Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on hospitalization for pneumonia in children: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 31 January 2017
Received in revised form 28 August 2017
Accepted 1 September 2017
Available online xxxx

Keywords:
Pneumonia
CAP
Streptococcus pneumoniae
Hospitalization
Prevention
Vaccines
PCV10
PCV13
Meta-analysis

ABSTRACT

Background: This systematic review and meta-analysis aimed at summarizing available data on the impact of PCV10 and PCV13 in reducing the incidence of CAP hospitalizations in children aged <5 years.
Methods: A systematic search of the literature was conducted. We included time-series analyses and before-after studies, reporting the incidence of hospitalization for pneumonia in the periods before and after the introduction of PCV10 or PCV13 into the immunization program. Pooled estimates of Incidence Rate Ratio (IRR) were calculated by using a random-effects meta-analytic model. Results were stratified according to age-groups (<24 months and 24–59 months) and case definitions of pneumonia (clinically and radiologically confirmed pneumonia).
Results: A total of 1533 potentially relevant articles were identified. Of these, 12 articles were included in the analysis. In children aged <24 months, the meta-analysis showed a reduction of 17% (95%CI: 11–22%, p-value < 0.001) an of 31% (95%CI: 26–35%, p-value < 0.001) in the hospitalization rates respectively for clinically and radiologically confirmed pneumonia, respectively, after the introduction of the novel PCVs.
Results: In children aged 24–59 months, the meta-analysis showed a reduction of 9% (95%CI: 5–14%, p-value < 0.001) and of 24% (95%CI: 12–33%, p-value < 0.001) in the hospitalization rates for clinically and radiologically confirmed pneumonia, respectively, after the introduction of the novel PCVs.
Results: High heterogeneity was detected among studies evaluating the hospitalization rate for clinically and radiologically confirmed pneumonia.
Conclusions: The results of this study revealed a significant impact of PCV10 and PCV13 in reducing the hospitalizations for pneumonia, particularly in children aged <24 months and for radiologically confirmed disease. Further appropriately designed studies, comparing the impact of PCV10 and PCV13, are needed in order to obtain solid data on which to establish future immunization strategies.

Contents

Abbreviations: CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease; IRR, incidence rate ratio; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; Sp, *Streptococcus pneumoniae*; VE, vaccine effectiveness; WHO, World Health Organization; 95%CI, 95% confidence interval.

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http://dx.doi.org/10.1016/j.vaccine.2017.09.005
0264-410X/

1. Introduction

Community-acquired pneumonia (CAP) represents a significant public health problem worldwide and a leading cause of death, especially in children. In 2010, 120 million episodes of pneumonia were globally estimated in children aged <5 years; the incidence in this age group is calculated in 0.29 episodes per child-year in developing and 0.05 episodes per child-year in developed countries [1–3]. Moreover, nearly 14 million of pneumonia cases progressed to severe episodes, and 1.3 million led to death [2,3]. The highest proportion of deaths (81%) was recorded mainly in children under 2 years of age living in low and middle-income countries [3].

Streptococcus pneumoniae (Sp) is the most frequent etiologic agent of bacterial CAP cases (2.2–50.9%) among children aged under five years and can cause serious complications requiring recourse to appropriate medical care and hospitalization [4].

Childhood vaccination against Sp was first recommended by the World Health Organization (WHO) in 2007 and is now the main means of preventing pneumococcal disease, together with other pneumonia control measures, such as appropriate case management, promotion of exclusive breastfeeding for the first 6 months of life and the reduction of known risk factors [5].

By the end of 2015, pneumococcal vaccines had been introduced into the standard infant immunization schedule in 129 countries, and the global coverage was estimated at 37% [6]. Pneumococcal conjugate vaccines (PCVs) have been proved to be a highly efficacious means of protecting children younger than 2 years of age against severe forms of pneumococcal disease, such as pneumonia, meningitis and bacteremia [7]. The first pneumococcal conjugate vaccine was a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7), licensed by the Food and Drug Administration for use in children in 2000 [8].

Since 2010, two novel PCV formulations protecting against 10 (PCV10) and 13 (PCV13) Sp serotypes have become available for use in children, offering better coverage for Sp serotypes that commonly cause disease in low- and middle-income countries [9,10]. Several studies have demonstrated the efficacy of PCV7 in reducing CAP hospitalizations in children, mostly in developed countries [11–16]. Since the introduction of PCV10 and PCV13 into national immunization programs, a number of studies have evaluated the impact of these formulations in terms of reduction of the burden of CAP.

This systematic review and meta-analysis aimed primarily at summarizing available data on the impact of PCV10 and PCV13 in reducing the incidence of CAP hospitalizations in children aged <5 years. The secondary objective was to study whether PCV10 and PCV13 displayed a different impact on CAP hospitalizations in the same age group.

2. Methods

We conducted a systematic review of the literature and meta-analysis based on data from impact studies that evaluated, in terms of rate ratio, the incidence reduction of hospitalization for clinical CAP and for radiologically confirmed pneumonia in children younger than 5 years of age in the period before and after the introduction of PCV10 or PCV13.

2.1. Data sources and searches

A literature search using the three different online medical databases (PubMed, SciELO and Lilacs) was conducted in order to identify relevant articles published up to December 15th 2016.

The syntax and keyword combinations used to develop the search string are presented in Table S1.

References from the selected studies were manually examined to identify any other potentially suitable publications.

2.2. Inclusion and exclusion criteria

We included all studies published after the year 2000, when the first conjugate pneumococcal vaccine was licensed. The reports were in English, Spanish and Portuguese, but no restrictions were placed on language.

