Systematic review on the impact of the pneumococcal conjugate vaccine ten valent (PCV10) or thirteen valent (PCV13) on all-cause, radiologically confirmed and severe pneumonia hospitalisation rates and pneumonia mortality in children 0-9 years old

Rita Reyburn[1], Anthea Tsatsaronis[2], Claire von Mollendorf[1,3], Kim Mulholland[1,3,4], Fiona M Russell[1,3]; for the ARI Review group

[1]Murdoch Children's Research Institute, Melbourne, Victoria, Australia
[2]Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia
[3]Department of Paediatrics, The University of Melbourne, Melbourne, Victoria, Australia
[4]London School of Hygiene and Tropical Medicine, London, UK

Correspondence to:
Rita Reyburn, Epidemiologist,
Honorary MCRI
Murdoch Children Research Institute
Royal Children's Hospital,
50 Flemington Rd,
Parkville VIC 3052:
Australia
rita.reyburn@gmail.com

Background There is an ongoing need to assess the impact of pneumococcal conjugate vaccines (PCVs) to guide the use of these potentially valuable but under-utilized vaccines against pneumonia, which is one of the most common causes of post-neonatal mortality.

Methods We conducted a systematic review of the literature on PCV10 and PCV13 impact on all-cause, radiologically confirmed and severe pneumonia hospitalisation rates as well as all-cause and pneumonia-specific mortality rates. We included studies that were published from 2003 onwards, had a post-licensure observational study design, and reported on any of our defined outcomes in children aged between 0-9 years. We derived incidence rates (IRs), incidence rate ratios (IRRs) or percent differences (%). We assessed all studies for risk of bias using the Effective Public Health Practice Project (EPHPP) quality assessment tool.

Results We identified a total of 1885 studies and included 43 comparing one or more of the following hospitalised outcomes of interest: all-cause pneumonia (n = 27), severe pneumonia (n = 6), all-cause empyema (n = 8), radiologically confirmed pneumonia (n = 8), pneumococcal pneumonia (n = 7), and pneumonia mortality (n = 10). No studies evaluated all-cause mortality. Studies were conducted in all WHO regions except South East Asia Region (SEAR) and low- or middle-income countries (LMICs) in the Western Pacific Region (WPR). Among children <5 years old, PCV impact ranged from 7% to 60% for all-cause pneumonia hospitalisation, 8% to 90% for severe pneumonia hospitalisation, 12% to 79% for radiologically confirmed pneumonia, and 45% to 85% for pneumococcal confirmed pneumonia. For pneumonia-related mortality, impact was found in three studies and ranged from 10% to 78%. No obvious differences were found in vaccine impact between PCV10 and PCV13. One study found a 17% reduction in all-cause pneumonia among children aged 5-9 years, while another found a reduction of 81% among those aged 5-17 years. A third study found a 57% reduction in all-cause empyema among children 5-14 years of age.

Conclusion We found clear evidence of declines in hospitalisation rates due to all-cause, severe, radiologically confirmed, and bacteraemic pneumococcal pneumonia in children aged <5 years, supporting ongoing use of PCV10 and PCV13. However, there were few studies from countries with the highest <5-year mortality and no studies from SEAR and LMICs in the WPR. Standardising methods of future PCV impact studies is recommended.

Pneumonia is the single largest infectious cause of childhood mortality globally, accounting for 14% of deaths in children <5 years old [1]. The burden of disease is predominantly present in children <2 years old and in South East Asian and African regions [2]. The bacterium *Streptococcus pneumoniae*, known as the pneumococcus, is responsible for a significant proportion of this global burden and is estimated to cause 18.3% of severe bacterial pneumonia and 30% of all pneumonia deaths in childhood [2].

Pneumococcal conjugate vaccines (PCVs) have been in use for more than 20 years with increasing global coverage. By the end of 2019, PCVs had been introduced in 149/195 (76%) countries and global coverage was estimated to be 48% [3]. However, cost has been a major barrier to introduction, especially for middle-income countries. Currently three PCVs are WHO-pre-qualified. Two are 10-valent PCV10s (*Synflorix* and *Pneumosil*), covering different serotypes, and one is 13-valent PCV13 (*Prevnar13®*). The recently WHO-pre-qualified PCV10, *Pneumosil*, is less expensive. The WHO recommends a three-dose schedule delivered either as a two dose primary series with one booster (2 + 1) or a three dose primary series (3 + 0) [4].

Studies evaluating the impact of PCV10 and PCV13 have been conducted in various settings. PCV10 and PCV13 have been found to be effective at reducing hospitalisation for invasive pneumococcal disease (IPD), clinical pneumonia, and radiologically confirmed pneumonia both directly (in age groups targeted for vaccination) and indirectly (in unvaccinated individuals living in close proximity to other vaccinated individuals) when used in a three dose (3 + 0 or 2 + 1) or four dose (3 + 1) schedule [4,5]. These studies face several challenges, most particularly the absence of a gold standard case definition of pneumonia. For pneumococcal pneumonia, the causative organism is often not isolated and radiologically confirmed, and clinical features vary widely [6]. Additionally, there are constraints in the quality or availability of radiologically confirmed diagnosis and functioning health information systems in resource-poor countries that bear the highest burden of disease. Therefore, for epidemiological purposes, there are numerous pneumonia outcomes that are commonly used to measure the impact of PCV: hospitalised all-cause pneumonia, severe pneumonia (2005 or 2013 WHO definition), radiologically confirmed pneumonia, and bacteraemic pneumococcal pneumonia or mortality. There is limited data on the indirect impact of PCV10 and PCV13 on pneumonia burden in children aged above five years, as identified in our literature search.

We aimed to summarize the impact of the PCVs used in national immunisation programs (NIPs) for three years or more, in children 0-9 years old with hospitalised pneumonia using the following five outcomes: all-cause pneumonia hospitalisation, radiologically confirmed pneumonia hospitalisation, severe pneumonia (including empyema) hospitalisation, pneumonia mortality, and all-cause mortality.

METHODS

Literature search

We searched Medline (Ovid), Embase (Ovid), and Cochrane Library databases using Medical Subject Headings (MeSH), thesaurus terms, and keywords to identify relevant studies. The search strategy and keywords are available in the Online Supplementary Document. We additionally searched PubMed using keywords only, to source any publications and items not indexed in Medline. We manually searched the references of selected relevant published systematic reviews to ensure that important studies were not missed in the initial search. We then assessed the compiled publications, with two reviewers first screening their titles and abstracts followed by their full text. Disagreements on the inclusion were resolved through discussion among the reviewers.

Inclusion and exclusion criteria

We limited the database searches to studies published from 2003 onwards, as the first PCV was introduced globally in 2000 and one of our inclusion criteria was its use at least for three years or more post-introduction. We further applied limits to exclude randomized controlled trials, case-control studies, case reports, and case series studies, as the impact of a vaccination programs is evaluated with post-licensure observational studies [7,8]. We also restricted the searches to English language publications. The inclusion criteria for this review were: post-licensure observational studies reporting on incidence rates, rate ratios, or percent difference and comparing the outcomes of hospitalised pneumonia, all-cause empyema, all-cause mortality, or pneumonia mortality in any time period before to at least three years after the introduction of either PCV10 or PCV13 into the NIP, allowing more time for indirect and total effects to occur [9]. Full details of the inclusion and exclusion criteria are available in the Online Supplementary Document. We include studies in settings where PCV10 or PCV13 were the first PCV to be introduced into the NIP or where

PCV7 was first introduced and subsequently replaced by either PCV10 or PCV13. We excluded studies if the population did not include children 0-9 years, if less than 50% of the catchment population received PCV in the post-PCV period, or if they compared only the PCV7 period to PCV10 or PCV13 period (Table S1 in the **Online Supplementary Document**). Two reviewers independently extracted the data and any disagreements were resolved through discussion.

