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Systematic Literature Review

Effectiveness of Pneumococcal Vaccines on Otitis Media in Children: A Systematic Review

Lays P. Marra, MSc, Ana L. Sartori, PhD, Martha S. Martinez-Silveira, PhD, Cristiana M. Toscano, MD, PhD, Ana L. Andrade, PhD

ABSTRACT

Objectives: We aimed to determine the effectiveness of pneumococcal vaccines on otitis media (OM) and acute otitis media (AOM) in children.

Methods: We conducted a systematic search in databases PubMed (MEDLINE), Embase, Lilacs, and Web of Science. We included observational studies that evaluated any pneumococcal vaccine – including 7, 10, and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) and 23-valent polysaccharide vaccines (PPSV23) as the intervention, in children aged less than five years.

Results: Out of the 2112 screened studies, 48 observational studies complied with the eligibility criteria and therefore were included in this review. Of the included studies, 30 (63%) were before-after, eleven (23%) cohort, six (13%) time series, and one (2%) case-control study designs. Vaccine effectiveness (VE) in preventing OM or AOM varied by vaccine type. In children under 24 months VE ranged from 8% and 42.7% (PCV7), 5.6% to 84% (PCV10) and 2.2% to 68% (PCV13). In children aged less than 60 months, VE ranged between 13.2% and 39% for PCV7, 11% to 39% for PCV10 (only children under 48 months), and 39% to 41% (PCV13).

Conclusions: Our results demonstrate significant effect of pneumococcal vaccination in decreasing OM or AOM in children under five years old in several countries supporting the public health value of introducing PCVs in national immunization programs.

Keywords: comparative effectiveness research, conjugate vaccines, otitis media, pneumococcal vaccines, polysaccharide vaccine, systematic review.

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Introduction

Streptococcus pneumoniae is associated with significant morbidity and mortality in children < 5 years of age worldwide,[1,2] causing severe invasive diseases such as meningitis and septicemia and noninvasive disease including pneumonia and also milder but more frequent infections such as sinusitis and otitis media (OM).[3] Noninvasive diseases represent the highest burden of pneumococcal disease in childhood,[3] especially acute OM (AOM).[3,4] Evidence suggests that by the age of 1 year, 62% of all children will have experienced at least 1 AOM episode, reaching to 80% of all children up to 3 years of age.[5]

AOM is defined as middle ear effusion accompanied by ≥ 1 sign of acute inflammation in the middle ear, such as otalgia, otorrhea, fever, or irritability; it is one of the most common diseases in childhood,[6] imposing a significant burden for children, their families, and the health system.[7-9] Studies have shown that the nationwide implementation of pneumococcal conjugate vaccines (PCVs) has changed the frequency of the causative otopathogens involved in OM and AOM toward pneumococcal serotypes not included in the vaccines.[10,11] Two types of pneumococcal vaccines are available: polysaccharide and peptide (conjugate). In 1983, the 23-valent polysaccharide vaccine (PPSV23) had been approved in the United States for use in children aged ≥ 2 years with certain medical conditions that can lead to an increased risk of pneumococcal disease.[12] The first polysaccharide-protein conjugate vaccine, which includes 7 pneumococcal serotypes (PCV7), became available in 2000 in the United States. Currently, 2 PCV are recommended to use in childhood immunization programs: the 10-valent (PCV10) and the 13-valent (PCV13) vaccines.[2]

Until 2021, 147 countries have included pneumococcal vaccines in their immunization programs and 29 countries have not introduced. In total, 114 countries use PCV13, 26 countries use PCV10, and 7 countries use PCV10 + PCV13.[13,14] The decision of each country to introduce or not PCV in their vaccine calendar involves factors other than the efficacy, effectiveness, and safety of vaccines, such as geopolitical issues, socioeconomic contexts, surveillance practices, availability of resources financial, disease burden, economic evaluation, and cost-effectiveness of alternative interventions, the latter being increasingly used in the process of formulating vaccine introduction policies.[15,16]

Some studies suggest that although PCVs target only a few serotypes that cause OM, it can prevent early episodes and complications of AOM.[9,17,18] The efficacy of pneumococcal vaccines in reducing episodes of OM or AOM has been reported in some systematic reviews.[19-21] Nevertheless, these systematic reviews did not include observational studies, and the 2 types of results need to be reconciled (efficacy and effectiveness). Accumulation of effectiveness results for new vaccines takes some years, so PCV's policy decisions must still be based partly on effectiveness data. For this reason, the aim of this systematic review was to evaluate the effectiveness of all pneumococcal conjugate (PCV7, PCV10, and PCV13) and polysaccharide (PPSV23) vaccines on OM in children aged < 5 years. PPSV23 was also considered in the study, because it is indicated for groups of children at risk of pneumococcal disease in settings where PCV is not routinely used.[22]

Methods

Protocol and Registration

The study protocol was registered in PROSPERO under registration number CRD 42017055655. This review is reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[23]

Search Strategy

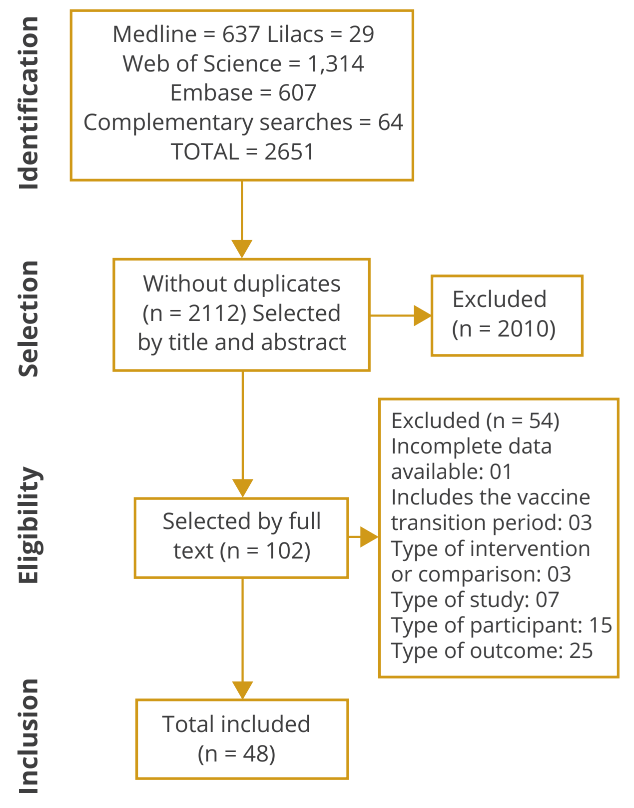
We performed a literature search without restriction of location, period, or language. Databases searched included MEDLINE (PubMed), Embase, Lilacs, and Web of Science, which were complemented by searches in proceedings and annals of congress and conferences, and hands searches from reference lists of included studies. Detailed search strategies are described in the Supplemental Material (see Appendix Table 1 in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012).

Eligibility Criteria

We included studies on healthy children aged < 5 years, of both sexes, which measured the effect of all PCVs and PPSV23 on OM or AOM. The interventions considered were PCV7, PCV10, PCV13, and PPSV23 in any immunization scheme, with or without catchup. The absence of vaccination by pneumococcal vaccine was considered as the comparator, which could be either as the pre-pneumococcal vaccination period or a group of nonvaccinated individuals. In addition, we considered a direct comparison between these vaccines. We considered observational studies, including cohort, case-control, quasi-experimental, time series ecological designs with at least 24 data points overall (before and after the intervention), and before-after studies.