Care was taken to ensure that the studies selected did not result in duplication of data. In the case of multiple reporting of the same data, we planned to group the results and reported them as extracted from a single study. Review articles, posters, oral presentations at conferences, abstracts and editorials were excluded.

In the systematic review and in the meta-analysis, we included quasi-experimental studies, namely time-series, interrupted time-series and before-after studies in which the incidence of hospitalization for pneumonia was calculated and the periods before and after the introduction of PCV10 or PCV13 into the immunization program were compared, regardless of the length of the periods of observation before and after the introduction of the novel PCVs. We included both studies conducted in settings in which the introduction of PCV10 or PCV13 was not preceded by the use of PCV7 and studies carried out in settings in which PCV7 was introduced into the immunization program and then replaced by PCV10 or PCV13.

Please cite this article in press as: Alicino C 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), http://dx.doi.org/10.1016/j.vaccine.2017.09.005

We excluded studies conducted among populations with chronic diseases, studies reporting only data on bacteremic pneumonia, studies performed in children younger than 5 years but which did not report results stratified according the age-groups considered for the analysis, studies performed in subjects older than 5 years of age and studies in which the duration of each period (before and after the introduction of vaccination) was unspecified.

2.3. Data extraction

The articles were assessed by two review authors, who read the titles of all reports identified by the electronic search, the abstracts of selected articles and all full texts of the articles that meet the above-mentioned inclusion criteria. The disagreements regarding inclusion were resolved by consensus.

All the studies included were interrogated for the following endpoints: children younger than 5 years, kind of conjugate vaccine used (PCV10 or PCV13), kind of comparator (PCV7 or no pneumococcal vaccine) and period before and after vaccine introduction.

The following data were recorded: the name of the first author, year of publication, country and setting of the study, kind of pneumococcal vaccine used, kind of comparator, study design, duration of the observation period before and after vaccine introduction, time between PCV10 or PCV13 introduction and when the analysis was conducted, year and month of vaccine introduction, case definition, source of data, pneumonia hospitalization rate before introduction of the novel PCVs, age-groups, vaccine coverage rate, immunization schedules and incidence rate ratios (IRR) with their 95% confidence intervals (95%CI).

2.4. Assessment of study quality

The quality of all included studies was independently evaluated by two reviewers by means of a checklist for before-after studies [17], and a modified version of Ramsey et al. criteria for time-series studies [18]. Disagreements between reviewers were resolved through discussion with a third reviewer, who served as an arbiter. The assessment of study quality is reported in Table S2.

2.5. Clinical outcomes

As different case definitions of pneumonia were used in the studies included in this systematic review and meta-analysis, the results were grouped into two categories:

- clinical pneumonia defined as the presence of clinical signs or symptoms of pneumonia in the absence of radiological examination or defined according to ICD9 or ICD10 codes when using secondary data sources;
- radiologically confirmed pneumonia, defined according or not to the WHO definition.

2.6. Impact measures

From all studies, we extracted the incidence rates per 100,000 children in the periods before and after PVC10 or PCV13 introduction in the following age-groups: <12 months, 12–23 months, 0–23 months, 2–23 months, 24–35 months, 24–48 months, 24–59 months.

For all age-groups, the impact measures extracted from all studies were the IRRs and their 95%CI, when comparing the period before and after PCV10 or PCV13 introduction. Whenever PCV10 or PCV13 introduction was preceded by PCV7 use, we only considered the PCV7 period as a comparator, without taking into consideration the no-vaccine period, as the use of PCV7 might have already reduced the burden of CAP, thus affecting the overall impact of the novel PCVs.

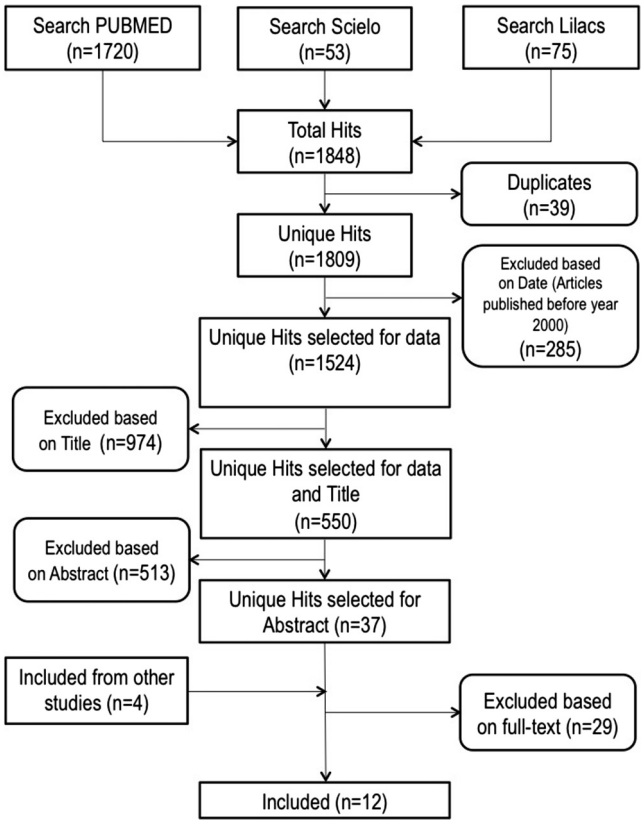

Fig. 1. Flowchart of the articles and abstracts evaluated for inclusion in the meta-analysis.