We used the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [10] to assess the level of risk of bias for each study, as well as to evaluate their internal validity of each study was evaluated considering eight methodological – selection bias of study participants, study design, confounders, blinding, data collection methods, withdrawals of study participants, intervention integrity, and analysis. The protocol is available upon request from the authors.

We did not conduct meta-analyses due to the heterogeneity between studies and case definitions of pneumonia outcomes (case definitions are shown in Table S2 in the **Online Supplementary Document**). Study results were stratified by age group, world bank country income status, time since PCV introduction, and PCV valency.

RESULTS

We identified a total of 1885 articles, 636 in Embase, 547 in Medline (Ovid), 410 in PubMed, and 291 in Cochrane Library. We did not find any additional missed papers through the manual examination of the references of selected relevant published systematic reviews. After excluding 608 duplicates, a total of 1277 studies were screened by title and abstract; 149 studies were subsequently screened in the full text review, with 43 studies included in the final review (**Figure 1**). The results of the EPHPP quality assessment are shown in the **Online Supplementary Document**.

Of the 43 studies included, 27 evaluated hospitalisation due to all-cause pneumonia, 6 severe pneumonia, 8 all-cause empyema, 8 radiologically confirmed pneumonia, 7 pneumococcal pneumonia and 10 pneumonia mortality. No studies directly evaluated all-cause mortality (Table 1). It is important to note the wide variety of case definitions for each outcome (Table 1). Twenty-one (43%) studies looked at high-income countries (HIC), 17 (35%) at upper-middle income countries (UMIC), 7 (14%) at lower-middle income countries (LMICs) and 4 (8%) at low-income countries (LIC). Studies were from all WHO regions apart from SEAR or LMICs in WPR. Out of the 43 studies, 23 (53%) included children aged <5 years only, while 20 (47%) included children 0-9 years of age. Twenty-one (49%) studies examined PCV13, 16 (37%) PCV10 and 6 (14%) both PCV10 and PCV13 combined.

Figure 1. Flow diagram for study selection.

All-cause pneumonia hospitalisation

Twenty-seven of the 43 included studies evaluated the effect of PCV10 or PCV13 on all-cause pneumonia hospitalisations [11-37] (Table S3 in the **Online Supplementary Document**). When we considered the 22 studies reporting vaccine impact with either an incidence rate ration (IRR) or percent decline and included age groups which were below 10 years of age [11-17,20,21,23,24,26-31,33-37], the median decline in all-cause pneumonia hospitalisation was 21% and ranged between 4% to 64% [29] Study results by age group were: for age group <12 months, median = 28% (range = 4% [23] to 55% [24]); for age group 12-23 months, median = 21% (range = 8% [15] to 48% [34]); for age group 24-59 months median = 22% (range = 7% [33] to 23% [12]); for age group <5 years, median = 18% (range = 7% [16] to 60% [37]); for age group 5-9 years one study found a reduction of 17% [13] and or children aged 5-17 years, median = 49% (range = 16% [29] to 81% [27]).
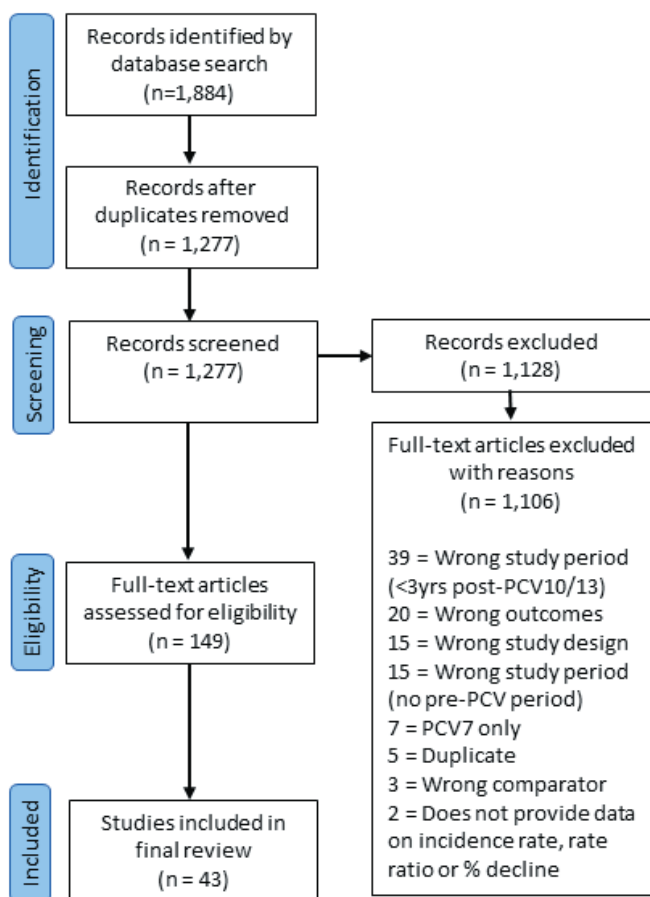
Three studies used time series analysis. Among Botswanan children aged <5 years there was a 6% annual decline [19]. Among Brazilian children aged <2 years annual declines were 4%, among children aged 2-4 years annual declines were 11% and among children aged 5-9 years there was no change [25]. Among children aged <5 years in Burkina Faso there was a 0.66 (95% confidence interval (CI) = 0.51, 0.84) change in intercept and a 0.97 (95% CI = 0.96, 0.98) change in slope, with sub-analysis by age groups; 0-23 months showed a 0.76 (95% CI = 0.59, 0.98) change in intercept and a 0.96 (95% CI = 0.95, 0.97) change in slope and 24-59 months showed a 0.50 (95% CI = 0.36, 0.70) change in intercept and a 0.98 (95% CI = 0.97, 1.002) change in slope [38]. Eight studies showed no change in one of the age groups reviewed.

Severe pneumonia hospitalisations

Six included studies evaluated the effect of PCV10 or PCV13 on severe pneumonia hospitalisations [35,38-42] (Table S4 in the **Online Supplementary Document**). One study claimed to use the WHO 2005 definition of severe pneumonia, while five studies did not state which version was used. When we considered the four studies reporting PCV10 and PCV13 impact as an IRR and included age groups below 10 years of age [35,40-42], the median decline in severe pneumonia hospitalisation was 52% and ranged between 8% [40] to 90% [42]. Study results by age group were: for age group <12 months, median = 54% (range = 51% [35] to 57% [40]); for age group 12-23 months, median = 56 (range = 39% [43] to 72% [40]; for age group 24-59 months, median = 41% (range = 30% [35] to 56% [12,44]); for age group <5 years, median = 58% (range = 8% [40] to 90% [42]); and no studies reported vaccine impact for age groups 5-9 years. One study used a time series analysis. Among children aged <5 years in Burkina Faso, there was a 0.64 (95% CI = 0.49, 0.84) change in intercept and a 0.970 (95% CI = 0.96, 0.98) change in slope, with sub-analysis by age groups; 0-23 months showed a 0.74 (95% CI = 0.56; 0.98) change in intercept and a 0.959 (95% CI = 0.944; 0.974) change in slope and 24-59 months showed a 0.45 (95% CI = 0.30, 0.68) change in intercept and a 0.996 (95% CI = 0.97, 1.02) change in slope [38].

