



Streptococcus pneumoniae vaccination strategies and its expected impact on penicillin non-susceptibility in children under the age of five: Let's recap!



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ABSTRACT

The impact of pneumococcal conjugate vaccines (PCVs) on invasive pneumococcal disease (IPD) burden has been extensively studied in children aged <5 years; however, a pooled estimation of the effect of PCVs on penicillin non-susceptible pneumococci (PNSP) has not yet been performed. We aimed to identify whether the introduction of PCV-10 and PCV-13 had led to the decrease of the overall PNSP rate in children < 5 years. We conducted a systematic review of published surveillance studies reporting the rate of PNSP rates in children < 5 in countries where PCV10/13 were introduced. The overall observed trend onwards the introduction of PCV-10 and PCV-13 is a decrease in PNSP among children < 5 years in surveillance sites located in PCV-13 countries. We identified an increase of PNSP rates (serotype 19A) in PCV-10 settings. Resistant NVT strains are emerging in IPD in children < 5 years mainly serotypes 24F, 15A, 11A and 33F along with serotype 19A in PCV-10 settings. Continuous surveillance is necessary in IPD in children under five to monitor the long-term effect of PCV-10 and PCV-13 on penicillin resistance trends.

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1. Introduction

Streptococcus pneumoniae is considered one of the leading infectious pathogens both among adults and children [1]. This gram-positive encapsulated bacterium is responsible for severe forms of infections in infants and young children including pneumonia, meningitis, and bacteremia, which are among the main causes of severe morbidity and mortality in children under five [2,3]. The pneumococcal capsule, one of the most important virulence factors in pneumococcus, is the target of pneumococcal conjugate vaccines (PCVs) currently used in routine immunization programs [4]. Ten-valent and 13-valent pneumococcal conjugate vaccine, PCV-10 and PCV-13 respectively, protect against 10 to 13 of the one hundred pneumococcal capsular serotypes known [5,6]. These vaccines have demonstrated to be highly effective at decreasing the burden of invasive pneumococcal disease and related mortality in under five children [7–9]. Nonetheless, mass vaccination with PCVs has been considered a source of selective pressure on the

environment of pneumococcal strains whose most virulent serotypes evolve and adapt by developing resistance [10,11].

A surge of highly invasive and resistant non-vaccine type (NVT) serotypes, a phenomenon known as serotype replacement, has been documented worldwide after the widespread use of PCVs in children [12–14]. The eradication of vaccine-type (VT) serotypes by vaccination or/and antibiotics use, leaves an ecological niche to be partly filled by the expansion of NVT lineages that are more likely to be resistant [15]. Pneumococcal strains feature the capacity of horizontally gaining new phenotypic characteristics through the acquisition of foreign DNA that confers resistance to antibiotics from other commensal bacterial species of the nasopharynx such as *Streptococcus mitis* and *Streptococcus oralis* [16,17]. Furthermore, penicillin-binding protein (PBP), a major component of the bacterial cell wall, can be the main target of resistance in pneumococci [18]. PBP mediated resistance occurs through the acquisition of mosaic PBP genes, notably as a result of mutations in three of the six variations of PBP (1a, 2x, 2b) [18]. The successive acquisition of multiple mutations in PBPs different variations can lead to an increase in minimum inhibitory concentrations (MICs) for penicillin and other beta-lactam drugs [19]. Consequently, invasive

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pneumococcal disease (IPD) resulting from penicillin-no susceptible pneumococci (PNSP) might possibly end in treatment failure and in increased occurrence of more severe clinical complications especially in infants and under five children [20,21]. Moreover, resistance has been associated with worse clinical outcomes in all age patients with pneumococcal meningitis, yet the clinical implications for patients with PNSP strains mediated non-meningitis invasive infections are controversial [19,22–32].

In order to better comprehend and respond to the global rise of antibiotic non-susceptibility, the World Health Organization (WHO) called for action through its “Global action plan on antimicrobial resistance” that recommends the gathering of key data and information through close monitoring and surveillance of rapidly emerging resistant strains [33]. Likewise, the Clinical Laboratory Standards Institute (CLSI) suggested the use of different sensitivity breakpoints for pneumococcal meningitis ($\leq 0.06 \mu\text{g} / \text{ml}$) and non-meningitis pneumococcal disease ($\geq 2 \mu\text{g} / \text{ml}$) for an optimal long-haul reporting of pneumococcal penicillin resistance rates in epidemiological surveillance studies [34,35]. Prior to the development of PCV-7, several pneumococcal surveillance sites reported increased resistance rates of pneumococcal serotypes in pediatric populations worldwide [36–39]. While substantial cutbacks in

resistance rates of VT serotypes associated with IPD were reported in under five children shortly after the introduction of PCV-7, a surge of highly resistant and invasive NVT strains was reported globally, serotype 19A especially [36,37,39–47]. Thereafter, PCV-13 and PCV-10 were developed to curb the extensive surge of NVT strains and they have been used today for more than a decade in national immunization programs around the world [48].