Studies evaluating children with sickle cell disease, human immunodeficiency virus infection, or conditions known to affect immune response were excluded. We also excluded studies that included the transition period in their analysis. Cross-sectional studies, case series, and case reports, as well as studies that only reported data before or after vaccine introduction, but not for both periods, were excluded. For before-after studies, those reporting only the number of cases without denominator information or incidence estimates were excluded.

Figure 1. PRISMA flow diagram for the literature search. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



Selection Process and Data Extraction

Titles, abstracts, and full-text articles identified were read and selected by 2 independent reviewers, who were not blind to the journal titles or to the study authors or institutions. Disagreements were resolved by a third reviewer.

Two reviewers independently extracted data, using a form (evidence table) developed for us in this systematic review. Variables considered in the data extraction included author, country, contact details, type and source of financial support, publication status from reports, year of publication, study design, sample size, demographic information (average age, sex, ethnicity), number of intervention groups, number of cases and controls, presence of otitis, number of outpatient care and hospitalization because of otitis, cochlear implant, myringotomy or ventilation tube insertion and other complications, intervention details (generic and the trade name of the vaccines, vaccination schedule, number of doses, changes in vaccine type), all reported outcomes, outcome definition, secondary outcomes, diagnostic criteria, and comorbidities.

Primary outcomes evaluated were number, percentage or rates of episodes, outpatient visits, or hospitalizations because of OM or AOM. Episodes of OM and AOM were defined according to the American Academy of Pediatrics and the American Academy of Family Physicians recommendations to primary care clinicians for the management of children from 6 months to 12 years of age. OM was defined as the accumulation of infected fluid in the middle ear, bulging of the eardrum, and pain in the ear. AOM was defined considering one of the following criteria: (1) bulging of the tympanic membrane or new onset of otorrhea not because of acute otitis externa and (2) bulging of the tympanic membrane and

Table 1. Summary of included studies.

Reference	Study design	Country	Study period	Vaccine	Dose schedule	Year of introduction	Coverage	Age, mo	Sample/population analyzed
Ansaldi et al., 2008[27]	Before-after*	Italy	2000-2005	PCV7	2 + 1	May 2003	2003: 39.8%-65.9%; 2004: 80.2%-85.2%; 2005: 82.2%-93.3%	< 24	Pre: 67 892; Post: 70 904 person-years
Ben-Shimol et al., 2016[37]	Before-after	Israel	2004-2015	PCV7	3 + 1	2009	NR	< 36	7475 episodes
				PCV13	3 + 0	2010			
Brico et al., 2017[58]	Case-control	Russia	NR	PCV13	2 + 1	Dec 2014	83.5% (2016)	< 24	790 vaccinated
									1290 matched controls
Carrasquilla et al., 2020[53]	Before-after	Colombia (cities: Bogota DC	2005-2016	PCV 10	2 + 1	2012	84%	< 24	2 864 538 children
		Barranquilla					104%		485 791 children
		Medellin)					84%		698 798 children
Chu and Cachola, 2014[56]	Cohort	Philippines	NR	PCV10	NR	March 2009	NR	< 24	176 participants
Cunha et al., 2012[41]	Cohort *	Brazil	2008-2010	PCV7	NR	NR	NR	< 36	NR
Edmondson-Jones et al., 2021[42]	Retrospective cohort	Sweden (2 regions: Skåne	2005-2013	pre-PCV	-	-	97%	< 24	123 794 children
				PCV 7	3 + 1	2009			17 811 children
				PCV 10	2 + 1	2010			49 991 children
		Västra Götalands regionen [VGR])		pre-PCV	-	-			165 683 children
				PCV 7	3 + 1	2009			14 324 children
				PCV13	2 + 1	2010			70,32 children
Eythorsson et al., 2018[55]	Before-after	Iceland	2008-2015	PCV 10	NR	April 2011	97% (2011, at least 2 doses)	< 48	Outpatient clinics of the Children's Hospital, and inpatient admissions.
Eythorsson et al., 2019[69]	Before-after	Iceland	2005-2016	PCV 10	2 + 1	2011	97%	< 60	53 218 children
Fortanier et al., 2019[43]	Cohort	The Netherlands	2004-2015	PCV 7	3 + 1	2006	93.6% to 95.1% over the entire study period	< 48	18 237 children
				PCV 10	2 + 1*	2011			
Fortunato et al., 2015[44]	Before-after	Italy	2001-2012	PCV7	2 + 1	2002	Puglia region: PCV7: 2006: 75.3%; PCV7/PCV13: 2010 95.1%; PCV13: 2011: 93%	< 60	4.361 episodes
				PCV13	2 + 1	2010			
Gisselsson-Solen et al., 2017[56]	Before-after	Swedish	2007-2014	Pre-PCV		2007-2008	97.5%	< 48	NR
				PCV 10/PCV13	2 + 1	2013-2014			
Grijalva et al., 2006[45]	Before-after	US	1994-2003	PCV7	NR	2000	≥ 3 doses of PCV7: 68.1%	< 24	From 1415 to 1072 OM visits per 1000 children
Grijalva et al., 2009[46]	Before-after	US	1995-2006	PCV7	NR	2000	NR	< 60	6,2 billion ambulatory visits
Groth et al., 2015[67]	Before-after	Denmark	2001-2011	PCV7	2 + 1	October 2007	2007: 86% 1 dose; 82% 2 doses; 81% 3 doses	< 24	NR
				PCV13	2 + 1	April 2010	2011: 93% 1 dose; 93% 2 doses; 92% 3 doses		
Hasegawa et al., 2015[47]	Cohort	Japan	2011-2014[†]	PCV7	NR	2009	NR	< 36	614 children
Howitz et al., 2017[68]	Before-after	Denmark	2000-2014	PCV7 (2009-2010)	NR	2007	69% in 2007, 87% in 2008	< 48	NR
				PCV13 (2011-2014)			90% in 2014		
Jardine et al., 2009[71]	Time series	Australia	1998-2007	PCV7	3 + 0	January 2005-June 2007	NR	< 48	238 634 children