Four studies [40] included results which showed no change, with only one showing no change in all outcomes and age groups; this study conducted in Canada assessed changes in the specific case definition of pediatric complicated pneumonia (empyema, parapneumonic effusion, necrotizing pneumonia, and lung abscess) among children <18 years and found that serotype replacement following PVC7 had contributed to increased rates of empyema [39]. The other three studies [40] all used multiple age groups and outcomes and found a proportion of their point estimates did not indicate a decline. A study in Kenya assessing two different severe pneumonia outcomes in five age groups found that all 10-point estimates declined, but that the the confidence intervals (CIs) for 7/10 results crossed the null [43]. One study in the Netherlands showed a decline in the point estimate, but the CIs crossed the null for the age group 5-17 years, and a 90% decline was observed among children <5 years [42]. A study from The Gambia found no decline in clinical pneumonia among 1-4-year-olds, but a large reduction in hypoxic pneumonia among the same population and age group [40].

All-cause empyema hospitalisations

Eight included studies evaluated the PCV10 or PCV13 on all-cause empyema hospitalisations [12,30, 32,35,42,45-47], a sub-category of severe pneumonia (Table S5 in the **Online Supplementary Document**). All studies focused on the age group <5 years and showed a median decline of 43%, ranging from 23% [46] to 68% [46]. The minimum and maximum declines were from the same study and age group (<2 years of age), but the outcome differed; parapneumonic empyema reduced by 23%, while the more specific outcome of pneumococcal parapneumonic empyema reduced by 68%. No studies assessed vaccine impact against all-cause empyema hospitalisation among children <12 months, 12-23 months, 24-59 months, or 5-9 years of age separately. One study in the UK reported a 57% decline in the rate of hospitalisation among children aged 5-14 years with empyema [35].

Radiologically confirmed pneumonia hospitalisations

Eight included studies evaluated the PCV10 or PCV13 on radiologically confirmed pneumonia hospitalisations [16,33,40,41,48-51] (Table S6 in the **Online Supplementary Document**). All but two [48,50] specified that they used the WHO-defined radiologically confirmed pneumonia definition [52]. When we considered these eight studies, which included age groups below 10 years of age, the median decline in radiologically confirmed pneumonia hospitalisation was 38% (range = 12% [33] to 79% [51]). Study results by age group were: for age group <12 months, median = 50% (range = 23% [40] to 53% [49]); for age group 12-23 months,

median = 29% (range = 25% [33] to 70% [49]); for age group 24-59 months, median = 60% (range = 12% [33] to 79% [51]); for age group <5 years, median = 48% (range = 22% [40] to 70% [51]); and there were no vaccine impact studies for the 5-9 years age group. Four studies among age groups <12 months, 12-23 months, 24-59 months, 5-10 years, and 5-14 years showed no change.

Pneumococcal pneumonia hospitalisations

Seven included studies evaluated the impact of PCV10 or PCV13 on pneumococcal pneumonia hospitalisations [30,35,40,50,53-55] (Table S7 in the **Online Supplementary Document**). When we considered the five studies reporting PCV10 and PCV13 impact as an IRR and included age groups below 10 years of age [35,40,53-55], the median decline in pneumococcal pneumonia hospitalisation was 67% (range = 45% [55] to 85% [54]). Study results by age group were: for age group <12 months, median = 62% (range = 52% [53] to 66% [55]); for age group 12-23 months, median = 75% (range = 67% [53] to 75% [40]); for age group 24-59 months, median = 64% (range = 53% [35] to 77% [53]); for age group <5 years, median = 69% (range = 45% [55] to 85% [54]); and no studies assessed vaccine impact for age groups 5-9 years. A study from Finland showed a relative rate reduction of 77 (95%CI = 64-86) among age groups 3-24 months and 70 (95% CI = 49, 84) among age groups 7-71 months [30]. A study from Japan reported a decline but no point estimate [50].

Pneumonia-related mortality

Ten included studies evaluated the PCV10 or PCV13 on pneumonia mortality [15,18,19,25,28,29,33,38,42,56] (Table S8 in the **Online Supplementary Document**), three of which showed an impact on mortality. Among children aged <5 years in Burkina Faso, there was a 0.49 (95% CI = 0.31, 0.78) change in intercept and a 0.97 (95% CI = 0.94, 0.99) change in slope. When further sub-analyzed by age groups, the following was observed; the 0-23 months age group showed a 0.60 (95% CI = 0.37, 0.99) change in intercept and a 0.95 (95% CI = 0.92, 0.97) change in slope and 24-59 months showed a 0.22 (95% CI = 0.08, 0.60) change in intercept and a 1.03 (95% CI = 0.98, 1.08) change in slope [38]. Among Spanish children <18 years in-hospital mortality fell by an odds ratio of 0.82 (95% CI = 0.77, 0.89) [25]. Among Botswanan children aged 1-59 months there was a 22% (95% CI = 8, 33) annual decline in the five years post PCV13 introduction [19].

The seven remaining studies showed no change in mortality: among Nicaraguan children aged 0-4 years, the IRR = 1.01 (95% CI = 0.67, 1.52) and 5-14 years IRR = 0.22 (95% CI = 0.02, 2.47) [15]. Among Dutch children aged <5 years, the IRR was 1.46 (95% CI = 0.37, 5.80); among those aged 5-17 years, the IRR was 0.88 (95% CI = 0.06, 13.3) [42]. Among Swedish children aged <2 years, the IRR was 0.36 (95% CI = 0.07, 1.83), while it was 0.42 (95% CI = 0.08, 2.31) among those aged 2-4 years and 0.9 (95% CI = 0.35, 2.33) among those aged 5-17 years [29]. Three studies were conducted in Brazil and all noted dramatic declines in mortality in the pre-PCV era. One of these studies showed no decline in pneumonia mortality associated with PCV introduction among children aged <5 years using their primary analysis synthetic control time series, but the secondary time trend analysis showed an approximately 10% decline in mortality, which was greater (in areas in lower socio economic status 20%-50%, depending on the age group) [56]. The second study in Brazil showed an annual decline of 6.5% (95% CI = 6.3, 6.7) in the post-PCV period among children <5 years old, but this was not statistically significant [18]. The third Brazilian study among children <5 years showed no decline in the case-fatality ratio [33]. All three Brazilian studies noted a substantial decline in child mortality in the years prior to PCV introduction. Among Zambian children, there was no change in in-hospital deaths among children <5 years (no point estimate for the change was provided) [28].

PCV impact by country income status, vaccine valency, and time since introduction

PCV impact on pneumonia hospitalisation appears to be slightly higher in high-income countries (HICs) compared to low-income countries (LIC), LMICs, or upper-middle income countries (UMICs), but the heterogeneity in study results make it challenging to draw strong conclusions (**Table 1**). PCV impact on pneumonia was similar for PCV10 and PCV13 (**Table 2**). There is some evidence that PCV impact on pneumonia was slightly higher in the studies which were conducted >5 years vs 3-5 years post-PCV introduction. However, there were few studies in the former group, so definitive conclusions cannot be drawn (**Table 3**).

Reyburn et al.