2.7. Data analysis

With respect to the primary objective, we stratified the results according to case definitions of pneumonia (clinical pneumonia and radiologically confirmed pneumonia) and according to the following age-groups: children aged <24 months (including also studies reporting data for children aged 0–12 months) and children aged 24–59 months (including also studies reporting data for children aged 24–36 months or 24–48 months). Pooled estimates of IRR were calculated by using a random-effects model based on the Generic Inverse Variance method. Between-study heterogeneity was quantified by means of the I^2 statistic.

In order to assess the secondary objective, we also performed a subgroup analysis according to the kind of conjugate vaccine (PCV10 or PCV13) introduced. Moreover, a subgroup analysis was conducted according to the kind of comparator (PCV7 or no pneumococcal vaccine) used in the studies.

The meta-analysis was performed by means of Review Manager (RevMan) version 5.3.5, provided by the Cochrane Collaboration.

3. Results

A total of 1533 potentially relevant articles were identified through the literature search, after the exclusion of duplicates and articles published before 2000 (Fig. 1).

After checking titles and abstracts and including hits identified through references from the selected studies, 41 articles were

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Table 1
Characteristics of the studies included in the meta-analysis.

First Author, year	Country	Setting	Vaccine	Control	Study design	Period of analysis pre-PCV10/13	Period of analysis post-PCV10/13	Transition period	Month (when available) and year of PCV10/13 introduction	Data source	Vaccine coverage (completed schedule)	Vaccine schedule	Case definition	Pneumonia hospitalization rate before PCV10/13 introduction (rates/100,000)	Adjusting factors	Age-groups	IRR	95%CI
Afonso E.T., 2013 [48]	Brazil, Belo Horizonte	Municipality hospitals	PCV 10	No vaccine	Interrupted time-series	January 2005 – February 2010	July 2010-August 2011	4 months	March 2010, except Porto Alegre, where PCV10 were introduced in June 2010	Secondary data from the Hospitalization Information System of the National Unified Health System	80%	3 + 1	Clinical pneumonia (ICD-10; J12-J18)	164.3	Non-respiratory disease hospitalization rate	2–24 months	0.71	0.60–0.85
	Brazil, Curitiba													79.0			0.77	0.64–0.91
	Brazil, Recife													130.4			0.73	0.58–0.91
	Brazil, Sao Paolo													124.7			0.98	0.87–1.11
	Brazil, Porto Alegre													29.1			0.98	0.79–1.21
da Silva S.R., 2016 [49]	Brazil	Superintendência Regional de Saúde de Alfenas	PCV10	No vaccine	Before-after	2007–2009	2011–2013	12 months	March 2010	Tabwin database	Nearly 100%	3 + 1	Clinical pneumonia	Not available	No adjusting factors	<12 months	0.81	0.74–0.89
Laaksonen N., 2016 [50]	Finland	Tampere University Hospital, Tampere	PCV 10	No vaccine	Before-after	2008–2009	2012–2013	15 months	September 2010	Hospital records	95%	2 + 1	X-ray confirmed pneumonia. Not following the WHO definition.	37	No adjusting factors	1–11 months	0.34	0.15–0.75
														199		12–23 months	1.15	0.51–2.55
														Not available		0–23 months	1.45	0.41–5.20
														97		24–35 months	0.51	0.27–0.97
Sgambatti S., 2016 [51]	Goiânia, Brazil	All pediatric hospitals of Goiânia municipality	PCV 10	No vaccine	Before-after	May 2007-April 2009	November 2011-October 2013	17 months	June 2010	Daily active search of pneumonia cases	93.3% in 2011; 91.3% in 2012; and 92.0%, in 2013	3 + 1	Clinical pneumonia	6788	Secular trends of pneumonia monthly rates in the pre-vaccination period were analyzed. Monthly hospital capacity from 2007 thought 2013 was assessed	2–11 months	0.87	0.87–0.88
														4760		12–23 months	0.86	0.85–0.86
														5728		2–23 months	0.87	0.87–0.87
														2408		24–35 months	0.93	0.92–0.93
													X-ray confirmed pneumonia According to the WHO definition	2871		2–11 months	0.75	0.74–0.75
														2151		12–23 months	0.75	0.74–0.76
														2497		2–23 months	0.75	0.74–0.75
														1009		24–35 months	0.88	0.87–0.89
Becker-Dreps S., 2013 [52]	Nicaragua	107 public health facilities in the Department of León	PCV13	No vaccine	Interrupted time series	January 2008-December 2010	January 2011-December 2012	0 month	12 December 2010	Department database	63%, in 2011 and 97% in 2012	3 + 0	X-ray confirmed pneumonia Not following the WHO definition	6440/100,000 24907100,000	Used control outcome: diarrhea. Analyzed outpatients setting (ambulatory visits)	<12 months	0.67	0.59–0.75
																12–23 months	0.74	0.67–0.81
														Not available		0–24 months	0.71	0.64–0.78
														Not available		24–59 months	0.73	0.66–0.81
Gaiano A., 2013 [53]	Argentina	Nationwide	PCV13	No vaccine	Before-after	2011	2013	12 months	1st January 2012	Sistema Nacional de Vigilancia de la Salud (SNVS)	Unknown	2 + 1	Clinical pneumonia	2880	No adjusting factors	<12 months	0.73	0.71–0.74
														3270		12–24 months	0.70	0.68–0.71
														Not available		0–24 months	0.71	0.70–0.72
Gentile A., 2014 [54]	Argentina	Reference hospitals in Pilar, Buenos Aires	PCV13	No vaccine	Before-after	2003–2005	2012–2013	0 month	January 2012	Hospital population based surveillance	48.3% in 2012, 61.3% in 2013	2 + 1 2 catch up doses for children 12–24 months	X-ray confirmed pneumonia (inpatients and outpatients) According to	1922	Analyzed outpatients setting (ambulatory visits)	0–11 months	0.61	0.47–0.78
														931		12–23 months	0.62	0.43–0.89
														1437		0–23 months	0.61	0.49–0.75
														321		24–	0.80	0.57–1.11