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Table 1. Continued

Reference	Study design	Country	Study period	Vaccine	Dose schedule	Year of introduction	Coverage	Age, mo	Sample/population analyzed
Kostenniemi et al., 2018[28]	Before-after	Sweden	2005-2014	PCV 7 PCV 13 PCV 10	3 + 1 2 + 1 2 + 1	2009 2010 2011	98%	< 48	NR
Lau et al., 2015[18]	Interrupted time series	United Kingdom	January 2002-December 2012	PCV7	2 + 1	September 2006-March 2010	93.5%	< 48	NR
				PCV13			88.6%		NR
Laurenz et al., 2016[29]	Before-after	Germany	2003-2014	PCV7	NR	2007	NR	< 8	NR
				PCV10		April 2009			
				PCV13		December 2009			
Leach et al., 2014[62]	Before-after	Australia	2008-2012	PCV7	3 + 1	July 2001	NR	< 36	895 children
				PCV10	3 + 1	October 2009	NR		
Leach et al., 2016[66]	Before-after	Australia	2010-2013	PCV10	3 + 1	October 2009	NR	< 36	651 children
				PCV13	3 + 1	October 2011	NR		
Mackenzie et al., 2009[30]	Before-after	Australia	1996-2004	PCV7 + PPSV23 (booster)	3 + 1	July 2001	NR	< 24	NR
Magnus et al., 2012[31]	Cohort	Norway	1999-2008	PCV7	2 + 1	July 2006	NR	< 36	NR
Marom et al., 2014[63]	Time series*	US	2001-2011	PCV7	NR	2000	90%-93% for ≥ 3 doses	< 24	5.51 million child-years
				PCV13	NR	March 2010	75%-84% for ≥ 4 doses		
Oliveira et al., 2016[57]	Prospective cohort	Brazil	2009-2013	PCV10	NR	July 2010	NR	6-23	422 children
Poehling et al., 2007[32]	Before-after	US	1998-2002	PCV7	3 + 1	2000	3 doses: 73% in Tennessee and 82% in New York	< 24	Tennessee: 150 122 children
							4 doses of PCV7: 35% in Tennessee and 53% in New York.		New York: 26 409 children
Sartori et al., 2017[48]	Interrupted time series	Brazil	August/2008-July/2015	pre-PCV			90%-95% since 2011	2-23	4793 children
				PCV 10	3 + 1	2010			
Sasaki et al., 2018[61]	Before-after	Japan	2005-2015	PCV7	3 + 1	2011	NR	< 60	NR
Sigurdsson et al., 2015[49]	Before-after	Iceland	2008-2013	PCV10	NR	April 2011	95%	< 36	Pre-PCV10: 2747 Post-PCV10: 2495
Sigurdsson et al., 2017[50]	Before-after	Iceland	2008-2015	PCV10	NR	2011	97%-98% (primary vaccine doses)	< 36	NR
Sigurdsson et al., 2018[51]	Before-after	Iceland	2005-2015	PCV 10	2 + 1	2011	97% (2015, at least 2 doses)	< 36	53 150 children
Singleton et al., 2018[65]	Before-after	US	2003-2013	PCV7	3 + 1	2000	NR	< 60	2003-2005: 361 701 Outpatient Visits AI/AN
				PCV13	3 + 1	2010	> 90%		2010-2011: 175 068 Outpatient Visits AI/AN
Sohn et al., 2020[52]	Retrospective cohort	Korea	2013-2015	PCV 10	3 + 1	2014	98%	< 48	990 224 children
				PCV 13		2014			
Suarez et al., 2016[33]	Interrupted time series	Peru	2006-2012	PCV7	2 + 1	2009	87.2% (2010), 91% (2011), 95% (2012)	< 12	70 670 acute otitis media outpatient visits
				PCV13	2 + 1				
Sugino et al., 2015[70]	Before-after	Japan	2008-2012	PCV7	2 + 1	January/11	100% (2011), 76% (2010), 69% (2009), 53% (2008), and 53% (2007).	< 60	1916 cases of myringotomy for a AOM
Tawfik et al., 2018[72]	Before-after*	US	2000-2012	PCV7	NR	2000	19-35 mo: 40.8% (2002), 68.1% (2003), 82.8% (2005)	< 48	2000: 7 291 032 pediatric hospital discharges;
				PCV13	NR	2010			2003: 7 409 162, 2006: 7 558 812

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Table 1. Continued

Reference	Study design	Country	Study period	Vaccine	Dose schedule	Year of introduction	Coverage	Age, mo	Sample/population analyzed
									2009: 7 370 203; 2012: 6 675 222
Thorrington et al., 2018[59]	Before-after	England	2004-2015	PCV7	3 + 0	2006	NR	< 48	All otitis media < 2 yr: 38 763
									All otitis media 2-4 yr: 105 549
									OM with tympanostomy < 2 yr: 14 694
									OM with tympanostomy 2-4 yr: 89,65
Van Deursen et al., 2012[34]	Before-after	The Netherlands	1995-2009	PCV7	NR	June 2006	NR	< 24	NR
Villaseñor-Sierra et al., 2012[35]	Cohort*	Mexico	NR	PCV7	NR	NR	NR	< 36	NR
DeWals et al., 2009[36]	Time series	Canada	2001-2007	PCV7	2 + 1	2002-2004	90%	< 60	25 679 (2001)
									25 089 (2007)
DeWals et al., 2009[38]	Retrospective cohort	Canada	1994-2010	PCV7	3 + 1	2002	90%	< 60	825 children
				PCV 10	2 + 1	2009			
				PCV13	2 + 1	2011			
				PCV10 + PCV13	3 + 1	2018			
Wiese et al., 2019[65]	Retrospective cohort	US	2006-2016	PCV7	3 + 1	2000	NR	< 24	368 063 children
				PCV13	3 + 1	2010			
Zhou et al., 2008[4]	Before-after	US	1997-2004	PCV7	3 + 1	2000	41% (2002) 83% (2005)	< 24	From 20 628 to 153 812 children
Zhou et al., 2012[40]	Before-after	US	1994-1999 vs 2001-2009	PCV7	NR	2000	NR	< 60	NR
Zhou et al., 2007[39]	Before-after	Canada	2000-2014	PCV7	2 + 1	NR	NR	< 24	700 658 children
Zhou et al., 2019[60]	Before-after	US	1997-2013	Pre-PCV7	—	1997-1999	NR	< 24	NR
				PCV7	3 + 1	2000		< 60	
				PCV13	3 + 1	2010		< 24	
								< 60	

AI/AN indicates American Indian/American Native; AOM, acute otitis media; Dec, December; NR, not reported; OM, otitis media; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent polysaccharide vaccine; US, United States.
*According to our evaluation.
†The authors mentioned the period of study was not defined completely, it was from birth to 30 April 2014, and as the authors included children under 3 years of age, we assume that this is the study period (2011-2014).

recent (< 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane.[6] For studies considering secondary data, OM and AOM were ascertained considering the International Classification of Diseases, ninth version codes (381, nonsuppurative OM and eustachian tube disorders; 382, suppurative and unspecified OM; or 384, other disorders of the tympanic membrane) or the International Classification of Diseases, tenth version codes (H65, nonsuppurative OM; H66, suppurative and unspecified OM; or H67, OM in diseases classified elsewhere). Secondary outcomes were the percentage or rate of cochlear implantation, myringotomy, tympanostomy with or without ventilation tube placement, tympanoplasty, and other complications.

Study Risk of Bias Assessment

The quality assessment was evaluated by 2 independent reviewers using the National Heart, Lung, and Blood Institute checklist for case-control, cohort, and before-after studies.[24] Time series studies were evaluated with a modified version of Ramsay et al[25] 2003 criteria. Quasi-experimental study designs were evaluated using the relevant items from the Downs and Black[26] (1998) checklist. Disagreements on methodological quality were resolved by consulting a third reviewer.

Data Analysis and Synthesis Methods

The numbers of studies throughout the process of study selection were represented in a flowchart. The descriptive information for each study were presented in excel tables, by type of study design and type of vaccine. For all studies, the main measure of interest was the vaccine effectiveness (VE) in reducing the outcome of interest. In case-control and cohort studies, the association between the effect of pneumococcal vaccine and the occurrence of AOM was measured by odds ratio and relative risk, respectively. The effectiveness of the vaccines was estimated as 1-odds ratio (case-control studies) and 1-risk ratio (RR) (cohort studies).

For time series studies, the effect (percentage of reduction) of the pneumococcal vaccines on the AOM was measured as the

Table 2. Reported vaccine effectiveness for PCV7.