Table 1. PCV impact by age group, outcome and country income status

Outcome	Income Status	<2y Range of decline in point estimate	<2y No. of study results that changed in post-PCV period	<2y No. of study results that did not change in post-PCV period	2-4y Range of decline in point estimate	2-4y No. of study results that changed in post-PCV period	2-4y No. of study results that did not change in post-PCV period	<5y Range of decline in point estimate	<5y No. of study results that changed in post-PCV period	<5y No. of study results that did not change in post-PCV period	5-9y Range of decline in point estimate	5-9y No. of study results that changed in post-PCV period	5-9y No. of study results that did not change in post-PCV period	<18y Range of decline in point estimate	<18y No. of study results that changed in post-PCV period	<18y No. of study results that did not change in post-PCV period
All-cause pneumonia	LIC	Decline but no point estimate	1	0	Decline but no point estimate	1	0	9%-22%	4	0	-	0	0	-	0	0
	LMIC	8%-38%	5	1	5%	1	0	29%-35%	2	1	No change	1	0	-	0	0
	UMIC	13%-39%	7	0	7%-22%	3	0	8%-39%	3	0	17%	1	0	-	0	0
	HIC	7%-60%	13	1	20%-47%	6	0	8%-18%	2	1	12%-81%	6	1	43%-40%	2	0
Severe pneumonia	LIC	Decline but no point estimate	1	0	Decline but no point estimate	1	0	Decline but no point estimate	1	0	-	0	0	-	0	1
	LMIC	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
	UMIC	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
	HIC	51%	1	0	30%	1	0	90%	1	0	10%-58%	2	1	-	0	0
All-cause empyema	LIC	-	0	0	-	0	0	-	1	3	48%-57%	2	2	-2%-56%	2	1
	LMIC	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
	UMIC	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
	HIC	33%-68%	2	1	42%-43%	1	1	-	0	0	57%	1	0	-	0	0
Radiologically confirmed pneumonia	LIC	23%-29%	2	0	22%	1	0	-	0	0	-	0	0	-	0	0
	LMIC	-	0	2	-	0	1	48%	1	0	-	0	1	-	0	0
	UMIC	25%-70%	5	0	12%-73%	3	0	65%	1	0	-	0	0	-	0	0
	HIC	53%-57%	2	2	60%-79%	2	1	40%-70%	4	0	41%	1	1	-	0	0
Pneumococcal Pneumonia	LIC	58%-86%	4	0	57%-66%	2	0	-	0	0	-	0	0	-	0	0
	LMIC	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
	UMIC	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
	HIC	52%-81%	5	0	53%-77%	2	0	45%-70%	5	0	69%	1	0	-	0	0
Pneumonia mortality	LIC	Decline but no point estimate	1	0	Decline but no point estimate	1	0	Decline but no point estimate	1	0	-	0	0	-	0	0
	LMIC	-	0	1	-	0	0	-	0	2	-	0	1	-	0	0
	UMIC	2%-40%	12	2	1%-52%	5	2	2%-78%	7	4	-	0	0	-	0	0
	HIC	-	0	0	-	0	0	-	0	1	-	0	1	18%	1	0

PCV – pneumococcal vaccine, y – years, LIC – low-income country, LMIC – low- and middle-income country, UMIC – upper-middle income country, HIC – high-income country

Table 2. PCV impact by age group, outcome and PCV valency

Outcome	PCV valency	<2y Range of decline in point estimate	<2y No. changed in post-PCV period	<2y No. did not change in post-PCV period	2-4y Range of decline in point estimate	2-4y No. changed in post-PCV period	2-4y No. did not change in post-PCV period	<5y Range of decline in point estimate	<5y No. changed in post-PCV period	<5y No. did not change in post-PCV period	5-9y Range of decline in point estimate	5-9y No. changed in post-PCV period	5-9y No. did not change in post-PCV period	<18y Range of decline in point estimate	<18y No. changed in post-PCV period	<18y No. did not change in post-PCV period
All-cause pneumonia	PCV10	13%-48%	13	2	7%-22%	4	0	8%-29%	4	2	12%-26%	3	0	-	0	0
	PCV13	8%-60%	10	0	5%-44%	5	1	9%-39%	6	0	33%-81%	3	1	43%-49%	2	0
Severe pneumonia	PCV10	49%	1	1	61%	1	0	40%-90%	2	0	10%-17%	2	0	-	0	0
	PCV13	2%-72%	5	1	30%-56%	3	1	8%-61%	4	0	58%	1	1	-	0	0
All-cause empyema	PCV10	-	0	1	-	0	2	-	0	1	-	0	0	-	0	0
	PCV13	33%-68%	4	0	42%-43%	2	0	-	0	1	48%-57%	2	1	-2%-56%	2	1
Radiologically confirmed pneumonia	PCV10	25%	3	4	12%-23%	2	2	40%-48%	0	2	-	0	1	-	0	0
	PCV13	23%-70%	6	0	22%-79%	4	0	45%-70%	4	0	41%	1	0	-	0	0
Pneumococcal Pneumonia	PCV10	77%	1	0	-	0	0	70%-85%	2	0	-	0	0	-	0	0
	PCV13	52%-86%	8	0	53%-77%	4	0	45%-67%	4	0	69%	1	0	-	0	0
Pneumonia Mortality	PCV10	3%-27%	6	3	28%-52%	2	2	24%-25%	2	6	-	0	1	-	0	0
	PCV13	2%-35%	7	0	1%-10%	4	0	2%-78%	6	1	-	0	1	-	0	0

PCV – pneumococcal vaccine, y – years

Table 3. PCV impact by age group, outcome and time since PCV introduction

Outcome	Years since PCV introduction	<2 Range of decline in point estimate	<2 No. changed in post-PCV period	<2 No. did not change in post-PCV period	2-4y Range of decline in point estimate	2-4y No. changed in post-PCV period	2-4y No. did not change in post-PCV period	<5y Range of decline in point estimate	<5y No. changed in post-PCV period	<5y No. did not change in post-PCV period	5-9y Range of decline in point estimate	5-9y No. changed in post-PCV period	5-9y No. did not change in post-PCV period	<18y Range of decline in point estimate	<18y No. changed in post-PCV period	<18y No. did not change in post-PCV period
All-cause pneumonia	3-5y	2%-45%	23	2	5%-47%	11	1	8%-35%	9	2	12%-81%	7	2	43%-49%	2	0
	>5y	20%-48%	3	0	-	0	0	39%	2	0	-	0	0	-	0	0
Severe pneumonia	3-5y	2%-72%	6	2	30%-61%	4	1	8%-90%	6	0	10%-58%	3	1	-	0	1
	>5y	-	0	0	-	0	0	-	0	0	-	0	0	-	0	0
All-cause empyema	3-5y	33-68	4	1	42%-43%	2	1	-	0	3	48%-57%	2	2	-	0	1
	>5y	-	0	0	-	0	0	-	0	0	-	0	0	-2%-65%	2	0
Radiologically confirmed pneumonia	3-5y	-	0	2	-	0	1	40%-45%	2	0	41%	1	0	-	0	0
	>5y	53%-57%	2	0	60%-79%	2	0	55%-70%	2	0	-	0	0	-	0	0
Pneumococcal pneumonia	3-5y	66%-81%	3	0	53%	1	0	54%-70%	4	0	69%	1	0	-	0	0
	>5y	52%-67%	2	0	77%	1	0	67%	1	0	-	0	0	-	0	0
Pneumonia mortality	3-5y	2%-40%	9	3	1%-52%	5	2	2%-25%	6	5	-	0	2	18%	1	0
	>5y	3%-27%	4	0	28%	1	0	11%-78%	2	2	-	0	0	-	0	0

PCV – pneumococcal vaccine, y – years

DISCUSSION

Our findings reinforce the current global evidence of the effectiveness of PCV10 and PCV13 against pneumonia and support their continued and extended use in all settings. We found a consistent decline in pneumonia hospitalisations incidence among both vaccine eligible and non-vaccine eligible children despite the considerable heterogeneity in the magnitude of the decline, which is broadly consistent with the findings of the PCV Review of Impact Evidence (PRIME), an extensive WHO review of the impact of PCVs undertaken in 2017 [8]. Our review, to some extent, is an update of PRIME and includes higher-valency PCVs and a longer observation period since vaccine introduction. Reduction in mortality due to pneumonia-specific causes was evident in some, but not all studies. However, there was a lack of PCV impact studies undertaken in settings with the highest under-five mortality.