Nowadays, a similar NVT trend to the one observed after PCV-7 introduction has been described [14], while surveillance sites of IPD worldwide raise concerns about the emergence of virulent NVT serotypes that could possibly jeopardize all the benefits reaped from PCVs in the pediatric and elderly population [14]. Ergo, it is of high public health interest to monitor the epidemiological evolution of *S.pneumoniae* and the impact of PCVs on lessening the rate of PNSP serotypes over time essentially in the pediatric population aged under 5 years [1,49].

We thereby aimed to conduct a systematic review of published studies over 10 years to assess whether the introduction of PCV-10 or PCV-13 into routine immunization programs has been followed by a reduction in the overall PNSP rate in children under the age of five. We hypothesized that overall PNSP rate in children under the age of five decreased after the introduction of PCV-10 or PCV-13. In

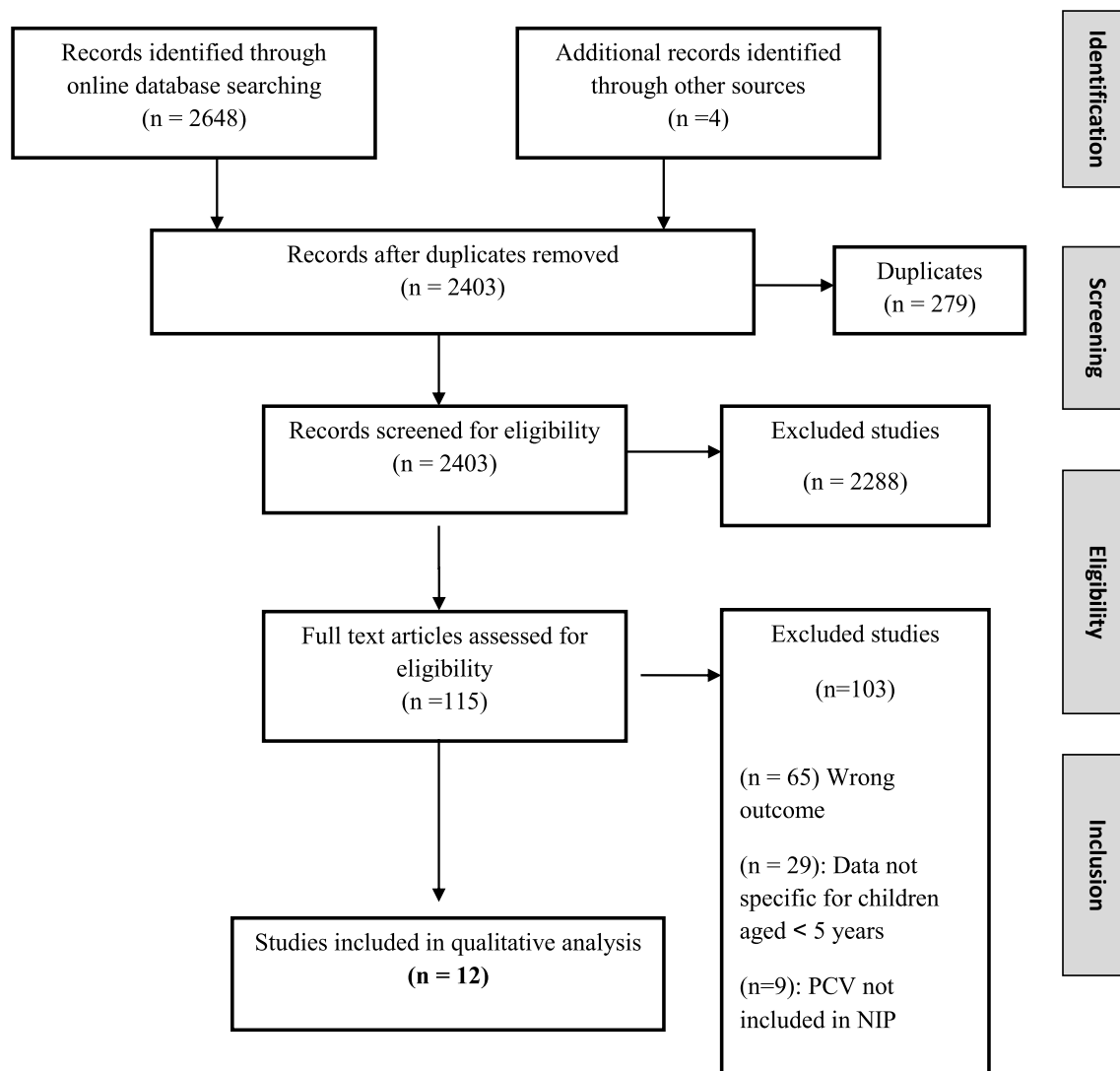


Fig. 1. Study PRISMA 2009 Flow diagram detailing the literature search process. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. PLoS Med. 2009;6(7):e1000097 (50).