Reference	Study design	Vaccine (schedule), time of use PCV	Outcome	Baseline rates-incidence in the prevaccine period (per 1000 Pop. or PY)
Ansaldi et al, 2008[27]	Before-after	PCV7 (2 + 1), 2 yr	Hospitalization AOM rate/1000 PY	4.52
Ben-Shimol et al, 2016[37]	Before-after	PCV7 (3 + 1), 2 yr PCV13 (3 + 0), 5 yr	All-cause OM rate/1000 children	Pre-PCV: 19.6 ± 2.5 (n = 3411) PCV7: 16.6 ± 1.5 (n = 1532)
Cunha et al, 2012[41,*]	Cohort[†]	PCV7 (3 + 1), NR	AOM incidence/1000 PY	169.3[‡,§]
Edmondson-Jones et al, 2021[42]	Retrospective cohort	Pre-PCV	Cases of OM in inpatient and outpatient	60.14
		PCV7 (2 + 1), 1 yr		7.87
		PCV10 (2 + 1), 3 yr		9.95
		pre-PCV		77.97
		PCV7 (2 + 1), 1 yr		7.27
		PCV13 (2 + 1), 3 yr		17.25
Fortanier et al, 2019[43]	Cohort	PCV7 (3 + 1), 5 yr	First AOM episode	NR
		PCV 10 (2 + 1)[¶], 4 yr	Overall AOM episodes	
Fortunato et al, 2015[44]	Before-after	PCV7 (2 + 1), 7 yr	Hospitalization rates for AOM/100 000	NR
		PCV13 (2 + 1), 2 yr		
Grijalva et al, 2006[45]	Before-after	PCV7 (3 + 1), 3 yr	OM visit rates/1000 children	1415/1000 Pop.
Grijalva et al, 2009[46]	Before-after	PCV7 (3 + 1), 6 yr	OM visit rates//1000 children	950/1000 Pop.
Hasegawa et al, 2015[47]	Cohort	PCV7 (NR), 5 yr	Incidence rate for AOM	0.034
Kostenniemi et al, 2018[28]	Before-after	PCV7 (2 + 1), 1 yr PCV 13 (2 + 1), 1 yr PCV 10 (2 + 1), 3 yr	AOM (all-cause), number of cases	275
Lau et al, 2015[18]	Interrupted time series	PCV7 (2 + 1), 4 yr PCV13 (2 + 1), 2 yr	Monthly incidence of OM (number of OM episodes during the study period divided by the total PY of the study population during the time period)	< 24m: 204.4 episodes/1000
				24m-48m: 180.6 episodes/1000
Laurenz et al, 2016[29,*]	Before-after	PCV7 (NR), NR PCV10 (NR), NR PCV13 (NR), NR	Diagnosis rates of nonsuppurative OM	391.828 nonsuppurative OM episodes
Mackenzie et al, 2009[30]	Before-after	PCV7 (3 + 0) PPSV23 (booster), 4 yr	AOM incidence bilateral	1.83 episodes per PY
Magnus et al, 2012[31]	Cohort	PCV7 (2 + 1), 3 yr	AOM incidence	
				224.4/1000 Pop.
				433.5/1000 Pop.
Poehling et al, 2007[32]	Before-after	PCV7 (3 + 1), 2 yr	Cumulative proportion of frequent otitis media	Tennessee[**]: 330/1000 Pop. New York[**]: 380/1000 Pop.
Suarez et al, 2016[33]	Interrupted time series	PCV7 (2 + 1), 3 yr PCV13 (2 + 1), 2 yr	Rates of AOM outpatient visits/100 000 children < 1 yr	NR
Van Deursen et al, 2012[34,*]	Before-after	PCV7 (NR), 3 yr	Hospitalization rates of OM	NR
Villaseñor-Sierra et al, 2012[35,*]	Cohort[†]	PCV7 (NR), NR	AOM incidence/1000 person-years	77.8[‡,§]
DeWals et al, 2009[36]	Time series	PCV7 (2 + 1), 3 yr	Monthly OM claim rates/100 person-mo	number of visits predicted: 308 759
DeWals et al, 2020[38]	Retrospective cohort	PCV7 (3 + 1), 7 yr PCV 10 (2 + 1), 2 yr	OM, first episode	NR
		PCV13 (2 + 1), 7 yr PCV10 + PCV13 (3 + 1), 2 yr		
Zhou et al, 200[84]	Before-after	PCV7 (3 + 1), 4 yr	AOM-related ambulatory visit rates/1000 person-year	2173/1000 PY
Zhou et al, 2007[39,*]	Before-after	PCV7 (2 + 1), NR PCV10 (2 + 1), NR PCV13 (2 + 1), NR	Cumulative otitis media episodes	1.96/child
Zhou et al, 2012[40,*]	Before-after	PCV7 (3 + 1), 9 yr	Ambulatory care visit rates for AOM /100 children	NR

Table 2. Continued

Data analysis	Age group, mo	Result	Statistical significance (95% CI or *P*-value)	Vaccine effectiveness (%)	Statistical significance (95% CI or *P*-value)
Pre-PCV vs PCV7, Incidence rate/1000 PY	< 24	2.88	2.50-3.29	36.40	24.10-46.70
Pre-PCV vs PCV7, incidence rate ratio	< 36	0.85	0.80-0.90 (< .05)	15	NR
PCV7 vs nonvaccinated, incidence of AOM/1000 PY	0-36	233.9		38.16[‖,§]	NR
pre-PCV vs PCV7, adjusted hazard ratios in Skåne	< 24	0.792	0.771-0.814 (< .001)	20.8	(< .001)
pre-PCV vs PCV7, adjusted hazard ratios in VGR		0.997	0.969-1.025 (.821)	0.3	(.821)
Pre-PCV vs PCV7, hazard ratio respectively	< 48	0.94	0.84-1.05	6[‖]	NS
Pre-PCV vs PCV7, hazard ratio respectively		1.00	0.95-1.06	NS	NS
Pre-PCV vs PCV7/PCV13, HRRs	< 60	0.61	0.58-0.65	39[‖]	35-42
Pre-PCV vs PCV7, rate ratio	< 24	0.80	0.66-0.96 (.014)	20	2-38
Pre-PCV vs PCV7, rate ratio[£]	< 60	0.67	0.57-0.78	33	22-43 (.008)
PCV7 vs nonvaccinated, adjusted hazard ratio	< 36	0.37	0.24-0.56 (< .001)	63[‖]	44-76[‖]
Pre-PCV vs PCV 7/PCV 13/PCV10, cases per 1.000 persons	< 48	161	155-167	41.5	38.5-44.5 (< .01)
Pre-PCV vs PCV7, rate of incidence (segmented linear regression)	< 24	NR	NR	19.8	16.0-23.5 (< .05)
	24-48	NR	NR	23.0	20.4-25.4 (< .05)
Pre-PCV vs PCV7, rates of Nonsuppurative in 2009	< 48	NR	NR	17.5	(< .0001)
Pre-PCV vs PCV7 + PPSV23, AOM absolute rate reduction Incidence rate ratio adjusted	< 24	0.88	0.69-1.13	12[‖]	NS
PCV7 vs nonvaccinated, adjusted relative risks	0-12	0.86[#]	0.81-0.91	14[‖]	9-19[‖]
	12-18	0.87[#]	0.82-0.92	13[‖]	8-18[‖]
	18-36	0.92[#]	0.90-0.94	8[‖]	6-10[‖]
Pre-PCV vs PCV7, hazard ratio (Tennessee)[***]	< 24	0.92	0.89-0.94	8	6-11[‖]
Pre-PCV vs PCV7, Hazard ratio (New York)[***]	< 24	0.67	0.62-0.72	33	28-38[‖]
Pre-PCV vs PCV7/PCV10, observed and predicted rates	< 12	NR	NR	26.2	16.9-34.4 (< .001)
Pre-PCV vs PCV7, Hospitalization rates of OM	< 24	NR	NR	35.2	NR
PCV7 vs nonvaccinated, incidence of AOM	0-36	88.1	NR	13.24[‖,§]	NR
Pre-PCV vs PCV7, % reduction in observed and predicted rates	< 60	n° of visits observed: 268 130	NR	13.2	NR
PCV 7/PCV 10/PCV 13 (4 doses) vs Unvaccinated, rate ratio	< 60	0.80	(*P* < .001)	20	(*P* < .001)
PCV 7/PCV 10/PCV 13 (at least 1 dose) vs unvaccinated, hazard ratios		0.73	(*P* = .05)	27	(*P* = .05)
Pre-PCV vs PCV7, AOM-related ambulatory visit rates/1000 person-year	< 24	1.244/1000 PY	NR	42.7	42.2-43.1 (< .001)
Pre-PCV vs PCV7, annual OM rate	< 24	1.43	NR	27.04[‖]	(< .0001)
Pre-PCV vs PCV7, rate ratio	< 24	0.67	0.59-0.75	33	25-41[‖]
	24-60	0.81	0.71-0.92	19	8-29[‖]