Table 1 (*continued*)

First Author, year	Country	Setting	Vaccine	Control	Study design	Period of analysis pre-PCV10/13	Period of analysis post-PCV10/13	Transition period	Month (when available) and year of PCV10/13 introduction	Data source	Vaccine coverage (completed schedule)	Vaccine schedule	Case definition	Pneumonia hospitalization rate before PCV10/13 introduction (rates/100,000)	Adjusting factors	Age-groups	IRR	95%CI
													the WHO definition			59 months		
Berglund A., 2014 [55]	Sweden	Nationwide	PCV10 PCV13	PCV7 PCV7	Time-series	2007–2010	2010–2012 The choice of PCV use was different between County Councils	0 month	In 2010 both PCV10 and PCV13 were licensed	National Inpatient Registry administrated by the National Board of Health and Welfare	PCV coverage for children in Sweden born in 2010 was 97.6%	2 + 1	Clinical pneumonia (ICD-10; J12-J18)	615	The total number of hospital admissions for any cause of disease was identified	<24 months	1.03 0.82	0.82–1.3 0.66–1.01
Simonsen L., 2014 [56]	U.S.	Convenience sample of roughly 500 non-federal short-stay US hospitals	PCV13	PCV7	Interrupted time-series	2007–2009	2011–2012	2 years	In March 2010 PCV13 replaced PCV7	IMS Charge Data Master Hospital Database	0.54	3 + 1	Clinical pneumonia (ICD9 480–486) Pneumococcal pneumonia ICD 9 (4 8 1)	799 414.6 Not available Not available	Used control outcomes: urinary tract infection and total number of admissions to hospital. Secular trends in pneumonia hospitalizations before PCV13, influenza pathogenicity and PCV13 coverage were accounting in the model.	0–23 months 24–48 months 0–23 months 24–48 months	0.83 0.88 0.68 0.72	0.82–0.84 0.87–0.89 0.61–0.75 0.65–0.79
Greenberg D., 2015 [57]	Israel	Soroka University Medical Center (SUMC)	PCV13	PCV7	Time-series	PCV7 was introduced in July 2009. July 2010-June 2011 PCV7 era	July 2012-June 2013	21 months	In November 2010 PCV13 replaced PCV7	Ongoing prospective population-based study	PCV13 coverage (≥ 2 doses) was 86% in 2012 and 89% in 2013	2 + 1	X-ray confirmed pneumonia. According to the WHO definition	1870 990 Not available 390	Analyzed outpatients setting (emergency room visits without hospitalization)	<12 months 12–23 months 0–23 months 24–59 months	0.62 0.70 0.65 0.64	0.52–0.74 0.55–0.9 0.57–0.74 0.51–0.79
Saxena S., 2015 [58]	England	Nationwide	PCV13	PCV7	Interrupted time-series	PCV 7 was introduced from September 2006. September 2006-March 2010 PCV7 era	April 2010-March 2014	1 year Authors carried out a sensitivity analysis excluding admission for 1 year post PCV13	PCV13 replaced PCV7 from April 2010	Hospital Episodes Statistics (HES) database	91% in 2010–2011	2 + 1	Clinical pneumonia (ICD-10; J12-J18)	120.2	Used control outcome: all-cause unplanned hospital admission. Child's sex, seasonality and influenza-like illness (ILI) admissions were accounting in the model	0–23 months 24–48 months	0.91 0.75	0.75–1.05 0.62–0.91
Nair H., 2016 [59]	Scotland	Nationwide	PCV13	PCV7	Before-after	2007–2009	2010–2012	0 months	April 2010	Scottish Morbidity Record (SMR01)	65%	2 + 1	Clinical pneumonia (ICD 10; J12-18, J10.0, J11.0)	298.65 183.85	No adjusting factors	<24 months 24–48 months	0.86 0.99	0.78–0.95 0.90–1.08