addition, the widespread use of PCV-10 and PCV-13 in children aged under five might have possibly led to the expansion of resistant NVT strains. Thus, our primary objective was to compare the percentage of PNSP strains before and after widespread use of PCV-10 and PCV-13.

2. Materials and methods

2.1. Study design

We conducted a systematic review following PRISMA guidelines for the research and reporting of our findings and AMSTAR-2 as a critical appraisal tool [50]. We have defined beforehand the review question, the search strategy, the inclusion/exclusion criteria and the risk of bias assessment.

2.2. Search strategy

From January 1, 2021 to March 31, 2021, we searched PubMed[®], Science Direct[®], Scopus[®] using the e-resources database [51] for articles whose abstract is written in English and published in either English, French, German, Spanish and Portuguese during the period spanning from January 2010 to March 2021.

Our target population was children under the age of five diagnosed with laboratory confirmed IPD who were vaccinated by PCV-10 or/and PCV-13.

The main outcome was to compare the rate of PNSP before and after the introduction of PCV-10 or/and PCV-13. The Key words we have used for this purpose were: "PCV-10", "PCV-13", "Pneumococcal conjugate vaccination", "IPD", "Invasive pneumococcal disease", "Children under five", "Penicillin non-susceptibility", "Antibiotic resistance", "Drug resistance", "antimicrobial resistance".

We searched the reference lists of included studies and grey literature for eligible studies. (Fig. 1: PRISMA Flowchart). We manually searched articles that reported surveillance data in all age patients and included data specific to children aged under five using the advanced search stated below.: ((((((impact) AND (pneumococcal vaccine)) OR (PCV-10)) OR (PCV-13)) AND (incidence)) AND (IPD)) OR (Invasive pneumococcal disease)) AND (Children)))) ((((((impact) AND (pneumococcal vaccine)) OR (PCV-10)) OR (PCV-13)) AND (Antibiotic Resistance)) OR (Drug Resistance)) OR (Penicillin non-susceptibility)) AND (Children))))).

2.3. Study selection

We assessed the eligibility of each publication for inclusion using the Rayyan software for.

90 systematic reviews [52]. Two readers were previously trained to conduct systematic reviews, assessed the eligibility of each study for inclusion and exclusion; consensus was reached between readers about the inclusion of a study regarding initial divergence.

Definitions.

- **Invasive pneumococcal disease, IPD**, defined as the identification of *Streptococcus pneumoniae* in an isolate from a normally sterile site (e.g. blood, cerebrospinal, pleural effusions, or joint fluid)
- **Penicillin susceptibility breakpoints**, defined according to CLSI guidelines: pneumococcal meningitis isolates ($\leq 0.06 \mu\text{g} / \text{ml}$) and non-meningitis isolates ($\geq 2 \mu\text{g} / \text{ml}$) [34].

Box 1 : Eligibility criteria:

Inclusion criteria:

Full text studies published in English, French, German, Spanish and Portuguese.
 IPD surveillance studies of antibiotic resistance published between January 2010 and March 2021.
 Study population included children aged <5 years, with laboratory confirmed IPD, without underlying co-morbidities, vaccinated with PCV-10 or/and PCV-13 from settings where PCVs are universally provided for children under a routine immunization program with coverage $\geq 60\%$.
 The study includes a clear definition of the following elements: type of study conducted, existence of a surveillance system, study population, study setting, study duration, pre-PCV and post-PCV periods, used PCV, measured outcome, definition of an IPD case and breakpoints used for assessment of Penicillin non-susceptibility.

Exclusion criteria:

Studies available as conference summaries proceedings or published in a language other than English, French, German, Spanish and Portuguese.
 Study populations aged over five years and / or with underlying medical conditions.
 125 Studies that evaluate penicillin resistance in non-invasive infections samples that are *Streptococcus pneumoniae* positive and where isolated from a non-sterile site.
 Studies that include both adults and children and do not stratify results by age.
 Studies that do not specify the study setting, duration, location, target population, number of patients included and vaccine used.
 Studies that examine the effect of PCV-7 on penicillin no susceptibility only.