AOM indicates acute otitis media; CI, confidence interval; HRR, hospitalization risk ratio; NR, not reported; NS, nonsignificant; OM, otitis media; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; Pop., population; PPSV23, 23-valent polysaccharide vaccine; PY, person-year; VGR, Västra Götalandsregionen.
*Only abstract was available.
[†]According to our evaluation.
[‡]Unvaccinated children.
[§]Retrospective data.
[‖]Calculated from data available in the article.
[¶]Initially given at ages 2, 4, and 11 months; from November 28, 2013, a 3-dose schedule at ages 2, 4, and 11 months was changed.
[£]The period considered in the comparisons: 1995-1996 vs 2005-2006.
**Prevaccine period considered: 1998-1999.
***The period considered in the comparisons: 1989-1999 vs 2001-2002.
[#]3 or more immunizations.

Table 3. Reported vaccine effectiveness for PCV10.

Reference	Study design	Vaccine (schedule), time of use PCV	Outcome	Baseline rates-incidence in the prevaccine period (per 1000 Pop. or PY)
Carrasquilla et al, 2020[53]	Before-after	PCV 10 (2 + 1), 5 yr	OM, number of cases	98.2
				10.4
				120.6
Chu et al, 2014[54,*]	Cohort	PCV10 (NR), NR	Overall incidence of AOM	5.11%
Edmondson-Jones et al, 2021[42]	Retrospective Cohort	pre-PCV	Cases of OM in inpatient and outpatient	60.14
		PCV7 (2 + 1), 1 yr		7.87
		PCV10 (2 + 1), 3 yr		9.95
		pre-PCV		77.97
		PCV7 (2 + 1), 1 yr		7.27
		PCV13 (2 + 1), 3 yr		17.25
Eythorsson et al, 2018[55]	Before-after	PCV 10 (NR), 4 yr	AOM incidence	47.5 per 1000 person-years
Fortanier et al, 2019[43]	Cohort	PCV 7 (3 + 1), 5 yr	first AOM episode	NR
		PCV 10 (2 + 1)[‖], 4 yr	overall AOM episodes	
Gisselsson-Solen et al, 2017[56]	Before-after	PCV7 (2 + 1), 2 yr PCV 10 (2 + 1), 4 yr PCV13 (2 + 1), 4 yr	AOM outpatients IRs/100 000	47.09/1000 pop.
Laurenz et al 2016[29,*]	Before-after	PCV7 (NR), NR PCV10 (NR), NR PCV13 (NR), NR	Diagnosis rates of nonsuppurative OM	391.828 nonsuppurative OM episodes
Oliveira et al, 2016[57]	Prospective cohort	PCV10 (3 + 1), 3 yr	Episodes of AOM	NR
Sartori et al, 2015[48]	Interrupted time series	PCV 10 (3 + 1), 5 yr	Outpatient visits because of OM	5.76/100 patients[‡]
Sigurdsson et al, 2017[49]	Before-after	PCV10 (NR), 2 yr	Yearly incidence of AOM/10 000 children-years	< 1 yr: 910
				1 to < 2 yr: 1426
				2 to < 3 yr: 371
Sigurdsson et al, 2017[50,*]	Before-after	PCV10 (NR), 4 yr	Annual IR for OM	NR
				NR
				NR
Sigurdsson et al, 2018[51]	Before-after	PCV 10 (2 + 1), 4 yr	all-cause AOM visits	53 150 children
Sohn et al, 2020[52]	Retrospective cohort	PCV 10 or PCV 13 (3 + 1), 2 yr	AOM visits	NR
Suarez et al, 2016[33]	Interrupted time series	PCV7 (2 + 1), 3 yr PCV13 (2 + 1), 2 yr	Rates of AOM outpatient visits/100 000 children < 1 yr	NR
Zhou et al, 2007[39,*]	Before-after	PCV7 (2 + 1), NR PCV10 (2 + 1), NR PCV13 (2 + 1), NR	Cumulative otitis media episodes	1.96/child

difference in the observed rates in relation to the predicted rates in the post vaccination periods. For the before-after studies, the effect of the vaccines was assessed as the percentage of change in the incidence rates of AOM considering the pre- and post-vaccination periods. For both study designs mentioned earlier, we did not consider data referring to the vaccine transition period.

We reported the incidences of the various results in the study arms, together with estimates of VE, with 95% confidence intervals (CIs), when it was available.

Data analysis considered the following subgroups: study design, methodological quality (low, moderate, high), type of vaccine (PCV7, PCV10, PCV13, and PPSV23), and age (< 2 years and < 5 years) for the main outcome. Furthermore, heterogeneity between studies was assessed by using visual assessment of forest plots.

Because we avoided pooling data, we reported the effect estimates as presented by the individual studies. For studies reporting of both national and regional pooled results, we chose to report on national data. The various types of designs and methods used in the included studies made it inappropriate to perform a meta-analysis. Effect estimates of PCV were stratified by vaccine valence, type of comparison group, age that vaccine effect was measured, and type of outcome (primary vs secondary).

Results

We screened 2112 titles and abstracts, assessed 102 full texts, and included 48 observational studies (Fig. 1). The reason for excluding

Table 3. Continued

Data analysis	Age group, mo	Result	Statistical significance (95% CI or *P*-value)	Vaccine effectiveness (%)	Statistical significance (95% CI or *P*-value)
Pre-PCV vs PCV10, incidence proportion in Bogota DC	< 24	48.0	NR	51.1	50.3-51.8
pre-PCV vs PCV10, incidence proportion in Barranquilla		20.4	NR	−95.8	−110.8 to −81.9
pre-PCV vs PCV10, incidence proportion in Medellin		69.8	NR	42.1	41.0-43.2
PCV10 vs nonvaccinated group, Relative risks (RR)	2-6	0.6[†]	0.155- 2.323	40[‡]	NS
Pre-PCV vs PCV 10/PCV13, adjusted hazard ratios in Skåne	< 24	0.673	0.654-0.692 (< .001)	32.7	(< .001)
Pre-PCV vs PCV 10/PCV13, adjusted hazard ratios in VGR		0.867	0.849-0.886 (< .001)	13.3	(< .001)
Pre-PCV vs PCV10, IRR	24-36	0.71	0.63-0.80	29[‡]	< .001
Pre-PCV vs PCV10, hazard ratio respectively	< 48	0.79	0.70-0.89	21	11-30[‡]
Pre-PCV vs PCV10, hazard ratio respectively		0.89	0.84-0.95	11	5-16
Pre-PCV vs PCV10/PCV13, Rate ratio of AOM outpatients	0-48	0.61	0.60-0.61 (< .0001)	39	39-40[‡]
Pre-PCV vs PCV10/PCV13, rates of nonsuppurative OM in 2013	< 48	NR	NR	24.4	(< .0001)
PCV10 and nonvaccinated group, Odds ratio	6-23	0.16	0.05-0.52	84[‡]	48-95[‡]
Pre-PCV vs PCV10, Relative reduction difference of predicted and observed monthly rates for all-cause OM and for all-other causes	2-23	7736.78/15 680.33	NR	43	41.4-44.5 (< .010)
Pre-PCV vs PCV10, IRRs	< 12	1.08	0.94-1.23	8	NS
	12 to < 24	0.74	0.66-0.83	26	(< .001)
	24 to < 36	0.85	0.70-1.03	15	(< .1)
Pre-PCV vs PCV10, IRRs	< 12	0.877	NR	12.3	NR
	< 24	0.944	NR	5.6	NR
	< 36	0.961	NR	3.9	NR
PCV10 and nonvaccinated group, hazard ratio	< 36	0.78	NR	22	12-31
PCV 10 or PCV 13 vs nonvaccinated, hazard rate ratio	< 48	NR	NR	19.1	13.42-24.46
Pre-PCV vs PCV7/PCV10, observed and predicted rates	< 12	NR	NR	26.2	16.9-34.4 (< .001)
Pre-PCV vs PCV10, annual OM rate	< 24	1.43	NR	27.0[‡]	(< .0001)