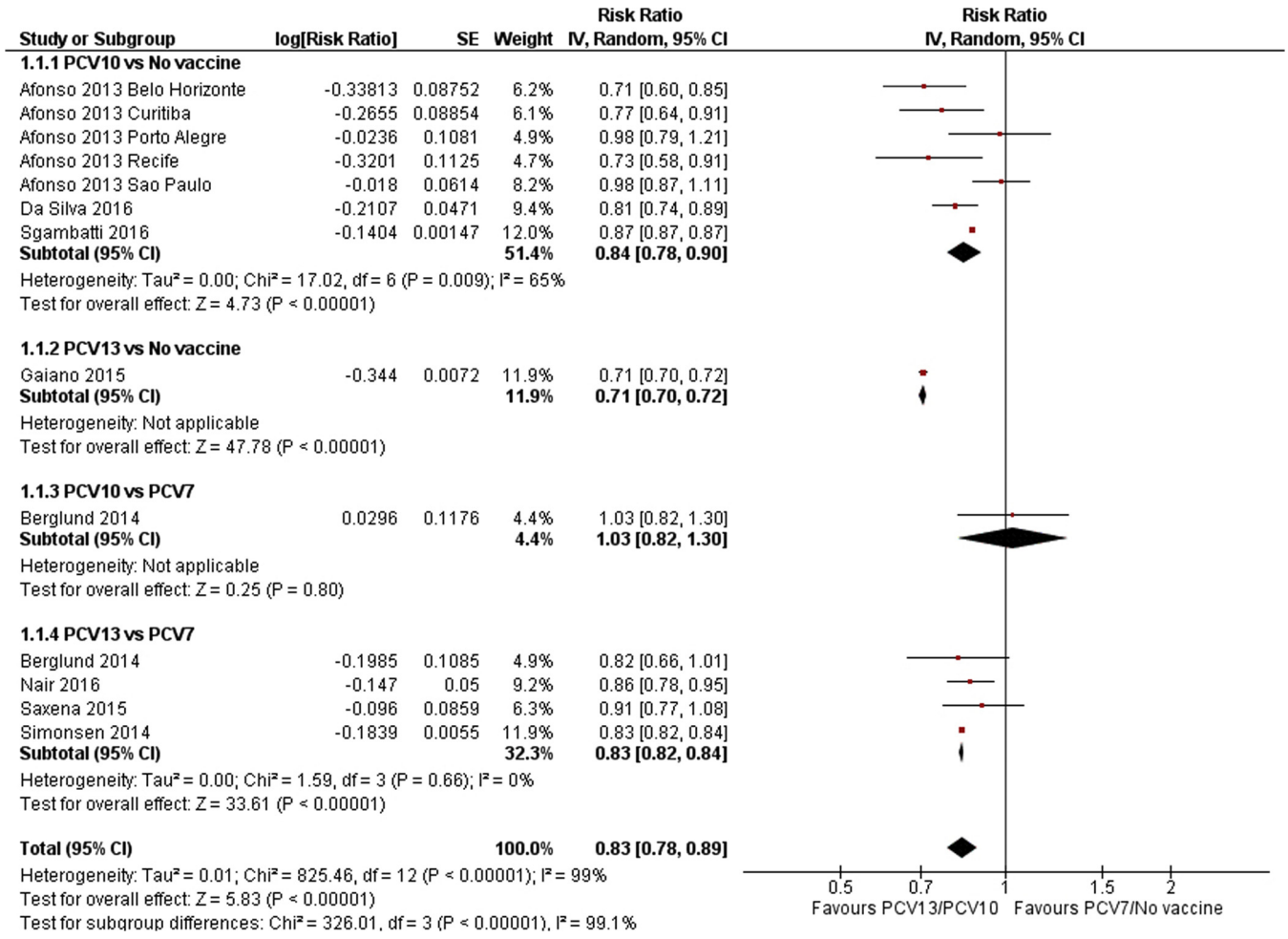

Fig. 2. Meta-analysis of studies reporting hospitalization rates for clinical pneumonia among children aged <24 months.

identified for full-text review, 29 of which were excluded for the following reasons: data reported only on IPD (6) [19–24], data reported only on adult population (4) [25–28], unacceptable study design (13) [29–41], lack of disaggregated data on children aged <5 years (4) [42–45], and insufficient data (2) [46,47] (Table S3). Finally, 12 articles met all the inclusion criteria and were included in the analysis.

Characteristics of the studies included are summarized in Table 1.

Six studies (50%) were performed in Central or South America [48,49,51–54], 4 (33.3%) in Europe [50,55,58,59], 1 (8.3%) in the US [56] and 1 (8.3%) in Israel [57]. Four (33.3%) studies examined PCV10, all of which in comparison with no pneumococcal vaccine [48–51]. Seven (58.3%) studies examined PCV13 [52–54,56–59], 4 of which in comparison with PCV7 [56–59] and 3 in comparison with no pneumococcal vaccine [52–54]. One study reported data on both PCV10 and PCV13 in comparison with PCV7 [55]. Six (50%) studies reported data on hospitalization for clinical pneumonia [48,49,53,55,58,59], 4 (33.3%) for X-ray confirmed pneumonia [50,52,54,57], and 2 (16.7%) for both outcomes [51,56].

3.1. Hospitalization for clinical pneumonia

From the ten studies reporting data on clinical pneumonia [48,49,51,53,55,56,58,59] 21 estimates of IRR with their 95%CI were extracted.

3.1.1. Children aged <24 months

IRR in children aged <24 months were extracted from eight studies [48,49,51,53,55,56,58,59]. In two studies [49,51] these data were available only for children aged <12 months. Three studies reported data on PCV10 in comparison with no vaccine [48,49,51], three studies on PCV13 in comparison with PCV7 [56,58,59], one study on both PCV13 and PCV10 in comparison with PCV7 [55] and another study on PCV13 in comparison with no vaccine [53].

The overall pooled estimate showed an IRR of 0.83 (95%CI: 0.78–0.89, p-value < 0.001), corresponding to a reduction of 17% (95%CI: 11–22%) (Fig. 2). The heterogeneity of the estimates extracted from the studies included in the meta-analysis varied substantially, as evidenced by the $I^2 = 99\%$.

In subgroups analysis, a similar impact was registered in the settings in which the introduction of PCV10 or PCV13 was not preceded by the use of PCV7 (IRR: 0.81, 95%CI: 0.73–0.91) than in the settings in which PCV10 or PCV13 replaced PCV7 and the additional effect over what already obtained with this latter formulation was measured (pooled IRR: 0.85, 95%CI: 0.81–0.88).