All WHO regions were represented, apart from SEAR and low- or middle-income countries in WPR. However, a recently published study from Fiji found a 21%-46% reduction in hospitalised pneumonia among children 2-23 months and 2-4 years of age, depending on the case definition and age group [57]. Few countries in SEAR and WPR have introduced PCV. Of the 27 countries in WPR, only 67% (n = 18) have PCV in their NIP [58]. A study published after our search date from Bangladesh showed that PCV10 was 47% (95% CI = 11, 69) effective against radiographically confirmed pneumonia among children aged 3-11 months of age [59]. A phased introduction evaluation of PCV in Mongolia is ongoing, but preliminary findings have found a 24%-63% reduction in incidence pneumonia rates (as of December 2019), depending on which pneumonia outcome was used (ranging from all to very severe pneumonia) in children 2-59 months of age (Claire von Mollendorf, personal communication, 2021).

Our review has demonstrated the impact of PCV on reducing pneumonia incidence and mortality across all included age groups, particularly evident for three outcomes: all-cause hospitalization, radiologically confirmed, and pneumococcal pneumonia. There was a trend of rising impact as the pneumonia outcome increased in specificity, as exemplified by children <5 years of age showing the highest declines for bacteraemic pneumococcal pneumonia, then followed by radiologically confirmed pneumonia, the historical gold standard epidemiological outcome used in clinical trials [60-63]. Rates of hospitalised pneumonia are not a good indicator of trends in pneumonia incidence, as changes in admission criteria and referral patterns may lead to apparent increases or decreases in hospitalised pneumonia, even in the absence of any intervention.

We would expect the decline to be greatest in infants, as they experience the highest incidence of WHO-defined pneumonia and are the target group for vaccination, although the relative impact of PCV may be affected with increasing incidence of respiratory syncytial virus (RSV) [64]. This was demonstrated in a previous systematic review that found higher cumulative reductions in children <2 years compared to children aged 24-59 months of age for both clinical and radiologically confirmed pneumonia [65]. However, we did not detect a trend of decreasing impact with increasing age, most probably due to the heterogeneity in case definitions and settings across studies. Children <2 years of age are most affected by pneumococcal pneumonia; however, the vaccine covers only 10-13 pneumococcal serotypes that cause most invasive pneumococcal disease. It is unclear if the introduction of PCV has shifted the age distribution of pneumonia cases, and/or caused increases in replacement disease, so these should be assessed further.

Only three studies [13,27,35] included the older pediatric population (children ≥5 years), two assessed the impact on all-cause pneumonia hospitalisation [13,27] and the other on all-cause empyema hospitalisation [35], and all studies documented a decline in their respective outcomes following PCV introduction. All studies were from high-income settings. Further data on this age group from low- and middle-income settings is needed. The impact of serotype replacement on pneumonia outcomes is unknown. Serotype 3, generally considered a vaccine failure, is a common cause of pneumococcal empyema in the post-PCV era [66,67]. Reductions were found in the few studies from HICs assessing PCV impact on empyema hospitalisation incidence. However, as serotype replacement may become more apparent over time and may differ by the degree of pneumococcal transmission, the etiology of empyema and bacteraemic pneumonia should be monitored along with other invasive pneumococcal disease, especially pneumococcal meningitis.

It is important to recognize that 54% of the global burden of pneumonia mortality is concentrated in five countries (India, Nigeria, Pakistan, Democratic Republic of the Congo, and Ethiopia) [68], all of which introduced PCV at some point between 2011 and 2017, but none are included in any of the PCV impact studies we reviewed. Three studies from Burkina Faso [38], Botswana [19], and Spain [25] demonstrated a de-

cline in pneumonia mortality and an additional four studies demonstrated a modest decline in pneumonia mortality, but 95% confidence intervals crossed the null [15,29,42,56], possibly due to small case numbers. Mortality is a rare outcome in many countries where impact studies were conducted and all studies are hospital based and would therefore not capture deaths which occur outside of the hospital setting. A recent study from Fiji found mortality reduced by 39% for all-cause pneumonia/bronchiolitis/asthma admissions in children 2-23 months old [57]. In high mortality settings, there is a need for large-scale studies to demonstrate the evidence of vaccine impact on mortality [69].

We found that the impact on pneumonia was similar for PCV10 and PCV13. The only head-to-head clinical trial comparison of PCV10 and PCV13 found similarly highly immunogenicity for individual serotypes when used in 2 + 1 schedule, which is expected to translate into similar vaccine impact [70].

There is some suggestion that PCV impact on pneumonia was slightly higher in studies that collected post-PCV data for more than five years compared to 3-5 years. However, there were few studies in the former group, making it difficult to draw conclusions. A longer time from vaccine introduction would expectedly elicit greater population impact as PCV prevents carriage of vaccine serotype pneumococci with an expected greater impact on unvaccinated age groups over time. Additionally, other relevant factors such as variations in case definition and settings could not be accounted for in the cross tabulation used for the sub-group analysis.

To improve pneumococcal detection and serotyping capacity, countries, especially those with high mortality in children <5 years should be supported to join the Tier 1, 2, and 3 (invasive disease, including meningitis and pneumonia) of the WHO Invasive Bacterial Vaccine Preventable Diseases Surveillance global network to monitor trends in meningitis and severe pneumonia admissions, empyema and deaths, which includes serotyping of invasive samples. Sentinel sites should also include hospitals in high-risk areas. Similarly, PCV may have changed the age distribution of pneumococcal disease. There is a need to understand the age distribution of pneumococcal pneumonia cases following the introduction of PCV.
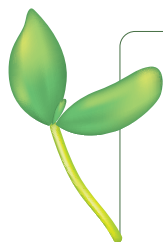
Limitations

The main limitation of this review is the heterogeneity in the pneumonia case definitions and analytical methods prohibiting a meta-analysis. Although studies agreed on the radiologically confirmed and culture positive pneumococcal pneumonia definitions, defining clinical features varied across studies according to the locally available clinical data. This heterogeneity would influence the sensitivity or specificity in detecting pneumococcal disease [71], preventing the comparison of results across studies [60]. The 2013 revision of the 2005 WHO definition of severe pneumonia regarding admission criteria affects the apparent incidence rates and therefore may affect the findings of PCV impact studies [25]. Most studies did not document whether the 2005 or 2013 WHO severe pneumonia case definition was used. We did not explore schedules or previous use of PCV7, which may have had some influences on results. An additional limitation is the confounders associated with observational studies, such as changes to health care access or delivery, case definition, baseline pneumonia trends, pneumococcal nasopharyngeal carriage rates, and serotype distribution across settings.