2.4. Data extraction

We analyzed the studies eligible for inclusion in their entirety and we collected data in a customized template of systematic review form established by Cochrane [53]. We compiled Data from all included studies in an Excel file. (Table 1 and Table 2) We extracted the Country of the study and the country economy level according to the economy rankings provided by the World Bank and lending Groups Country Classification of the 2021 fiscal year [54]. In addition, we extracted the data regarding the: study design, study population, time frame, funding source, number of isolates, IPD surveillance system type and year of establishment, PCV valency in use, vaccine schedule and year of introduction, national PCV coverage (when the coverage rate was not mentioned in the study, we extracted last year of the study PCV coverage from the WHO vaccine-preventable diseases: Monitoring system – 2020 Global Summary) [55]. We collected the rates of PNSP strains before and after PCV-10 or PCV-13 while specifying the used breakpoints for susceptibility interpretation. We reviewed all potentially eligible studies that included specific data on children aged under five. When a study has not met our pre-defined inclu-

Table 1
 Characteristics of included studies in the systematic review assessing the impact of Pneumococcal Conjugate Vaccines on Penicillin non-susceptibility in children < 5 years in settings where PCVs are included in the National Immunization Program, before and/or after their widespread use.

Study	NHIB quality of evidence (1)	Country	Economic Status - World Bank ranking(2)	Study design	Number of isolates	Study time frame	PCV used (year of introduction)	Vaccine Schedule (age in months)	Coverage rate	Surveillance system (date of establishment)
Al jardani et al.(3)	Good	Oman	High	Prospective	35	2014–2016	PCV-7 (2008)	3 + 0 (2,4 & 6)	90%	National laboratory-based IPD surveillance program. (2014)
Ho et al(4)	Fair	Hong Kong, China	High	Retrospective	319	1995–2017	PCV-13 (2012) PCV-7 (2009) PCV-10(2010–11) PCV-13 (2011)	3 + 1 (2,4,6 &12–15)	97%	Territory-wide laboratory-based surveillance for IPD. NR (Not Reported)
Camilli et al. (5)	Good	Italy	High	Laboratory surveillance study	364	2008–2014	PCV-7 (2006) PCV-13 (2013)	2 + 1 (3, 5& 11)	87%	National laboratory-based Surveillance System for Invasive Bacterial Diseases (2007)
Nhantumbo et al. (6)	Poor	Mozambique	Low	Laboratory surveillance study	119	2013–2014	PCV-10 (2010)	2 + 1 (1.5, 3.5 &9)	76%	Regional Sentinel surveillance system for pediatric acute bacterial meningitis (2013)
Hauser et al(7)	Good	Switzerland	High	Prospective surveillance study	657	2004–2014	PCV-7 (2006) PCV-13 (2010)	2 + 1 (2, 4 &12)	75%	National population-based passive surveillance of IPD (1999)
Diawara et al (8)	Fair	(Casablanca) Morocco	Lower-middle	Laboratory-based surveillance study	136	2007–2014	PCV-13(2010)	2 + 1 (2, 4 &12)	94%	Regional laboratory-based surveillance (1994)
Ben-shimol et al (9)	Good	Israel	High	Prospective, study	325	2004–2016	PCV-10 (2012) PCV-7 (2009) PCV-13 (2010)	2 + 1 (2, 4 & 12)	90%	Nationwide, population based and active surveillance (1989)
Desmet et al (10)	Good	Belgium	High	Surveillance study	365	2015–2018	PCV-7 (2007) PCV-13 (2011) PCV-10 (2015)	2 + 1 (2, 3 &12)	94%	Passive national laboratory-based surveillance network. (NR)
Park et al (11)	Poor	South Korea	High	Prospective study	48	2014–2016	PCV-7 (2003) PCV-13/10 (2014)	3 + 1 (2, 4, 6 &12–15)	NR	NR
Deng et al (12)	Good	Ontario (Canada)	High	Laboratory-based surveillance stud	341	2007–2012	PCV-7 (2002) PCV-13 (2010)	3 + 1 (2, 4, 6/12, 12/15/18)	70%	Regional laboratory-based IPD surveillance (2001)
Janoir et al (13)	Fair	France	High	Laboratory surveillance study	790	2008–2014	PCV- 7(2003) PCV- 13(2010)	2 + 1 (2, 4, & 11)	90%	National laboratory-based surveillance network of IPD (NR)
Cassiolato et al. (14)	Fair	Brazil	Upper-middle	Surveillance study	262	2005–2017	PCV-10 (2010)	2 + 1 (2,4& 12)	90%	National laboratory-based passive surveillance (1993)

Table 2

Penicillin-non susceptible pneumococci rates in children < 5 vaccinated with PCV10 or/and PCV-13 diagnosed with laboratory confirmed Invasive Pneumococcal Disease according to Clinical and Laboratory Standards Institute meningitis and non-meningitis breakpoints in countries where Pneumococcal Conjugate Vaccines were implemented prior and after their introduction in the National Immunization Program.