AOM indicates acute otitis media; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; NR, not reported; NS, nonsignificant; OM, otitis media; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; Pop., population; PY, person-year.
*Only abstract was available.
[†]Three or more immunizations.
[‡]Calculated from data available in the article.
[||]Initially given at ages 2, 3, 4, and 11 months; from November 28, 2013, a 3-dose schedule at ages 2, 4, and 11 months was changed.

studies after a complete reading is presented in Appendix Table 2 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012. Of the included studies, 30 (63%) were before-after, 11 (23%) cohort, 6 (13%) time series, and 1 (2%) case-control study designs. Ten studies were conducted in the United States, 5 in Iceland, 4 in Australia, 3 in Brazil, 3 in Canada, 3 in Japan, 3 in Sweden, 2 in the United Kingdom, 2 in Denmark, 2 in Italy, 2 in The Netherlands, and 1 study in each one of those countries, Colombia, Germany, Israel, Korea, Mexico, Norway, Peru, Philippines, and Russia. PCV7 was evaluated in 35 studies, PCV10 in 18 studies, and PCV13 in 19 studies. No study evaluated PPSV23. A variety of age subgroups were considered in all included studies, 18 studies evaluated children aged < 24 months, 10 studies children aged < 36 months, 10 studies children aged < 48 months, and 10 studies children aged < 60 months. The main characteristics of the included studies are reported in Table 1.[4,18,27-72] A list of all included studies with corresponding references is provided in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012.

Primary Outcomes

PCV7 versus pre-PCV period or nonvaccinated children

Twenty-three studies evaluated the use of PCV7, considering as comparator the pre-PCV period or with groups of nonvaccinated people.[4,18,27-47] All studies showed a significant reduction OM or AOM in children < 5 years old, except for 2 studies, which did not present a significant difference between groups.[30,43] The VE in

Table 4. Reported vaccine effectiveness for PCV13.

Reference	Study design	Vaccine (schedule), time of use PCV	Outcome	Baseline rates-incidence in the prevaccine period (per 1000 Pop. or PY)
Ben-Shimol et al, 2016[37]	Before-after	PCV7 (3 + 1), 2 yr PCV13 (3 + 0), 5 yr	All-cause OM rate/1000 children	Pre-PCV: 19.6 ± 2.5 (n = 3411) PCV13: 6.3 ± 0.3 (n = 636)
Brico et al, 2017[58,†]	Case-control	PCV13 (2 + 1), NR	Incidence of otitis	NR
Fortunato et al, 2015[44]	Before-after	PCV7 (2 + 1), 7 yr PCV13 (2 + 1), 2 yr	Hospitalization rates for AOM/100 000	NR
Gisselsson-Solen et al, 2017[56]	Before-after	PCV7 (2 + 1), 2 yr PCV 10 (2 + 1), 4 yr PCV13 (2 + 1), 4 yr	AOM outpatients Incidence rates/100 000	47.09/1000 pop.
Laurenz et al, 2016[29,*]	Before-after	PCV7 (NR), NR PCV10 (NR), NR PCV13 (NR), NR	Diagnosis rates of nonsuppurative OM	391.828 nonsuppurative OM episodes
Sasaki et al, 2018[61]	Before-after	PCV7 (3 + 1), 2 yr PCV13 (NR), 2 yr	incidence of visits to medical institutions because of all-cause AOM	NR
Sohn et al, 2020[52]	Retrospective cohort	PCV 10 or PCV 13 (3 + 1), 2 yr	AOM visits	NR
Thorrington et al, 2018[59]	Before-after	PCV7 (2 + 1), 4 yr	Incidence of OM/100 000 PY	0.78 (0.76-0.81)
		PCV13 (3 + 0), 5 yr	Incidence of OM/100 000 PY	0.82 (0.81-0.84)
Zhou et al, 2007[39,†]	Before-after	PCV7 (2 + 1), NR PCV10 (2 + 1), NR PCV13 (2 + 1), NR	Cumulative otitis media episodes	1.96/child
Zhou et al, 2019[60]	Before-after	pre-PCV7, 3 yr	OM, visits	840
		PCV7 (3 + 1), 7 yr		590
		PCV13 (3 + 1), 3 yr		1220

reducing OM or AOM in children < 2 years ranged between 8% and 42.7%, in children < 3 years between 8% and 63%, in children < 4 years between 17.5% and 41.5%, and in children < 5 years of age varied between 13.2% and 39% (Table 2[4,18,27-47]).

PCV10 versus pre-PCV period or nonvaccinated children

PCV10 was evaluated in 15 studies considering as comparator the pre-PCV period or an unvaccinated group.[29,33,39,42,43,48-57] The effect of the vaccine was a significant reduction in cases and episodes of OM or AOM in all studies, except for 2 studies, which demonstrate no differences between groups.[49,54] The effectiveness of PCV10 in reducing OM or AOM in children < 2 years ranged from 5.6% to 84%, between 3.9% and 29% in children < 3 years, and between 11% and 39% in children < 4 years of age (Table 3[29,33,42,43,48-57]).

PCV13 versus pre-PCV period or nonvaccinated children

There were 10 studies that evaluated the use of PCV13 compared with the pre-PCV period or to a group of nonvaccinated children < 5 years of age.[29,37,39,44,48,52,56,58-60] In 2 studies, there was no significant difference between the groups[59,61]; in the others, PCV13 was associated with effectiveness between 2.2% and 68% in the reduction of OM or AOM (Table 4[29,37,39,44,52,56,58-61]).

PCV7 versus PCV10

Only 1 study compared the effectiveness between PCV7 and PCV10, in children < 3 years of age. Leach et al[62] showed a significant effectiveness of 9% for PCV10 relative to PCV7 in reducing AOM without perforation. For AOM with perforation, the result was not statistically significant (Fig. 2 and Appendix Table 3 in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012).