CONCLUSIONS

We identified important gaps in the existing literature, including the lack of PCV impact studies undertaken in setting with the highest under-five mortality and the lack of studies from the SEA region and LMICs in WPR. There is a need for large-scale studies in high mortality settings to demonstrate the evidence of vaccine impact on mortality.

There is clear evidence of declines in all-cause, severe, radiologically confirmed, bacteraemic pneumococcal pneumonia hospitalisations, as well as mortality across children of all age groups following PCV10 and PCV13 national introduction, although the magnitude was highly variable. These data support the ongoing use and introduction of PCV10 and PCV13 in countries that have not yet introduced PCV.

1 Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health. 2022;6:106-15 Medline:34800370 doi:10.1016/S2352-4642(21)00311-4

2 Walker CLRI, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, et al. Global burden of childhood pneumonia and diarrhoea. Lancet. 2013;381:1405-16. Medline:23582727 doi:10.1016/S0140-6736(13)60222-6

3 WHO. Pneumococcal conjugate 3rd dose (PCV3) immunization coverage. Available: https://www.who.int/gho/immunization/pneumococcal/en/. Accessed: 15 January 2023.

4 WHO. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Wkly Epidemiol Rec. 2019;8:85-104.

5 USCDC. Global Pneumococcal Disease and Vaccine. 2022. Available: https://www.cdc.gov/pneumococcal/global.html. Accessed: 15 January 2023.

6 Goodman D, Crocker ME, Pervaiz F, McCollum ED, Steenland K, Simkovich SM, et al. Challenges in the diagnosis of paediatric pneumonia in intervention field trials: recommendations from a pneumonia field trial working group. Lancet Respir Med. 2019;7:1068-83. Medline:31591066 doi:10.1016/S2213-2600(19)30249-8

7 Cohen O, Maria K, O'Brien K, Ramakrishnan M, Farrar JL, Pilishvili T, et al. Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME) Summary of Findings from Systematic Review October 2017. 2017. Available: https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2017/9_session_PCV/Oct2019_session9_PCV_PRIMEsummary.pdf. Accessed: 15 January 2023.

8 Cohen O, Maria K, O'Brien K, Ramakrishnan M, Farrar JL, Pilishvili T, et al. Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME). WHO, World Health Organization. 2017.

9 Tsaban G, Ben-Shimol S. Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: A systematic review of the literature. Vaccine. 2017;35:2882-91. Medline:28449971 doi:10.1016/j.vaccine.2017.04.032

10 Effective Public Health Practice Project. Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies. 1998. Available: https://www.nccmt.ca/knowledge-repositories/search/14. Accessed: 15 January 2023.

11 Alvarado S, Cavada G, Villena R, Wilhelm J, Budnik I, Lara C, et al. [Impact of the 10-valent pneumococcal conjugate vaccine on the southern area of Santiago (Chile), 2009-2015Efeito da vacina pneumococica 10-valente conjugada na regiao sul de Santiago, Chile, 2009-2015]. Rev Panam Salud Publica. 2018;42:e155. [Spanish]. Medline:31093183

12 Anderson G, Deceuninck G, Zhou Z, Boucher FD, Bonnier Viger Y, Gilca R, et al. Hospitalisation for lower respiratory tract infection in children in the province of Quebec, Canada, before and during the pneumococcal conjugate vaccine era. Epidemiol Infect. 2017;145:2770-6. Medline:28803551 doi:10.1017/S0950268817001510

13 Andrade AL, Afonso ET, Minamisava R, Bierrenbach AL, Cristo EB, Morais-Neto OL, et al. Direct and indirect impact of 10-valent pneumococcal conjugate vaccine introduction on pneumonia hospitalizations and economic burden in all age-groups in Brazil: A time-series analysis. PLoS One. 2017;12:e0184204. Medline:28880953 doi:10.1371/journal.pone.0184204

14 Andriatahirintsoa EJ, Raboba JL, Rahajamanana VL, Rakotozanany AL, Nimpa MM, Vuo Masembe Y, et al. Impact of 10-Valent Pneumococcal Conjugate Vaccine on Bacterial Meningitis in Madagascar. Clin Infect Dis. 2019;69:S121-5. Medline:31505632 doi:10.1093/cid/ciz504

15 Becker-Dreps S, Blette B, Briceno R, Aleman J, Hudgens MG, Moreno G, et al. Changes in the incidence of pneumonia, bacterial meningitis, and infant mortality 5 years following introduction of the 13-valent pneumococcal conjugate vaccine in a "3+0" schedule. PLoS One. 2017;12:e0183348. Medline:28813518 doi:10.1371/journal.pone.0183348

16 Ben-Shimol S, Givon-Lavi N, Greenberg D, Dagan R. Cocontribution of Rotavirus and Pneumococcal Conjugate Vaccines to the Reduction of Pediatric Hospital Visits in Young Children. J Pediatr. 2017;182:253-259e2. Medline:27939127 doi:10.1016/j.jpeds.2016.11.041

17 Berger Y, Adler A, Ariel T, Rokney A, Averbuch D, Grisaru-Soen G. Paediatric community-acquired bacteraemia, pneumococcal invasive disease and antibiotic resistance fell after the pneumococcal conjugate vaccine was introduced. Acta Paediatr. 2019;108:1321-8. Medline:30506762 doi:10.1111/apa.14670

18 Camargos P, Nascimento-Carvalho CM, Teixeira R, Franca E. Lower respiratory infections mortality among Brazilians under-five before and after national pneumococcal conjugate vaccine implementation. Vaccine. 2020;38:2559-65. Medline:32033849 doi:10.1016/j.vaccine.2020.01.084

19 Congdon M, Hong H, Young RR, Cunningham CK, Enane LA, Arscott-Mills T, et al. Effect of Haemophilus influenzae type b and 13-valent pneumococcal conjugate vaccines on childhood pneumonia hospitalizations and deaths in Botswana. Clin Infect Dis. 2021;73:e410-e416. Medline:32634831 doi:10.1093/cid/ciaa919

20 Silva SR, Mello LM, Silva AS, Nunes AA. Impact of the pneumococcal 10-valent vaccine on reducing hospitalization for community-acquired pneumonia in children. Rev Paul Pediatr. 2016;34:418-24. Medline:27108092 doi:10.1016/j.rppede.2016.03.008

21 de Oliveira LH, Shioda K, Valenzuela MT, Janusz CB, Rearte A, Sbarra AN, et al. Declines in pneumonia mortality following the introduction of pneumococcal conjugate vaccines in Latin American and Caribbean countries. Clin Infect Dis. 2021;73:306-313 Medline:32448889 doi:10.1093/cid/ciaa614

22 Dondo V, Mujuru H, Nathoo K, Jacha V, Tapfumanei O, Chirisa P, et al. Pneumococcal Conjugate Vaccine Impact on Meningitis and Pneumonia Among Children Aged <5 Years-Zimbabwe, 2010-2016. Clin Infect Dis. 2019;69:S72-80. Medline:31505631 doi:10.1093/cid/ciz462

23 Faye PM, Sonko MA, Diop A, Thiongane A, Ba ID, Spiller M, et al. Impact of 13-Valent Pneumococcal Conjugate Vaccine on Meningitis and Pneumonia Hospitalizations in Children aged <5 Years in Senegal, 2010-2016. Clin Infect Dis. 2019;69:S66-71. Medline:31505625 doi:10.1093/cid/ciz457

24 Izu A, Solomon F, Nzenze SA, Mudau A, Zell E, O'Brien KL, et al. Pneumococcal conjugate vaccines and hospitalization of children for pneumonia: a time-series analysis, South Africa, 2006-2014. Bull World Health Organ. 2017;95:618-28. Medline:28867842 doi:10.2471/BLT.16.187849

