045 / LYG (Four Dose; Payer)	Cost-Effective	PCV13-PFE
			$18,299 LYG (Four Dose; Societal)	Cost-Effective	
			$22,050 LYG (Three-Dose; Payer) and	Cost-Effective	
			$2,304 LYG (Three-Dose; Societal)	Cost-Effective	
Wu et al. 2013	Taiwan	PCV7 vs. No Vaccination	NT$1,183,028 / LY (payer)	Cost-Effective	PCV13-PFE
			NT$619,862 / LY (societal)	Cost-Effective	
Dilokthornsakul et al. 2019	Thailand	PCV10-GSK vs. No Vaccination	Dose (3 + 1): 215,948 THB	Not Cost-Effective	None
			Dose (2 + 1): 170,437 THB	Not Cost-Effective	
		PCV13-PFE vs. No Vaccination	Dose (3 + 1): 97,269 THB	Cost-Effective	
			Dose (2 + 1): 73,674 THB	Cost-Effective	
Kulpeng et al. 2013	Thailand	PCV10-GSK vs. No Vaccination	THB 1,368,072 / QALY	Not Cost-Effective	None
		PCV13-PFE vs. No Vaccination	THB 1,490,305 / QALY	Not Cost-Effective	
Haasis et al. 2015	Philippines	PCV10-GSK vs. No Vaccination	68,182 Php / QALY (Herd Protection)	Cost-Effective	PCV13-PFE
			112,640 Php / QALY (No Herd Protection)	Cost-Effective	
		PCV13-PFE vs. No Vaccination	54,510 Php / QALY (Herd Protection)	Cost-Effective	
			84,654 Php / QALY (No Herd Protection)	Cost-Effective	
		PCV13-PFE vs. PCV10-GSK	15,795 Php / QALY (Herd Protection)	Cost-Effective	
			23,836 Php / QALY (No Herd Protection)	Cost-Effective	
Zhang et al. 2014	Philippines	PCV10-GSK vs. No Vaccination	50,913 Php / QALY	Cost-Effective	PCV13-PFE
		PCV10-GSK vs. PCV13-PFE	Dominant	Cost-Effective	
Tyo et al. 2011	Singapore	PCV7 vs. No Vaccination	$5,562-43,275 / QALY	Cost-Effective	PCV13-PFE
		PCV10-GSK vs. No Vaccination	$45,100 / QALY	Cost-Effective	
		PCV13-PFE vs. No Vaccination	$37,644 / QALY	Cost-Effective	
Sundaram et al. 2017	Mongolia	PCV13-PFE vs. No Vaccination	Dominant (Societal)	Cost-Effective	None
			$52 / DALY Averted (Healthcare)	Cost-Effective	

(*Continued*)

Table 2. (Continued).

STUDY	SETTING	COMPARISON	OUTCOME	RESULT	NIP STATUS
Dorji et al. 2018	Bhutan	PCV10-GSK vs. No Vaccination	$36 / QALY	Cost-Effective	None
		PCV13-PFE vs. No Vaccination	$40 / QALY	Cost-Effective	
		PCV13-PFE vs. PCV10-GSK	$92 / QALY	Cost-Effective	

Vaccine; PCV10= 10-Valent Pneumococcal Conjugate Vaccine; PCV13=13-Valent Pneumococcal Conjugate Vaccine; PFE=Pfizer Inc.; Php= Philippine Peso; PNE=Pneumonia; THB=Thai Bhat; YLL= Years Life Lost; QALY=Quality Adjusted Life-Year

industry sponsored analyses. When herd effect was considered, a PCV was found to be cost-effective in 84.8% (n = 28) of the analyses compared with 90.9% (n = 10) when herd effect was not considered. Similarly, the inclusion or exclusion of serotype replacement did not drive cost-effectiveness. Analyses with serotype replacement considered were cost-effective 89.5% of the time compared to 82.4% when serotype replacement was not considered and 87.5% when it was not mentioned in the study

PCV7 was cost-effective compared to no vaccination in all studies with the exception of Che et al. (2014) [19] and Mo et al. (2016) [23] in China, and Sohn et al. (2010) [35] in Korea. All three studies were non-industry sponsored and reported that vaccine costs were the primary driver resulting in the lack of cost-effectiveness from their models. Sohn et al. also suggested that a limiting factor in the analysis may have been the exclusion of indirect vaccination effects [35].