PCV7 versus PCV13

The effectiveness of PCV13 compared with PCV7, assessed in 6 studies, was between 6.6% and 62% in reducing the incidence of OM or AOM in children < 5 years of age (Fig. 2 and Appendix Table 3 in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012).[18,37,60,63-65]

Table 4. Continued

Data analysis	Age group, mo	Result	Statistical significance (95% CI or *P*-value)	Vaccine effectiveness (%)	Statistical significance (95% CI or *P*-value)
Pre-PCV vs PCV13, Incidence rate ratio	< 36	0.32	0.29-0.35 (< .05)	68	65-71*
Pre-PCV vs PCV13, incidence of otitis	< 24	NR	NR	2.2	NR
Pre-PCV vs PCV7/PCV13, HRRs	< 60	0.61	0.58-0.65	39*	35-42*
Pre-PCV vs PCV10/PCV13, rate ratio of AOM outpatients	0-48	0.61	0.60-0.61 (< .0001)	39	39-40*
Pre-PCV vs PCV10/PCV13, rates of nonsuppurative OM in 2013	< 48	NR	NR	24.4	(< .0001)
Pre-PCV vs PVC7/PCV13,	< 60	NR	NR	NR	NS
PCV 10 or PCV 13 vs nonvaccinated, hazard rate ratio	< 48	NR	NR	19.13	13.42-24.46
Pre-PCV vs PCV13, incidence rate ratios	< 24	0.76	0.58-1.01	24*	NS
	24-48	0.92	0.70-1.27	8*	NS
Pre-PCV vs PCV13, annual OM rate	< 24	1.34	NR	31.63*	(< .0001)
Pre-PCV vs PCV13, rate ratios	< 24	0.52	NR	48	37-59
	< 60	0.59	NR	41	30-52

AOM indicates acute otitis media; CI, confidence interval; HRR, hospitalization risk ratio; NR, not reported; NS, nonsignificant; OM, otitis media; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; Pop., population; PY, person-year.
*Calculated from data available in the article.
†Only abstract was available.

PCV10 or PCV13 versus PCV7

The effectiveness of PCV10 or PCV13 compared with PCV7, evaluated in 1 study,[42] was 13% and 15.1% in reducing the incidence of OM in children < 2 years of age, in 2 Swedish regions—*Västra Götalandsregionen and Skåne*, respectively (Fig. 2 and Appendix Table 3 in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012).

PCV10 + PCV13 versus PCV7

Only 1 study compared the effectiveness between mixed PCV10 + PCV13 schedule and PCV7.[38] De Wals et al[38] showed no significant difference between the groups in reduction of the first episode of OM (9%, $P = .65$) for PCV10 + PCV13 relative to PCV7 in children < 5 years of age (Fig. 2 and Appendix Table 3 in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012).

PCV10 versus PCV13

Only 1 study[66] conducted the comparison between the effectiveness of the PCV10 and PCV13, which demonstrated that there was no significant difference between them, regarding the reduction of AOM without perforation and AOM with perforation (Fig. 2 and Appendix Table 3 in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012).

Secondary Outcomes

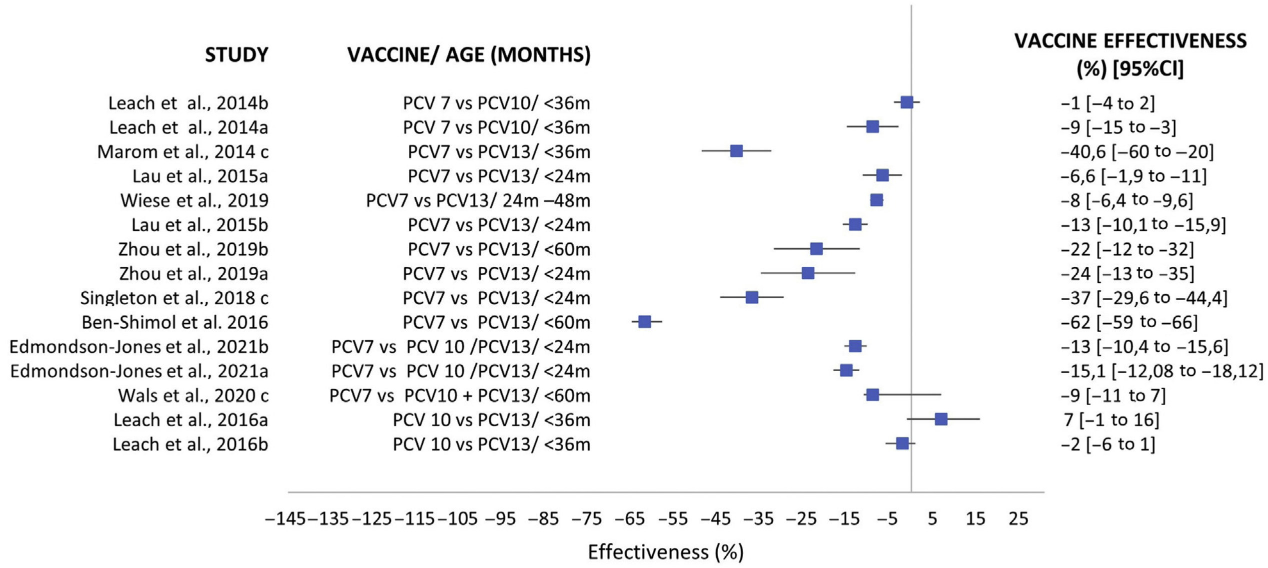
The results of the evaluated secondary outcomes are described in Appendix Table 4 in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012.

The effectiveness of PVCs in reducing tympanic membrane perforation, assessed in 3 studies, ranged from 2% to 49% in children < 3 years old.[30,62,66]

The effectiveness of PCVs in reducing ventilation tubes insertion in children < 4 years of age was assessed in 6 studies.[56,59,65,67-69] The results were divergent, varying between a significant reduction of 5% to 49% and a significant increase of 0.6% to 56% in ventilation tubes insertion.

Four studies evaluated the effects of PCVs on myringotomy rates.[56,61,70,71] All studies on PCVs showed a significant reduction in myringotomy rates, ranging from 6% to 29% in children < 5 years of age, except in the study by Jardine et al[71] in

Figure 2. Vaccine effectiveness between PCVs against OM and AOM. AOM indicates acute otitis media; CI, confidence interval; OM, otitis media; PCV, pneumococcal conjugate vaccine.



children aged 36 and 48 months that did not show significant differences.

Mastoiditis was evaluated in 2 studies[64,72]; in both, PCVs were associated with a significant reduction in mastoiditis rates, varying between 10% and 52%.

Quality Assessment

The methodologic quality of the included studies was assessed according to the study design, the studies presented fair quality in general, and the main limitations were related to the absence of blinding of the evaluators, the presence of uncontrolled confounding factors, and concerns about validity external part of the study. A complete reading with the quality assessment is provided in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.12.012.

Discussion

Our systematic review of real-world data available in observational studies shows a considerable effect of PCV vaccines in reducing OM or AOM incidence n children aged < 5 years. Of the 41 studies included, 18 evaluated the effectiveness of PCVs in children < 24 months; of these 16 studies demonstrated effectiveness between 2.2% and 43% in reducing OM or AOM, compared with the pre-PCV period or to a group of nonvaccinated individuals. Only 2 studies[30,59] found no significant differences in the compared groups.

Among the 20 studies that examined PCVs in children < 5 years of age, significant effectiveness between 8% and 68% in reducing OM or AOM was reported; in only 4 studies, this reduction was not significant.[43,51,59,61]

The effectiveness results corroborate data from clinical trials reporting on the efficacy of these vaccines.[19-21,73] Efficacy reported in 2 systematic reviews[21,73] also varied PCVs reduced the risk of AOM by all causes by 7% (RR 0.93; 95% CI 0.86-1.00) and by 43% of pneumococcal AOM (RR 0.57; 95% CI 0.39-0.83).[73]

Taylor et al[19] conducted a systematic review of the efficacy and effectiveness of PCV7 in reducing OM in children < 12 years of age. Efficacy data ranged from 0 to 9% in the included randomized controlled trials. As for effectiveness, 8 observational studies were included, which demonstrated average effectiveness of 19% in reducing episodes of OM visits (CI 7%-48%). The authors highlighted that in observational studies a tendency of AOM reduction over time was observed, and confounding factors should be further assessed and taken into consideration.