25 Jimenez Trujillo I, Lopez de Andres A, Hernandez-Barrera V, Martinez-Huedo MA, de Miguel-Diez J, Jimenez-Garcia R. Decrease in the incidence and in hospital mortality of community-acquired pneumonia among children in Spain (2001-2014). Vaccine. 2017;35:3733-40. Medline:28558982 doi:10.1016/j.vaccine.2017.05.055

26 Kupek E, Vieira IL. [Impact of PCV10 pneumococcal vaccine on mortality from pneumonia in children less than one year of age in Santa Catarina State, Brazil]. Cad Saude Publica. 2016;32:e00131414. [Portugese]. Medline:27049314

27 Luca DL, Kwong JC, Chu A, Sander B, O'Reilly R, McGeer AJ, et al. Impact of Pneumococcal Vaccination on Pneumonia Hospitalizations and Related Costs in Ontario: A Population-Based Ecological Study. Clin Infect Dis. 2018;66:541-7. Medline:29029063 doi:10.1093/cid/cix850

28 Mpabalwani EM, Lukwesa-Musyani C, Imamba A, Nakazwe R, Matapo B, Muzongwe CM, et al. Declines in Pneumonia and Meningitis Hospitalizations in Children Under 5 Years of Age After Introduction of 10-Valent Pneumococcal Conjugate Vaccine in Zambia, 2010-2016. Clin Infect Dis. 2019;69:S58-65. Medline:31505628 doi:10.1093/cid/ciz456

29 Naucler P, Henriques-Normark B, Hedlund J, Galanis I, Granath F, Ortqvist A. The changing epidemiology of community-acquired pneumonia: nationwide register-based study in Sweden. J Intern Med. 2019;286:689-701. Medline:31278792 doi:10.1111/joim.12956

30 Palmu AA, Rinta-Kokko H, Nohynek H, Nuorti JP, Kilpi TM, Jokinen J. Impact of ten-valent pneumococcal conjugate vaccine on pneumonia in Finnish children in a nation-wide population-based study. PLoS One. 2017;12:e0172690. Medline:28249015 doi:10.1371/journal.pone.0172690

31 Petousis-Harris H, Howe AS, Paynter J, Turner N, Griffin J. Pneumococcal Conjugate Vaccines Turning the Tide on Inequity: A Retrospective Cohort Study of New Zealand Children Born 2006-2015. Clin Infect Dis. 2019;68:818-26. Medline:30032236 doi:10.1093/cid/ciy570

32 Saxena S, Atchison C, Cecil E, Sharland M, Koshy E, Bottle A. Additive impact of pneumococcal conjugate vaccines on pneumonia and empyema hospital admissions in England. J Infect. 2015;71:428-36. Medline:26159503 doi:10.1016/j.jinf.2015.06.011

33 Sgambatti S, Minamisava R, Bierrenbach AL, Toscano CM, Vieira MA, Policena G, et al. Early impact of 10-valent pneumococcal conjugate vaccine in childhood pneumonia hospitalizations using primary data from an active population-based surveillance. Vaccine. 2016;34:663-70. Medline:26706272 doi:10.1016/j.vaccine.2015.12.007

34 Sigurdsson S, Eythorsson E, Erlendsdottir H, Hrafnkelsson B, Kristinsson KG, Haraldsson A. Impact of the 10-valent pneumococcal conjugate vaccine on hospital admissions in children under three years of age in Iceland. Vaccine. 2020;38:2707-14. Medline:32063434 doi:10.1016/j.vaccine.2020.01.094

35 Thorrington D, Andrews N, Stowe J, Miller E, van Hoek AJ. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. BMC Med. 2018;16:13. Medline:29415741 doi:10.1186/s12916-018-1004-z

36 van Deursen AMM, Schurink-Van't Klooster TM, Man WH, van de Kassteele J, van Gageldonk-Lafeber AB, Bruijning-Verhagen P, et al. Impact of infant pneumococcal conjugate vaccination on community acquired pneumonia hospitalization in all ages in the Netherlands. Vaccine. 2017;35:7107-13. Medline:29146381 doi:10.1016/j.vaccine.2017.10.090

37 Wiese AD, Grijalva CG, Zhu Y, Mitchel EF Jr, Griffin MR. Changes in Childhood Pneumonia Hospitalizations by Race and Sex Associated with Pneumococcal Conjugate Vaccines. Emerg Infect Dis. 2016;22:1109. Medline:27197048 doi:10.3201/eid2206.152023

38 Kaboré L, Ouattara S, Sawadogo F, Gervaix A, Galetto-Lacour A, Karama R, et al. Impact of 13-valent pneumococcal conjugate vaccine on the incidence of hospitalizations for all-cause pneumonia among children aged less than 5 years in Burkina Faso: An interrupted time-series analysis. Int J Infect Dis. 2020;96:31-8. Medline:32234344 doi:10.1016/j.ijid.2020.03.051

39 Haji T, Byrne A, Kovesi T. Trends in Pediatric Complicated Pneumonia in an Ontario Local Health Integration Network. Children (Basel). 2018;5:36. Medline:29510484 doi:10.3390/children5030036

40 Mackenzie GA, Hill PC, Sahito SM, Jeffries DJ, Hossain I, Bottomley C, et al. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies. Lancet Infect Dis. 2017;17:965-73. Medline:28601421 doi:10.1016/S1473-3099(17)30321-3

41 Silaba M, Ooko M, Bottomley C, Sande J, Benamore R, Park K, et al. Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. Lancet Glob Health. 2019;7:e337-46. Medline:30784634 doi:10.1016/S2214-109X(18)30491-1

42 Vestjens SMT, Sanders EAM, Vlaminckx BJ, de Melker HE, van der Ende A, Knol MJ. Twelve years of pneumococcal conjugate vaccination in the Netherlands: Impact on incidence and clinical outcomes of invasive pneumococcal disease. Vaccine. 2019;37:6558-65. Medline:31500963 doi:10.1016/j.vaccine.2019.08.025

43 Silaba M, Ooko M, Bottomley C, Sande J, Benamore R, Park K, et al. Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. Lancet Glob Health. 2019;7:e337-46. Medline:30784634 doi:10.1016/S2214-109X(18)30491-1

44 Mackenzie GA, Hill PC, Sahito SM, Jeffries DJ, Hossain I, Bottomley C, et al. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies. Lancet Infect Dis. 2017;17:965-73. Medline:28601421 doi:10.1016/S1473-3099(17)30321-3

45 Chacon-Cruz E, Rivas-Landeros RM, Volker-Soberanes ML, Lopatynsky-Reyes EZ, Becka C, Alvelais-Palacios JA. 12 years active surveillance for pediatric pleural empyema in a Mexican hospital: effectiveness of pneumococcal 13-valent conjugate vaccine, and early emergence of methicillin-resistant Staphylococcus aureus. Ther Adv Infect Dis. 2019;6:2049936119839312. Medline:30984396 doi:10.1177/2049936119839312

46 Wiese AD, Griffin MR, Zhu Y, Mitchel EF Jr, Grijalva CG. Changes in empyema among U.S. children in the pneumococcal conjugate vaccine era. Vaccine. 2016;34:6243-9. Medline:27832918 doi:10.1016/j.vaccine.2016.10.062