Of the four studies considering either cross-protection or effectiveness of PCV10-GSK on NT*Hi*, all found PCV10-GSK to be cost-effective compared with no vaccination. In the remaining eight studies not considering cross-protection or effect on NT*Hi* [17,22,29,41–43,45], PCV10-GSK was found to be cost-effective in six (75%).

Seventeen of eighteen (94.4%) PCV13-PFE vs. no vaccination studies [16–18,22-25,29,31,37–39,41-43,45-47], with the exception of Kulpeng et al.'s (2013) study in Thailand [42], reported PCV13-PFE was cost-effective compared to no vaccination. Their study estimated neither PCV10-GSK and PCV13-PFE to be cost-effective due to the price of the vaccine. Sensitivity analyses showed significant price cuts to the vaccines of 70–90% would be needed to reach cost-effectiveness or cost-savings. Studies by Hoshi et al. (2013) in Japan [31] and Sundaram et al. (2017) in Mongolia [46] modified PCV13-PFE's effect on serotype 3. Both studies still found PCV13-PFE to be cost-effective against no vaccination even with the elimination of its effectiveness on serotype 3 for acute otitis media (AOM) by Hoshi et al. (2013) and reduction to 34% effectiveness by Sundaram et al. (2017) [31,46]

3.3. PCV13-PFE VS. PCV10-GSK

3.3.1. Study Characteristics

PCV10-GSK was compared to PCV13-PFE in six studies [27,28,32,33,36,47] and PCV13-PFE was compared to PCV10-GSK in three [29,43,47], for a total of nine analyses conducted in nine separate studies. The studies were set in Malaysia (n = 3) [27–29], the Philippines (n = 2) [43,44], Hong Kong (n = 2) [29,33], Bhutan (n = 1) [47], Japan (n = 1) [32], and Korea (n = 1) [36]. Study characteristics were similar for all publications with the majority (n = 7) of studies sponsored by pharmaceutical firms [27–29,32,33,36,44], specifically GlaxoSmithKline (n = 6) [27,28,32,33,36,44] and Pfizer (n = 1) [31].

3.3.2. Methodology and Assumptions

Serotype replacement and herd effect were considered in 33% [27,29,44] and 56% [27,29,33,43,47] of these studies, respectively. The two non-industry-sponsored studies did not consider serotype replacement but did consider herd effect. Vaccination coverage was assumed to be at least 95% in all studies with the exception of Lee et al. (2013) [33], which assumed a lower uptake ranging from 47% to 68.6% for PCV10-GSK and 71.6% to 91.4% for PCV13-PFE.

There were significant differences in the assumptions between the studies. All PCV10-GSK vs. PCV13-PFE studies assumed some level of cross-protection for serotypes 6A and 19A for PCV10-GSK. The level of cross-protection ranged from 63.7% to 76% for 6A and 26% to 82.2% for 19A. No cross-protection was assumed in the PCV13-PFE vs. PCV10-GSK analyses.

The effect of PCV13-PFE on serotype 3 was either reduced (n = 2) or assumed to be 0% (n = 3) in five (83.3%) of the PCV10-GSK vs. PCV13-PFE studies [27,28,32,36,44]. The studies by Zhang et al. (2018) in Korea [36] and Wu et al. (2016) in Malaysia and Hong Kong [29] reduced the effectiveness of serotype 3 to 26%. However, the prevalence of serotype 3 was assumed to be 0% in the Zhang et al. (2014) study, thus assuming no impact by PCV13-PFE on serotype 3 [44]. The PCV13-PFE vs. PCV10-GSK studies did not make any assumptions reducing the effectiveness of PCV13-PFE within serotype 3 [29,43,47].