Study	Country	PCV used (year of introduction)	Surveillance type	Pre (P1) - PostPCV10/13 period(P2)	Study population age (months)	Studied serotypes	% PNSP meningitis (P1-P2)	MIC (µg/mL)	% PNSP non meningitis (P1-P2)	MIC (µg/mL)
Countries that reported post PCV data only										
Al jardani et al. (3)	Oman	PCV-13 (2012)	laboratory-based.	2014–2016	0–59	All	62.9	> 0.06	0	>2
Camilli et al. (5)	Italy	PCV-13 (2013)	laboratory-based.	2008–2014	0–48	All	17	> 0.06	21	> 0.06
Nhatumbo (6)	Mozambique	PCV-10 (2010)	laboratory-based.	2013–2014	0–59	All	88.2	> 0.12		
Hauser et al(7)	Switzerland	PCV-13 (2010)	Population-based	2004–2014	0–59	All	17.4	> 0.06	1.5	>2
Park et al (11)	South Korea	PCV-13/10 (2014)		2014–2016	0–59	All	31.3	> 0.06	–	–
Deng et al (12)	Ontario (Canada)	PCV-13 (2010)	laboratory-based	2007–2012	0–59	All	–	–	8.5	>2
Countries that reported pre and post PCV data										
Ho et al(4)	Hong Kong, China	PCV-10(2010–11) PCV-13 (2011)	laboratory-based	2010–2014 2015–2017	0–59	All	(62.8–13.8)	> 0.06	(10.5–3.4)	>2
Diawara et al (8)	(Casablanca) Morocco	PCV-13(2010) PCV-10 (2012)	laboratory-based	2007–2010 2011–2014	0–24 24–59	All	(50.6–21.9) (41.7–30.8)	> 0.06	–	–
Ben-shimol et al (9)	Israel	PCV-13 (2010)	Population-based	2004–2005 2015–2016	0–59	All NVT	(40.5–9.6) (33.3–10.4)	> 0.06	–	–
Desmet et al (10)	Belgium	PCV-13 (2011) PCV-10 (2015)	laboratory-based	2015–2016 2017–2018	0–30	All 19A 24B 24A	(11.8–20.4) 23.5 40 76.9	> 0.064	–	–
Janoir et al (13)	France	PCV- 13(2010)	laboratory-based	2008–2009 2011–2012	0–23	All 19A 15 35B 24F	–	–	(35.5–23.9) (70.8–40.5) (100–79) (100–50) (28–23)	>2
Cassolato et al. (14)	Brazil	PCV-10 (2010)	laboratory-based	2005–2009 2016–2017	0–59	19A	–	–	(3.2–31.6)	>2w

sion criteria, we provided a justification for exclusion in the systematic review's Excel sheet. Whilst assessing eligibility for inclusion, we paid close attention to the studies' sources of funding in order to detect any potential source of conflict of interest that might bias published results.

2.5. Quality assessment

We assessed the quality of the included studies according to the Study Quality Assessment Tools of the "National Heart, Lung and Blood Institute" NHIBI [56]. We used the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group. Then, we rated the studies according to the NHIBI pre-established guidance criteria using the following rating system: good, fair or poor. We reached a consensus between the two reviewers in the event of a discrepancy in specifying the quality rating.

2.6. Data Analysis

The main outcome was the frequency of penicillin non-susceptible pneumococci as percentage (% PNSP). We performed a summary of all the included studies through descriptive analyses to feature an overview of studies' characteristics and outcomes.

3. Results

3.1. Literature review

We retrieved 2648 records by searching online databases. After duplicates elimination, we assessed 2403 records for eligibility based on title and abstract screening. We selected and fully reviewed one hundred fifteen articles, of which 12 studies reported PNSP rates in children under the age of five. Fig. 1 depicts the process to identify eligible studies for analysis (PRISMA flowchart). We summarized the characteristics of each study, country of origin, PCV used, and vaccination scheme implemented, vaccination coverage, and type of surveillance system in Table 1.

3.2. Characteristics of included publications

Of the 12 included studies, 6 studies (50%) [57–62] reported PNSP rates prior and after the introduction of PCV-10/13 in the children's immunization program while the 50% remaining studies [63–68] only reported data on resistance after the introduction of PCV-10/13 in routine immunization.