47 Zampoli M, Kappos A, Wolter N, Von Gottberg A, Verwey C, Mamathuba R, et al. Etiology and incidence of pleural Empyema in South African children. Pediatr Infect Dis J. 2015;34:1305-10. Medline:26267310 doi:10.1097/INF.0000000000000880

48 Laaksonen N, Rintamäki L, Korppi M. Pneumococcal vaccinations effectively prevent blood culture-negative infections that resemble occult pneumococcal bacteraemia or bacteraemic pneumococcal pneumonia at one to 36 months of age. Acta Paediatr. 2016;105:1487-92. Medline:27607346 doi:10.1111/apa.13580

49 Ruvinsky RO, Rearte A, Kupervaser J, Gentile F, Haidar A, Cafure ME, et al. Community acquired pneumonia incidence among children less than 5 years of age in Concordia, Argentina: vaccination impact. Rev Panam Salud Publica. 2018;42:e167. Medline:31093195 doi:10.26633/RPSP.2018.167

50 Takeuchi N, Naito S, Ohkusu M, Abe K, Shizuno K, Takahashi Y, et al. Epidemiology of hospitalised paediatric community-acquired pneumonia and bacterial pneumonia following the introduction of 13-valent pneumococcal conjugate vaccine in the national immunisation programme in Japan. Epidemiol Infect. 2020;148:e91. Medline:32299523 doi:10.1017/S0950268820000813

51 Triadou D, Givon-Lavi N, Greenberg D, Ben-Shimol S. Pneumococcal conjugate vaccines decrease community-acquired alveolar pneumonia with and without pleural effusion in children <60 months in Southern Israel, 2002-2016. Infect Dis (Lond). 2020;52:186-95. Medline:31774020 doi:10.1080/23744235.2019.1695060

52 Cherian T, Mulholland EK, Carlin JB, Ostensen H, Amin R, de Campo M, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ. 2005;83:353-9. Medline:15976876

53 Ben-Shimol S, Givon-Lavi N, Grisaru-Soen G, Megged O, Greenberg D, Dagan R, et al. Comparative incidence dynamics and serotypes of meningitis, bacteremic pneumonia and other-IPD in young children in the PCV era: Insights from Israeli surveillance studies. Vaccine. 2018;36:5477-84. Medline:28579230 doi:10.1016/j.vaccine.2017.05.059

54 Hammitt LL, Etyang AO, Morpeth SC, Ojal J, Mutuku A, Mturi N, et al. Effect of ten-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and nasopharyngeal carriage in Kenya: a longitudinal surveillance study. Lancet. 2019;393:2146-54. Medline:31000194 doi:10.1016/S0140-6736(18)33005-8

55 Meder KN, Jayasinghe S, Beard F, Dey A, Kirk M, Cook H, et al. Long-term Impact of Pneumococcal Conjugate Vaccines on Invasive Disease and Pneumonia Hospitalizations in Indigenous and Non-Indigenous Australians. Clin Infect Dis. 2020;70:2607-15. Medline:31388670 doi:10.1093/cid/ciz731

56 Schuck-Paim C, Taylor RJ, Alonso WJ, Weinberger DM, Simonsen L. Effect of pneumococcal conjugate vaccine introduction on childhood pneumonia mortality in Brazil: a retrospective observational study. Lancet Glob Health. 2019;7:e249-56. Medline:30683242 doi:10.1016/S2214-109X(18)30455-8

57 Reyburn R, Tuivaga E, Nguyen CD, Ratu FT, Nand D, Kado J, et al. Effect of ten-valent pneumococcal conjugate vaccine introduction on pneumonia hospital admissions in Fiji: a time-series analysis. Lancet Glob Health. 2021;9:e91-8. Medline:33227258 doi:10.1016/S2214-109X(20)30421-6

58 John Hopkins International Vaccine Access Center. Bloomburg School of Public Health View - Hub. Available: https://view-hub.org/map/?set=current-vaccine-intro-status&group=vaccine-introduction&category=pcv&who-region=western-pacific. Accessed: 15 January 2023.

59 McCollum ED, Ahmed S, Roy AD, Chowdhury NH, Schuh HB, Rizvi SJR, et al. Effectiveness of the 10-valent pneumococcal conjugate vaccine against radiographic pneumonia among children in rural Bangladesh: A case-control study. Vaccine. 2020;38:6508-16. Medline:32873404 doi:10.1016/j.vaccine.2020.08.035

60 Lynch T, Bialy L, Kellner JD, Osmond MH, Klassen TP, Durec T, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One. 2010;5:e11989. Medline:20700510 doi:10.1371/journal.pone.0011989

61 Goodman D, Crocker ME, Pervaiz F, McCollum ED, Steenland K, Simkovich SM, et al. Challenges in the diagnosis of paediatric pneumonia in intervention field trials: recommendations from a pneumonia field trial working group. Lancet Respir Med. 2019;7:1068-1083. Medline:31591066 doi:10.1016/S2213-2600(19)30249-8

62 Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139-46. Medline:15794968 doi:10.1016/S0140-6736(05)71876-6

63 Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349:1341-8. Medline:14523142 doi:10.1056/NEJMoa035060

64 Russell F, Sanderson C, Temple B, Henao-Restrepo AM, Mulholland K. Global review of the distribution of pneumococcal disease by age and region. Centre for International Child Health, Dept. of Paediatrics, University of Melbourne, Australia, London School of Hygiene and Tropical Medicine, London, UK, Menzies School of Health Research, Darwin, Australia, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia. 2011. Available: https://blogs.lshtm.ac.uk/vaccineschedules/files/6.-Russel-review-age-specific-epidemiology-PCV-schedules-session-nov11.pdf. Accessed: 15 January 2023.

65 Alicino C, Paganino C, Orsi A, Astengo M, Trucchi C, Icardi G, et al. The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on hospitalization for pneumonia in children: A systematic review and meta-analysis. Vaccine. 2017;35:5776-85. Medline:28911902 doi:10.1016/j.vaccine.2017.09.005

66 Goettler D, Streng A, Kemmling D, Schoen C, von Kries R, Rose MA, et al. Increase in Streptococcus pneumoniae serotype 3 associated parapneumonic pleural effusion/empyema after the introduction of PCV13 in Germany. Vaccine. 2020;38:570-7. Medline:31735502 doi:10.1016/j.vaccine.2019.10.056

67 Strachan R, Homahaira N, Beggs S , Bhuiyan M, Gilbert G, Lambert S, et al. Assessing the impact of the 13 valent pneumococcal vaccine on childhood empyema in Australia. 2021; 76:487-493

68 McAllister DA, Liu L, Shi T, Chu Y, Reed C, Burrows J, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. Lancet Glob Health. 2019;7:e47-57. Medline:30497986 doi:10.1016/S2214-109X(18)30408-X

69 King C, Beard J, Crampin AC, Costello A, Mwansambo C, Cunliffe NA, et al. Methodological challenges in measuring vaccine effectiveness using population cohorts in low resource settings. Vaccine. 2015;33:4748-55. Medline:26235370 doi:10.1016/j.vaccine.2015.07.062

70 Temple B, Toan NT, Dai VTT, Bright K, Licciardi PV, Marimla RA, et al. Immunogenicity and reactogenicity of ten-valent versus 13-valent pneumococcal conjugate vaccines among infants in Ho Chi Minh City, Vietnam: a randomised controlled trial. Lancet Infect Dis. 2019;19:497-509. Medline:30975525 doi:10.1016/S1473-3099(18)30734-5

71 Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health. 2013;3:010401. Medline:23826505