PCV10-GSK was assumed to provide effectiveness against NT*Hi* in all six of the GSK-sponsored PCV10-GSK vs. PCV13-PFE analyses [27,28,32,33,36,44]. The PCV13-PFE vs. PCV10-GSK studies did not make any assumptions in regard to the effectiveness of PCV10-GSK in NT*Hi* [29,43,47]. Within the GSK-sponsored PCV10-GSK vs. PCV13-PFE studies, the protection of PCV10-GSK on NT*Hi* -AOM ranged from 21.5% (n = 3) to 35% (n = 3) [27,28,32,33,36,44]. Additionally, Wang et al. (2017) considered PCV10-GSK had a 35% effectiveness on IPD caused by NT*Hi* [28].

3.3.3. Cost-Effectiveness Findings

All analyses (n = 6) comparing PCV10-GSK to PCV13-PFE found PCV10-GSK to be the cost-effective strategy and all

Table 3. Assumptions and Key Results Drivers

STUDY	COUNTRY(S)	SEROTYPE REPLACEMENT	HERD EFFECT	CROSS-PROTECTION	PCV13-PFE EFFECT ON ST3	IMPACT OF PCV10 ON NTHI
Nakamura et al. 2011	Middle-Income Countries	Considered	Considered	Yes (6A/6B)	Not Modified	Not Considered
Tasslimi et al. 2011	Global Analysis	Considered	Considered	Not Considered	Not Modified	Not Considered
Chen et al. 2019	GAVI-Eligible	Considered	Considered	Not Considered	Not Modified	Not Considered
Che et al. 2014	China	Not Considered	Considered	Not Considered	N/R	N/R
Hu et al. 2014	China	Not Considered	Considered	Not Considered	N/R	N/R
Caldwell et al. 2015	China	Not Considered	Considered	Not Considered	N/R	N/R
Maurer et al. 2016	China	Not Considered	Not Considered	Not Considered	Not Modified	Not Considered
Mo et al. 2016	China	Not Considered	Considered	Not Considered	Not Modified	Not Considered
Shen et al. 2018	China	Not Considered	Considered	Not Considered	Not Modified	N/R
Zhou et al. 2018	China	Considered	Considered	Not Considered	Not Modified	N/R
Aljunid et al. 2011	Malaysia	Not Considered	Considered	Not Considered	N/R	N/R
Aljunid et al. 2014	Malaysia	Considered	Considered	Yes (6A 76%; 19A 26%)	Assumed 0%	35% (IPD); 35.6% (AOM)
Wang et al. 2017	Malaysia	Not Considered	Not Considered	Yes (6A 63.7%; 19A 61%)	Reduced to 26%	21.5% (AOM)
Wu et al. 2016	Malaysia, Hong Kong	Considered	Considered	Not Considered	Not Modified	Assumed 0%
Hoshi et al. 2012	Japan	Not Considered	Not Considered	Not Considered	N/R	N/R
Hoshi et al. 2013	Japan	Not Considered	Not Considered	Not Considered	Excluded for AOM in Base Case A; Included in AOM Base Case B	N/R
Shiragami et al. 2015	Japan	Not Considered	Not Considered	Yes (6A 76%; 19A 82.2%)	Assumed 0%	21.5% (AOM)
Lee et al. 2013	Hong Kong	Not Considered	Considered	76.0% Against 6A for PCV10-GSK	Not Modified	35.6% (AOM)
Lee et al. 2009	Hong Kong	Not Considered	Considered	Not Considered	N/R	N/R
Sohn et al. 2010	Korea	Not Considered	Not Considered	Not Considered	N/R	N/R
Zhang et al. 2018	Korea	Not Considered	Not Considered	Yes (6A 76%; 19A 72%)	Reduced to 26%	21.5% (AOM)
Krishnamoorthy et al. 2019	India	Not Considered	Not Considered	Not Considered	Not Modified	N/R
Megiddo et al. 2018	India	Considered	Not Considered	Not Considered	Not Modified	N/R
Wu et al. 2012	Taiwan	Not Considered	Considered	Not Considered	Not Modified	N/R
Wu et al. 2013	Taiwan	Not Considered	Considered	Not Considered	N/R	N/R
Dilokthornsakul et al. 2019	Thailand	Not Considered	Considered	Not Considered	Not Modified	Not Considered
Kulpeng et al. 2013	Thailand	Considered	Considered	Not Considered	Not Modified	Not Considered
Haasis et al. 2015	Philippines	Not Considered	Considered	Not Considered	Not Modified	Assumed 0%
Zhang et al. 2014	Philippines	Considered	Not Considered	Yes (6A 76%; 19A 26%)	Assumed 0%	35.3% (AOM)
Tyo et al. 2011	Singapore	Considered	Considered	Not Considered	Not Modified	0% (AOM)
Sundaram et al. 2017	Mongolia	Considered	Considered	Not Considered	Reduced to 34%	N/R
Dorji et al. 2018	Bhutan	Not Considered	Considered	Not Considered	Not Modified	Not Considered