Overall, 75% (9/12) of included studies originated from high-income countries, 10.5% (2/12) from middle-income countries, and 8.33% (1/12) from a low-income country. PCV-13 is mostly used in high-income settings while PCV-10 is more frequently introduced in lower-income countries, 66.66% (8/12) and 33.33% (4/12) respectively. Belgium switched from PCV-13 to PCV-10 after 4 years of use. Likewise, Morocco switched to PCV-10 after an initial 2 years use of PCV-13. Hong Kong shifted to PCV-13 after 13 months of PCV-10 use.

We summarized an overview of the data collected on PNSP rates in children under five with IPD by age subgroups, country of origin, serotype, isolate site (meningitis or non-meningitis) and penicillin breakpoints in the Table 2. Of the 12 included studies, 6 reported PNSP rates before and after mass vaccination with PCV-10 or PCV-13, while the remaining 6 studies reported PNSP rates after the introduction of PCV-10 or PCV-13. Only six studies provided distribution of highly resistant serotypes.

3.3. PNSP meningitis trends in children under five

The overall trend after the introduction of PCV-10/PCV-13 was a decrease in PNSP meningitis rates among children under five vaccinated with PCV-13 or when a part of them had been vaccinated with PCV-13 prior to the switch to PCV-10 (Morocco). The decrease was noted in Hong Kong (PCV-10 then PCV-13) – 62.8% in 2010–2014 to 13.8% in 2015–2017– [58], Israel (PCV-13) – 40.5% in 2004–2005 to 9.6% in 2015–2016– [61] and Morocco (PCV-13 then PCV-10) – 50.6% to 21.9% and 41.7% to 30.8% in children aged < 24 months and 24–59 months in 2007–2010 and 2011–2014, respectively– [59].

The Israeli study (PCV-13) reported a decline in NVT PNSP meningitis rates in children aged under five, from 33.3% to 10.4% ($p = 0.049$). Occurrence of PNSP meningitis in under-five children was reported in Mozambique (PCV-10) (88.2% in 2013–2014) [67], Oman (PCV-13) (62.9% in 2014–2016) (63), South Korea (31.1% in 2014–2016)[68], Italy (PCV-13) (17% in 2008–2014) in children aged 0–48 months [64], and in Switzerland (PCV-13) (17.4% in 2004–2014) in children aged 0–59 months (66).- However, PNSP rates from before PCVs.

200 introduction were not provided.

Upward trends in PNSP were reported in Belgium (PCV-13 then PCV-10) for all serotypes, where PNSP meningitis rates almost doubled in the span of 3 years after the switch from PCV-13 to PCV-10 in 2015 ($p = 0.02$) (11.8% in 2015–2016 to 20.4% in 2017–2018) in children aged 0–30 months.(60). During the study period, serotype 24 A was the most resistant serotype (PNSP meningitis rate: 76.9%), followed by 24B (40%) and 19A (23.5%).

3.4. PNSP non-meningitis trends in children under five

After the implementation of PCV-10/13 in the National Immunization Program (NIP) of Hong Kong (PCV-10 then PCV-13), there was a decline in PNSP non-meningitis rates among children aged under five from 10.5% in 2010–2014 to 3.4% in 2015–2017. In France (PCV-13), non-meningitis PNSP rates in children aged < 23 months dropped from 35.5% in 2008–2009 (PCV-7 period) to 23.9% in 2011–2012, 2 years after the introduction of PVC-13. During the four years study period, a 43% decline in serotype 19A PNSP non-meningitis rates in children < 23 months was estimated in France (70.8% in 2008–2009 to 40.5% in 2011–2012) and a decrease in PNSP rates of NVT serotypes 15, 35B and 24F was reported in these children from 2008 to 09 to 2011–2012. These serotypes accounted collectively for nearly two-fifths (37.8%) of all PNSP non-meningitis strains in young children in France. Serotype 15 and 35B non-meningitis PNSP rates of dropped from 100% to 79% and 50%, respectively, while decline in serotype 24F non-meningitis PNSP did from 28% to 23%.

In contrast to the reported decline in serotype 19A PNSP non-meningitis rates in France, a ten-fold increase in serotype 19A PNSP non-meningitis rates in children aged under five was observed in Brazil (PCV-10) after PCV-10 implementation, from 3.2% in 2005–2009 to 31.6% in 2016–2017 together with an estimated 19A multidrug resistance of 79.1% [62].