In the present systematic review, although our data did not allow us to perform a comparative effectiveness evaluation considering the different pneumococcal vaccines, we found that ecologic studies evaluating PCV10 reported greater effectiveness than studies evaluating PCV 13 (PCV10 VE 27%-84% vs PCV13 VE 19%-68%). Nevertheless, the only head-to-head study that performed a direct comparison between these vaccines found no significant differences in this outcome.[66]

No included study compared the effectiveness of PPSV23 alone or in comparison with other PCVs. Only 1 study[30] included PPSV23 as a booster associated with PCV7, showing a nonstatistically significant effectiveness of 12% (95% CI 0.69-1.13) in reducing the incidence of AOM. As reported in previous studies, PPSV23 makes a small difference in children older than 2 years or children who have had AOM previously.[74]

The evidence gathered from global postmarketing studies of these vaccines presented in this review suggests that the effectiveness of PCVs on AOM is substantial in children aged < 5 years. Despite the great variability of the data, most of them point to the same direction of benefit in the assessed outcome.

Palmu et al[75] assessed the effectiveness of PCV10 introduction in Finland in 2010. The study demonstrated a reduction in the incidence rate of insertion of tympanostomy tubes by 14.8%, with greater reduction demonstrated in the public service than private (17.8% and 12.4%, respectively). The authors noted that the coverage of private health insurance for children also increased from 36% in 2009 to 41% in 2014 in Finland. Therefore, the availability of private insurance coverage and easy access to care may be associated with a lower threshold for office visits, antimicrobial use, and tympanostomy tube surgery with the potential to influence our downward effectiveness estimates. Notwithstanding, PCV10 effectiveness on tympanostomy tube surgery was lower in the private sector than the public.

A population-based study conducted in Denmark showed that the introduction of PCV into the childhood immunization program was not associated with a decrease in the rates of ventilation tube insertions; instead, rates continued to rise.[67] The study included children of all social strata given that the Danish health system provides free healthcare for all residents. Nevertheless, there is an innate risk of ecological fallacy, because vaccinated children are not necessarily the same ones who subsequently had or avoided the insertion of a ventilation tube. In contrast, PCV coverage in Denmark is approximately 90%, being likely to induce herd immunity over time. Changes over time in other AOM and ventilation tube risk factors may have influenced the observed rates of ventilation tube insertions.

In this study, we provide a complete summary of all available evidence on the effectiveness of PCVs on OM or AOM. We included the gray literature to include all available evidence on the use of PCVs, thus reducing the potential for publication bias. Nevertheless, the inclusion of unpublished data and before-after studies, despite minimizing publication bias, decreased the overall quality of the included studies. We tried to maximize the quality of the data by excluding studies that included the transition period in their analysis.

Despite the strengths of this review, some potential limitations should be addressed. The review did not assess serotype-specific effectiveness and did not differentiate between different vaccine schedules, which may have dismissed potentially relevant results. We did not assess the effect of socioeconomic indicators as a confounding factor in the outcomes of OM or AOM, because these data were not available in the included studies. Due to the great heterogeneity in the study design, reported dose, age, schedule and type of service used, and combinations across studies, it was not possible to perform a meta-analysis and provide pooled estimates of the VE.

The heterogeneity present studies that evaluated the introduction of PCVs in immunization programs should explore other aspects in addition to the methodological differences of the various designs used. Several aspects contribute to this variability, such as different schedules, geographic location, different socioeconomic contexts, surveillance practices, transmission dynamics, population risk factors, and pathogen evolution, in addition to considering the possibility that the impact of PCV against these parameters may vary depending on the vaccine configuration. Investigating the possible causes of this variability remains a broad aspect that should be better explored in future studies.

We are aware that the findings of observational studies require careful interpretation because of intrinsic factors of this design, such as variability in baseline incidence, studied population, and case definition, in addition to the various risk factors for AOM. Especially because time series was included, although this type of study is extremely useful to assess the impact of vaccines, there is an intrinsic limitation to the design regarding effectiveness, given that other changes may have occurred over time and have influenced the results. Nevertheless, we believe that these selected studies of real-world data could contribute to the scope of evidence demonstrating the effectiveness of PCVs in reducing OM, AOM, perforation of the tympanic membrane, myringotomy, and mastoiditis in children $<$ 5 years of age. Future studies are also needed to assess the comparative effectiveness of the various types of PCVs and monitoring the decline in OM or AOM.

Another limitation of this study is the lack of information from Asia and Africa. There have long been indications of country-specific epidemiological differences in the distribution of serotypes that would likely affect the impact of the vaccine, particularly between low- and high-income countries.[76,77] The incidence of pneumococcal disease in children varies widely across populations and countries. Overcrowding, poverty, comorbidities, birth rates, and host genetic factors are known to increase the incidence of pneumococcal disease.[78,79] Low-income countries account for a substantial amount of the global burden of pneumococcal disease and the majority of associated deaths.[80,81]

Given the magnitude and diversity of serotype substitution, it is important that future studies assess the comparative effectiveness of next-generation PCVs (PCV15 and PCV20). PCV15 includes serotypes 22F and 33F; PCV20 includes additional serotypes 8, 10A, 11A, 12F, and 15B.[82,83] In previous studies, PCV15 showed acceptable safety profiles and induced immunoglobulin G and opsonophagocytic activity for all 15 vaccine serotypes comparable with PCV13 in healthy infants between 2 and 15 months of age.[84] In a phase 2 study, conducted in infants aged 42 to 98 days, PCV20 had a safety profile consistent with that of PCV13.[79] Better immunogenicity is expected from these next-generation PCVs, and therefore, the long-term impacts of PCVs are expected to be better evaluated.

Conclusions

Although OM is not a life-threatening disease, its frequent occurrence makes it a public health problem. Our current results support the public health value of introducing PCV. The inclusion of PCVs in national immunization programs in several countries worldwide has had a positive effectiveness on decreasing OM or AOM and reducing the rate of tympanic membrane perforation, myringotomy, and mastoiditis in children $<$ 5 years old. The possibility of preventing OM or AOM, common diseases in childhood, using vaccines with proven effectiveness, such as PCVs, is a fundamental strategy, which allows reducing the burden of this disease.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.12.012.

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Author Affiliations: Department of Community Health, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Brazil (Marra, Toscano, Andrade); Institute of Health Sciences, Federal University of Mato Grosso, Sinop, Brazil (Sartori); Library, Gonçalo Moniz Institute, Oswald Cruz Foundation, Salvador, Bahia, Brazil (Martinez-Silveira).

Correspondence: Lays P. Marra, MSc, Institute of Tropical Pathology and Public Health, Federal University of Goiás, 235 St, Setor Universitário, Goiânia 74605-050, Brazil. Email: laysmarra@yahoo.com.br

Author Contributions: *Concept and design:* Marra, Sartori, Martinez-Silveira, Toscano, Andrade
Acquisition of data: Marra
Analysis and interpretation of data: Marra, Sartori, Martinez-Silveira, Toscano, Andrade
Drafting of the manuscript: Marra, Sartori, Martinez-Silveira
Critical revision of the paper for important intellectual content: Marra, Toscano, Andrade
Statistical analysis: Marra
Supervision: Toscano

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