NOTE: All assumptions are reported for base case analyses and do not include sensitivity or scenario analysis.
Abbreviations: AOM=Acute Otitis Media; GAVI=Gavi, the Vaccine Alliance; GSK=GlaxoSmithKline IPD= Invasive Pneumococcal Disease; N/R = Not Relevant to Study

(n = 3) analyses comparing PCV13-PFE to PCV10-GSK found PCV13-PFE to be cost-effective (Table 2). The PCV10-GSK vs. PCV13-PFE studies were all sponsored by GSK, while two of three PCV13-PFE vs. PCV10-GSK studies were non-industry sponsored, and the remaining study was sponsored by Pfizer.

4. Discussion

This study reviewed economic evaluations of PCV7, PCV10-GSK, and PCV13-PFE between 1 January 2006 and 11 October 2019 in East and Southeast Asia [16–47]. The inclusion and exclusion of factors such as herd effect and serotype replacement were largely driven by availability of epidemiological data and underlying modeling assumptions. Data measuring herd effect or the rate of serotype replacement are often unavailable locally for countries using PCVs, as well as for PCV-naïve countries, since there is no local data given lack of prior vaccination in the region. This trend was found in our review, as only 68.8% of studies considered herd effect and 34.4% of studies considered serotype replacement. Moreover, only 28.1% of studies considered both herd effect and serotype replacement, while 40.6% of studies included herd effect but not serotype replacement, thus may overestimate the indirect effect of the vaccine.

In studies where PCV7 [19,23,35], PCV10-GSK [42], and PCV13-PFE [42] were not cost-effective compared to no vaccination, the cost of the vaccine was a driving factor. In all of these studies the list price of the vaccine was used and may not reflect a discounted price that is often negotiated as part of an NIP.

Directly comparing PCV10-GSK and PCV13-PFE is challenging when conducting cost-effectiveness studies as there are no head-to-head clinical trials comparing the vaccines. Even with these methodological challenges of comparing PCV10-GSK vs PCV13-PFE, it should be noted that comparing incremental cost-effectiveness ratios (ICERs) results for PCVs vs no vaccination from different analyses is fundamentally flawed. First, in countries with a prior vaccination programs the comparator should not be no vaccination as the current situation is an incremental vaccination approach rather than a completely unvaccinated population [13]. Second, the incremental differences in serotype coverage between PCVs are highly influential on the results and will not be captured in two separate analyses compared to no vaccination. Nonetheless, the consensus of the included economic evaluations of PCVs compared to no vaccination was that they were cost-effective. Lastly, there are often significant methodological differences between studies as well as differences in the values of the variables due to significant variations of the health systems analyzed. The methodologies across the studies often assume different time horizons, perspectives, and modeling assumptions, while the values of inputs, specifically costs and burden of disease, make a fair comparison across analyses difficult. The cost of the vaccine, which was found to be a significant results driver, varies from health system to health system, leading to even more difficulty comparing results across studies.