The studies conducted in Italy (PCV-13), Ontario (Canada) (PCV-13) and Switzerland (PCV-13) provided non-meningitis PNSP rates after the implementation of PCV-13 only. The Italian surveillance study reported that 21% non-meningitis PNSP in children aged 0–48 months based on pneumococcal meningitis breakpoints MIC > 0.06. Lower rates were published by the Swiss and the Ontarian studies, (1.5% and 8.5% respectively, which assessed non-meningitis isolates using non-meningitis breakpoints MIC > 2).

3.5. Resistance of NVT serotypes

Declines in NVT PNSP rates were reported by both the Israeli study (PCV-13) and the French study (PCV-13) [57,61]. In Israel, figures declined from 33.3% (pre-PCV period) to 10.4% (PCV-13) in children under the age of five [61]. In France, serotypes 15A 35B and 24F accounted for 37.8% of all PNSP strains in children under the age of two after vaccination with PCV-13 [57]. The resistance of these serotypes decreased from 100% to 79%, 100% to 50%, and 28% to 23% respectively.

In Italy PNSP strains in the pre-PCV-13 period were mainly associated with PCV-13 serotypes, meanwhile after the widespread routine immunization with PCV-13, PNSP strains were mostly of NVT origin in 2014 mainly: 15A, 23B and 24F according to the published data [64].

3.6. IPD surveillance systems in the included studies

The IPD surveillance systems of the studies included in this review were heterogeneous. Of the 12 studies included, 5 (41.6%) countries implemented nationwide IPD laboratory-based surveillance, namely: Oman (PCV-13), Italy (PCV-13), France (PCV-13), Belgium (PCV-13 then PCV-10/ passive surveillance) and Brazil (PCV-10/ passive surveillance). Under this kind of surveillance, data were collected from regional laboratory references and health institutions from different locations within the country [57,60,62–64]. Regional laboratory-based surveillance systems were implemented in Mozambique (PCV-10/ Sentinel surveillance of pediatric meningitis), Hong Kong (PCV-10 then PCV-13), Casablanca (Morocco) (PCV-13 to PCV-10) and Ontario (Canada) (PCV-13) [58,59,65,67]. Population based surveillance was only conducted in Israel (PCV-13) and Switzerland (PCV-13) (16.66%). This surveillance system links laboratory findings to demographic and clinical data [61]. All included studies provided a detailed description of the implemented IPD surveillance system, with the exception of South Korean study (PCV-13) that didn't mention any information of the established surveillance system of IPD [68].

4. Discussion

This systematic review analyzed currently available studies on IPD PNSP rates prior to and after the implementation of PCV-10/-13 in children aged under five. Our results indicate different country PNSP trends and variations in IPD surveillance, data collection and analysis, PCV introduced and time of use, isolates (meningitis or non-meningitis) and MIC breakpoints. The six included studies that provided data prior to and after the introduction of PCV-10/13 in children under five reported a significant decline in PNSP meningitis and PNSP non-meningitis rates in children vaccinated with PCV-13, such as 78.03 % decline in 2010–2017 in Hong Kong (PCV-13) [58], 76.3% decline in 2004–2016 in Israel(PCV-13) [61] and 32.68% decline in 2008–2012 in France (PCV-13) [57] or, in the case of Morocco (PCV-13 then PCV-10), when only a part of children under the age of five had been vaccinated with PCV-13 prior to the switch to PCV-10, a 56.72% decrease was reported in children aged under 24 months and a 26.14% decline in children aged 24–59 months [59].

An increase in PNSP rates was observed in PCV-10 settings, namely Belgium and Brazil (serotype 19A), where figures increased throughout the study period by two-folds and ten-folds, respectively [60,62].

Resistance of pneumococcal serotypes to antimicrobial agents has been a major concern before and after the introduction of PCVs in children under 5 years of age [69]. After the first introduction of

PCV-7 in France, Spain (Navarre), United Kingdom, the United States, and Australia, an initial decrease in resistance to penicillin and other antibiotics was followed by a rise in PNSP rates in under five children, mainly serotype 19A [37,38,41,42,44,45,47,70,71]. This increase appeared to be more marked in countries with high antibiotic consumption, which offered a selective ecological advantage for the expansion of this serotype [40,72]. Interestingly, a similar effect has been described lately in countries where PCV-10 had been introduced. In Chile where PCV-10 was introduced in 2011, the Immunization Advisory Committee of the Chilean Society of Infectious Diseases reported that 100% of serotype 19A pneumococcal meningitis strains in 2014 were resistant to penicillin, and that serotype 19A accounted for a quarter of all IPD cases reported in fully vaccinated children ≤ 2 years old, along with the fact that nearly 25% of pneumococcal non-meningitis infections were resistant to penicillin [73]. In response to these disquieting data, the Chilean Immunization Advisory Committee called for a transition to PCV-13 to manage the 19A serotype resistance outbreak [73]. Likewise, New-Zealand shifted from PCV-10 to PCV-13 in response to the increasing numbers of IPD cases due to this highly resistant and invasive serotype 19A [74]. This is in line with findings by the Brazilian laboratory-based passive surveillance system, which notified a dramatic surge in the resistance of serotype 19A in children under five after PCV-10 introduction in 2010, from 3.2% in 2004 to 31.6 % in 2017 [62]. Serotype 19A PNSP rates increased ten-fold in Brazil among this population, and later serotype 19A was the most multidrug-resistant serotype after the PCV-10 era [62].