The subgroup analysis detected a significantly difference in the IRR in the settings where PCV13 (IRR: 0.71, 95%CI: 0.70–0.72) was introduced with respect to PCV10 (IRR: 0.84, 95%CI: 0.78–0.90), when the two novel formulations were compare to no vaccine (p-value < 0.001). A similar pattern was also observed in the comparison between PCV13 (IRR:0.83, 95%CI: 0.82–0.84%) or PCV10 (IRR: 1.03, 95%CI: 0.82–1.3) with PCV7, though the difference was not statistically significant (p-value = 0.07).

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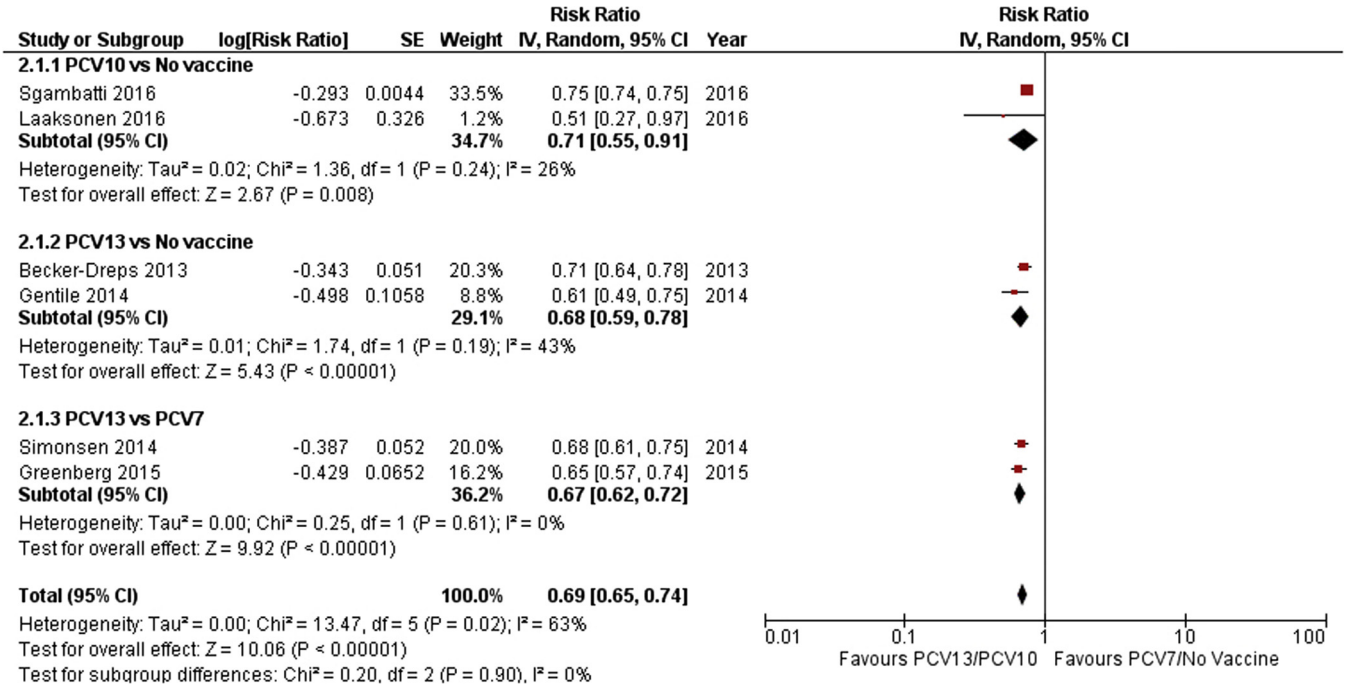

Fig. 3. Meta-analysis of studies reporting hospitalization rates for X-ray confirmed pneumonia among children aged <24 months.

3.1.2. Children aged 24–59 months

IRR in children aged 24–59 months were extracted from four studies [51,56,58,59]. In three studies [56,58,59] these data were available for children aged 24–48 months, while in one study [51] the data are available for children aged 24–35 months. Three studies compared PCV13 with PCV7 [56,58,59] and one study compared PCV10 with no vaccine [51].

The pooled estimate showed an IRR of 0.91 (95%CI: 0.86–0.95, p-value < 0.001), corresponding to a reduction of 9% (95%CI: 5–14%) (Fig. S1).

The heterogeneity of the estimates extracted from the studies included in the meta-analysis varied substantially, as evidenced by the I^2 = 96%.

3.2. Hospitalization for x-ray confirmed pneumonia

From the six studies reporting data on X-ray confirmed pneumonia [50–52,54,56,57], 22 estimates of IRR with their 95%CI were extracted. In three studies [51,54,57], radiologically confirmed pneumonia was defined according to WHO criteria.

3.2.1. Children aged <24 months

IRR in children aged <24 months were extracted from six studies [50–52,54,56,57]. Two studies reported data on PCV10 in comparison with no vaccine [50,51], two studies on PCV13 in comparison with no vaccine [52,54], and a further two studies on PCV13 in comparison with PCV7 [56,57].

The pooled estimate showed an IRR of 0.69 (95%CI: 0.65–0.74, p-value < 0.001), corresponding to a reduction of 31% (95%CI: 26–35%) (Fig. 3). The heterogeneity of the estimates extracted from the six studies included in the meta-analysis was moderate, as evidenced by the I^2 = 63%.