In the comparisons of PCV13-PFE and PCV10-GSK there were three assumptions that varied between the studies and were highly influential on the results 1) cross-protection for 6A and/or 19A, 2) effectiveness of the vaccine against IPD and/or AOM caused by NTHi, and 3) effectiveness of the vaccine against serotype 3 (Table 3). The validity of these assumptions remains highly debated in the literature [8,48] and are described below.

4.1. Cross-Protection

While the literature suggests some degree of cross-protection for PCV10-GSK against 6A and 19A, the magnitude of the effect is unclear. For example, whereas 3 case control studies have reported PCV10-GSK provides some direct protection against 19A [49–51], real-world evidence has shown significant increases in IPD caused by serotype 19A in countries utilizing PCV10-GSK [52–54]. Additionally, Belgium switched from PCV13-PFE to PCV10-GSK and within two years saw a rise in IPD cases caused by 19A prompting a recommendation back to PCV13-PFE by the Belgium Superior Health Council [55]. Two previous systematic reviews have shown that there is limited evidence of PCV10-GSK providing population-based protection against serotype 19A [52], due to limited impact on carriage [56].

Nonetheless, cross-protection for both 6A and 19A were considered in six studies comparing PCV10-GSK vs. PCV13-PFE [27,28,32,33,36,44]. The 2017 study in Malaysia by Wang et al. found the effectiveness of PCV10-GSK cross-protection for 19A in IPD was the second most influential parameter in the one-way sensitivity analysis [28]. Rates of cross-protection in the studies analyzed in this review ranged from 63.7% to 76% for 6A to between 26% and 82.2% for 19A [27,28,32,33,36,44].

4.2. Impact OF PCV10-GSK On IPD And/Or AOM Caused By Nthi

There were six studies [27,28,32,33,36,44] that considered at least some impact of PCV10-GSK on AOM caused by NT*Hi*, and one study [27] considered the impact of PCV10-GSK on IPD caused by NT*Hi*. The effectiveness of PCV10-GSK on NT*Hi*-caused AOM ranged from 21.5% to 35% in the six studies [27,28,32,33,36,44], and was 35% effective against NT*Hi*-caused IPD in Aljunid et al.'s analysis [27]. However, the effectiveness of PCV10-GSK against NT*Hi*-AOM has been contested due to a lack of scientific evidence supporting significant reductions in NT*Hi*-AOM [48,57–63]. The Clinical Otitis Media and Pneumonia Study (COMPAS) did not show a significant effect for PCV10-GSK on NT*Hi*-clinically confirmed AOM [63]. Randomized controlled trials by van den Bergh et al. (2012) and Vesikari et al. (2016) did not find an impact of PCV10-GSK on nasopharyngeal NTHI colonization when PCV10-GSK was compared to PCV7 and a control vaccination, respectively [57,62]. A real-world study comparing the PCV7 era to the PCV10-GSK era in New Zealand did not find a significant

difference in the prevalence of NTHI detected in the middle ear fluid [60].

While PCV10-GSK may have some effect on NTHi-AOM, the assumption of effectiveness for PCV10-GSK on NT*Hi*, coupled with an assumption of no effect for PCV7/13 on NT*Hi*, significantly influenced the cost-effectiveness study results [27,28,32,33,36,44]. The studies comparing PCV10-GSK with PCV13-PFE by Lee et al. (2013) and Shirigami et al. (2015) reported through the one-way sensitivity analysis that PCV10-GSK's assumed effectiveness against NT*Hi*-AOM was the most influential parameter on incremental QALYs gained and the incremental cost-effectiveness ratio, respectively [32,33]. PCV10-GSK's cost-effectiveness over PCV13-PFE in the study by Shiragami et al. (2015) was mostly driven by the significant difference in AOM-related costs for PCV10-GSK and PCV13-PFE [32]. Cost-effectiveness studies outside of this analysis have also reported PCV10-GSK was only cost-effective against PCV13-PFE when PCV10-GSK's effect on NT*Hi*-related AOM was considered [13,32,44,64–69].

4.3. Effectiveness Of PCV13-PFE On Serotype 3

The effectiveness of PCV13-PFE on serotype 3 was a divisive assumption among the PCV10-GSK vs. PCV13-PFE and PCV13-PFE vs. PCV10-GSK studies. All PCV13-PFE vs. PCV10-GSK studies did not give any special consideration to the effectiveness of PCV13-PFE on serotype 3 [29,43,47]. The six PCV10-GSK vs. PCV13-PFE studies provided assumptions either eliminating or limiting PCV13-PFE's effectiveness on serotype 3. Three studies assumed PCV13-PFE had no protection against serotype 3 [27,32,44], two studies reduced the effectiveness to 26% [28,36], and one study assumed full protection in the base case and 0% in a scenario analysis [33].

The primary rationale for the exclusion of PCV13-PFE's protection against serotype 3 was the minutes of a Joint Committee on Vaccination and Immunization (JCVI) meeting in 2012 [70]. However, a more recent meeting in 2014 by the same committee indicated an observed decline in serotype 3 cases after the introduction of PCV13-PFE to the United Kingdom's National Immunization Program [71]. This observation is supported by studies in the United States [72], Spain (Madrid) [73], and Germany [74]. A recent meta-analysis of observational studies reported vaccine effectiveness (VE) of 65.5% (95% CI: 37.3%-89.7%) for PCV13-PFE against serotype 3 IPD [75]. While the robustness of PCV13-PFE's protection against serotype 3 can be debated, the assumption of 0% VE for PV13-PFE against serotype 3 likely underestimates the impact of direct protection and should not be considered in the base case.

4.4. Limitations

This study includes several limitations. First, only English studies were included in the analysis. As this study focused on East and Southeast Asia, which includes a plethora of countries with different languages, it is possible studies in local languages were excluded. Second, only full-text studies were included in this analysis so conference abstracts and presentations that may not have been in peer-reviewed journals would have been missed. Third, there remains a challenge in comparing cost-effectiveness analysis across jurisdictions. The aim of this analysis was to assess key assumptions made in PCV economic evaluations made in Asia, but given the heterogeneity of countries included, it is a challenge to compare results. For example, local costs, including the cost of vaccines, and epidemiology vary greatly between countries and the impact of productivity and indirect costs may weigh differently at different socio-economic levels. Further work is necessary to get a more holistic picture of PCVs in low-income countries in contrast to higher income countries to address these nuances. Lastly, only country-level analyses were included. Large countries such as China and India may have regional or city level analyses done to reflect localization of immunization programs, such as the analysis by Hu et al. (2014) of PCV7 in Shanghai [76]. However, these were deemed outside the scope of this assessment.

5. Conclusion

In East and Southeast Asia vaccination with PCVs was found to significantly reduce the mortality and morbidity of pneumococcal diseases and was mostly cost-effective compared to no vaccination. Study assumptions, specifically vaccine local acquisition costs, the inclusion or exclusion of indirect effects (serotype replacement and herd effect), cross-protection, and protection against NT*Hi* and serotype 3, were highly influential on cost-effectiveness results within studies. The results of this study have important implications. Specifically, newly licensed PCVs (PCV10-SII and PCV13-WX) are now available and these include different serotype compositions or formulations than previously licensed PCVs. Furthermore, newer PCVs including 15- and 20-serotypes will be available in the next few years. Future PCV economic evaluations will need to carefully consider the totality of evidence when assessing new PCV formulations, such as serotype coverage, serotype-specific immunogenicity and efficacy/effectiveness against IPD, pneumonia, and AOM, since it cannot be safely assumed that in the absence of data new formulations will have equal or comparable effects to established PCVs. Moreover, economic evaluations will need to consider the evolution of data as vaccines are used in the real world given the historic PCV experience demonstrating serotype replacement, herd immunity, and changes in vaccine efficacy.

Declaration of interest

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ORCID

Nathorn Chaiyakunapruk http://orcid.org/0000-0003-4572-8794
Matt Wasserman http://orcid.org/0000-0003-3300-2742

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