In the subgroup analysis, in the settings in which the introduction of PCV10 or PCV13 was not preceded by PCV7 use, IRRs were 0.71% (95%CI: 0.55–0.91) and 0.68 (95%CI: 0.59–0.78), respectively, without any statistically significant difference. When PCV13 was compared with previous PCV7 immunization, IRR was 0.67 (95% CI: 0.62–0.74).

3.2.2. Children aged 24–59 months

IRR in children aged 24 – 59 months were extracted from six studies [50–52,54,56,57]. In three studies [52,54,57] these data were available for children aged 24–59 months, in two studies [50,51] the data were available for children aged 24–35 months, while in one study [56] the data were available for children aged 24–48 months. Two studies reported data on PCV10 in comparison with no vaccine [50,51], two studies on PCV13 in comparison with no vaccine [52,54], and a further two studies on PCV13 in comparison with PCV7 [56,57].

The pooled estimate showed an IRR of 0.76 (95%CI: 0.67–0.88, p-value < 0.001), corresponding to a reduction of 24% (95%CI: 12–33%) (Fig. S2). The heterogeneity of the estimates extracted from the six studies included in the meta-analysis was substantial, as evidenced by the I^2 = 87%.

The subgroups analysis revealed a significantly higher reduction in the settings in which PCV13 was compared with PCV7 (IRR: 0.70, 95%CI: 0.64–0.77, p < 0.001) and with no vaccine (IRR: 0.74, 95%CI: 0.67–0.81, p < 0.001) than of PCV10 compared with no vaccine (VE: 0.88, 95%CI: 0.87–0.89). No difference was registered between settings where PCV13 was introduced after PCV7 and those where PCV13 was not preceded by PCV7.

4. Discussion

This systematic review and meta-analysis assessed the impact of PCV10 and PCV13 on hospitalization for pneumonia in children aged <5 years, and included all impact studies conducted globally after the introduction of the novel PCVs into national immunization strategies. Our research focused on pneumonia, as this represents a relevant disease related to Sp in children, in terms of incidence, hospitalization and mortality [4].

With respect to our primary objective, the meta-analysis highlighted a decrease in the incidence of pneumonia hospitalization both among children aged <24 months and among those aged 24–59 months, after the introduction of novel available PCVs. Our findings confirmed those recently reported in a systematic review

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evaluating the impact of PCV10 and PCV13 in Latin American countries [60].

Specifically, our results showed a statistically significant cumulative reduction of 17% in the hospitalization rate for clinical pneumonia in children aged <24 months; notably, the reduction was even higher (31%) with regard to X-ray confirmed pneumonia.

The cumulative reductions in clinical pneumonia (9%) and X-ray confirmed pneumonia (24%) observed among children aged 24–59 months were inferior than those observed among children aged <24 months and confirmed a more marked relative reduction with respect to radiologically confirmed pneumonia. The reductions observed in this age-group could be due to both direct and indirect effects of PCVs immunization, although the study designs do not allow us to estimate the relative weight of each effect.

The observation of a more marked relative reduction in radiologically confirmed pneumonia was expected because of the higher specificity of this definition. Indeed, studies using narrower and more specific case definitions, such as WHO–standardized definition including radiological confirmation of pneumonia, probably provide a more accurate description of the impact of PCV on diseases specifically sustained by Sp [61]. On the other hand, more generic case definitions, such as those exclusively based on clinical signs and symptoms or on ICD codes, are more likely to include cases caused by pathogens other than Sp. Noteworthy, the lower relative reduction observed using less specific outcomes may correspond to greater absolute number of cases prevented due to the higher baseline incidence of these outcomes [62].

Marked heterogeneity was detected among the studies included in the meta-analysis, particularly among those that evaluated the less specific outcome of hospitalization rate for clinical pneumonia. This heterogeneity can be ascribed to several factors related to the differences in the methods and the settings of the studies included. First, the data source and the case definition of clinical pneumonia differed widely: 5 studies used secondary data from administrative databases that identified cases of pneumonia according to specific ICD10 (4 studies [48,55,58,59]) or ICD9 (1 study [56]) specific codes; 3 studies [49,51,53] used different clinical definitions of pneumonia and different data sources (clinical charts, *ad hoc* surveillance). This lack of standardization of case definitions may explain some of the variability in findings. Moreover, the use of secondary data from health information systems, hospital databases, administrative registries and other sources may affect the overall quality of observations, in terms of completeness, representativeness and reliability. Also in the studies reporting data on X-ray confirmed pneumonia, different definitions were used: in three studies [51,54,57], radiologically confirmed pneumonia was defined according to WHO criteria, while in further three studies [50,52,56] the definition of radiologically confirmed pneumonia differ from those criteria

Second, impact studies, such as before-after studies and time-series analysis (interrupted or not), evaluating the change in hospital admission rates for a disease before and after the introduction of a new vaccine, constitute the typical and most affordable means of assessing the impact of the vaccine at the population level. However, these observational studies are susceptible to specific biases and confounding by changes in epidemiology and healthcare delivery changes concomitant with vaccination [41,63].

Indeed, most studies [48,51,52,54–58] used different strategies to control potential biases caused by changes arising from these issues. In particular, six studies addressed potential biases due to changes in inpatient care by accounting for all-cause hospitalizations [55,56,58], for the hospitalization rates due to diseases not prevented by the novel PCVs, such as non-respiratory disease, urinary tract infections and diarrhoea [48,52,56], or for hospital capacity [51]. Three studies [52,54,57] adopted controls hypothetically sensitive to primary-care or outpatient-care changes as the expansion of these services was associated with reduced hospitalizations for pneumonia, showing that changes in this setting can be an relevant source of biases.

Finally, some studies [51,56] accounted in their analysis for the secular trends of pneumonia hospitalization rates before the introduction of the novel PCVs.

A further source of heterogeneity is represented by the periods of observation before and after the introduction of the novel PCVs. In the studies included in our research, pre-vaccination periods ranged from 12 to 42 months (median: 30 months). Most studies [48–51,53,56–58] considered a transition period (usually, the year of PCV introduction); in some studies [48–51], however, this period was excluded from, while in other it was included in either the pre-vaccination or post-vaccination period [53,56–58]. Post vaccination period ranged from 12 to 36 months. Regarding this aspect, the length of the observation period after the PCV introduction can markedly affect the impact of vaccination, owing to its effect on the nasopharyngeal (NP) carriage of vaccine-type serotypes. Indeed, a number of studies have shown that PCVs prevent vaccine-type NP acquisitions and reduce vaccine-type carriage, a necessary precursor to clinical disease [64,65]. Reductions in the NP carriage of Sp are a key factor in the indirect effects of vaccine introduction and the establishment of "herd" protection. For this reason, in studies with longer observation periods and high vaccination coverage rates, a higher impact of vaccination would be expected.

Moreover, at the population level, the impact of either PCV10 or PCV13 on pneumonia may be naturally shaped by a variety of other factors that are extrinsic to the study design or to the characteristics of the vaccine and vary according to the setting. Major differences in the impact of the novel PCVs may be related to the baseline trends in pneumonia, pneumococcal serotype distribution and the prevalence of nasopharyngeal carriage of vaccine-type serotypes, the prevalence of factors that may affect immunogenicity (such as HIV or malnutrition), vaccine coverage, implementation of catch-up campaigns, and organizational aspects such as cold chain capacity.

Furthermore, the majority of studies were performed in middle and low-income countries, located in Central and South America. These countries often have a higher incidence of pneumonia and a higher prevalence of children at greater risk of developing pneumonia because of underlying health conditions. Finally, as recently highlighted by Shuck-Paim and colleagues, estimating changes in hospitalization rates before and after the start of an health intervention, such as the introduction of a new vaccine, can be challenging in middle- and low-income countries, where healthcare systems are rapidly evolving [41].

As regards the secondary objective of this research, none of the studies included in this meta-analysis had been designed to directly compare the impact of PCV10 and PCV13; thus, only indirect comparisons were possible and the results should be considered with caution. Among children aged <24 months, a statistically significant higher reduction in clinical pneumonia hospitalization rates was observed in studies that compared PCV13 period with the pre-vaccine period than into those comparing PCV10 period with the pre-vaccine period. In children aged 24–59 months, the incidence of X-ray confirmed pneumonia hospitalization showed a statistically significant decrease in the post-PCV13 implementation period, while no significant differences were observed in studies comparing the PCV10 period with the pre-vaccine period. However, the above-mentioned differences in study designs and settings do not allow us to establish the superiority of one vaccine over the other with regard to their impact on pneumonia hospitalization reduction in children aged <5 years. The absence of head-to-head evaluations of the impact of the two novel pneumococcal vaccines reveals the need for additional research aimed at establishing the most effective immunization strategy.

Please cite this article in press as: Alicino C 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), http://dx.doi.org/10.1016/j.vaccine.2017.09.005

The limitations of this meta-analysis mainly concern the above-mentioned issues intrinsic in the study design and the heterogeneity of study methods and settings. All studies included in the meta-analysis had a before-after or an interrupted time series design. Indeed, the vast majority of studies evaluating the on-field effectiveness of PCV10 and PCV13 vaccines against hospitalization for pneumonia in children have been of this kind. Moreover, observational studies with a cohort or a case-control design are not able to measure the whole impact of the introduction of a PCV immunization strategy in terms of both direct and indirect effects. This meta-analysis did not consider any differences in the vaccine schedules used in the various different countries; however, there is considerable evidence that all schedules used display optimal efficacy in reducing clinical and radiological confirmed pneumonia [61,66].

5. Conclusions

In conclusion, the results of this study highlighted a significant impact of PCV10 and PCV13 use in reducing hospitalizations for pneumonia in children <5 years of age, thus supporting the introduction of these vaccines into national immunization programmes. Further, studies, with specific and standardized case definitions and which are appropriately designed to compare the impact of PCV10 and PCV13, are needed in order to obtain solid data on which to establish the future immunization strategies.

Acknowledgements

No financial support was received for this study.

The authors thank Dr Bernard Patrick for his linguistic review of the manuscript.

Author Contributions

CA conceived and designed the research, analysed the data and drafted the manuscript.

CP conceived the research, conducted the literature search, read and selected articles, extracted data and assessed the quality of the studies included, analysed the data and drafted the manuscript.

AO conceived and designed the research and drafted the manuscript.

MA read and selected articles, extracted data and assessed the quality of the studies included.

CT contributed to designing the research and revised the manuscript.

GI and FA conceived and designed the research and revised the manuscript.

All authors have read and approved the final manuscript.

Conflict of interest

Giancarlo Icardi and Filippo Ansaldi have previously participated in speaker's bureaux and advisory board meetings sponsored by GSK, Pfizer, Novartis and Sanofi Pasteur and have received research funding as investigators or principal investigators from GSK, Pfizer, Novartis and Sanofi Pasteur MSD. Cristiano Alicino, Chiara Paganino, Andrea Orsi, Matteo Astengo, and Cecilia Trucchi declare that they have no conflict of interest.

Appendix A. Supplementary materials

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.09.005.

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