On the other hand, downward resistant serotype 19A trends are observed in countries that introduced PCV-13, as PCV-13 has proved to be effective against this serotype [8,74–76]. France (PCV-13) showed a 30 percent points decrease on serotype 19A PNSP rates in under five children after 90% coverage of PCV-13 vaccination was achieved [57]. Continuous robust surveillance of the evolution of serotype 19A resistance in children under five is therefore necessary in France and other countries to monitor the effective impact of PCV-13 on further decrease of PNSP strains related to serotype 19A.

The perpetual emergence of highly invasive NVT serotypes features a major source of concern after the widespread vaccination with PCVs [12,14]. Upward trends of serogroup 24 resistance were reported by the Belgian (PCV-10 then PCV-13) surveillance study in children aged 0 to 30 months where figures almost doubled in 3 years (from 40% to 76.9%), which is a serious concern as the serotypes part of this serogroup have been proved to be highly invasive. According to the findings of a 2018 *meta*-analysis, NVT serotypes 24F, 8, 12F, and 33F were at the upper end of the invasiveness spectrum [14,60]. Other highly invasive NVT serotypes were frequently isolated in Belgian children hospitalized with IPD (12F, 19A, 10A and 33F). Serotype 24F was as well prevalent in French children (PCV-13) aged ≤ 2 years along with serotype 15A and 35B, similar to what was reported by the Italian national surveillance system (PCV-13) (serotypes 15A and 24F) [64]. In Italy, there was a nearly complete replacement of resistant serotypes after the introduction of PCV-13 [64]. In 2008, all penicillin resistant isolates belonged to serotypes PCV-13, while in 2014 resistant strains were mostly NVT serotypes, namely: 15A, 23B and 24F [64].

In South Korea (PCV-13), the most resistant serotypes in children under 5 years were 11A, 19A, 15A 19F, 23A, 15B, 13 and 6A [68]. In Switzerland (PCV-13), between 2004 and 2014, the four serotypes with the lowest penicillin susceptibility profile were VT serotypes 19A, 19F, and 14 [66]. In Mozambique (PCV-10), the most resistant serotypes were primarily PCV-13 serotypes 1, 3, 4, 6B, 14 and 23F in children under 5 years old [67]. However their specific PNSP rates were not published.

Regarding IPD surveillance, there is a need for a thorough and comprehensive description of the surveillance system used to collect data on IPD in future studies according to the WHO IPD surveillance systems classification (Sentinel hospital surveillance for meningitis, expanded sentinel hospital surveillance of all IPD, or population-based surveillance of all IPD) while specifying the methodology of data collection (prospective or retrospective) [77]. This will guide future estimations of the relative bias and the reliability of the published data. In the present review, only Israel (PCV-13) and Switzerland (PCV-13) dispose of a population-based surveillance system which links laboratory findings to demographic data, which is regarded as a more robust system [61,66,77]. While laboratory-based surveillances can provide pertinent data on the epidemiological situation of *S.pneumoniae*, it might be affected by under-reporting of IPD cases especially when notification of IPD is not mandatory or limited to certain regions of the country [78]. This was the case in the included studies from Oman (PCV-13), Italy (PCV-13), Morocco (PCV-13 then PCV-10), Mozambique (PCV-10) and Ontario (PCV-13) (Canada) [59,63–65,67]. The authors of the Omani surveillance study in fact mentioned IPD under-reporting from hospitals a possible limitation to their study along with the refusal of certain patients to perform lumbar punctures to collect CFS samples [63]. Under-reporting might also have affected the study from the Italian national laboratory-based surveillance that included data from five Northern Italian regions only, sites that have been consistent in their reporting of IPD cases [64]. Similarly, the reporting of IPD cases to the central laboratory in Casablanca, Morocco, and Ontario, Canada is underperformed as IPD notification is not mandatory [65].

Another inherent limitation to the laboratory-based surveillance is the discrepancies in the identification and reporting of IPD cases which might result in heterogeneous results adding to the absence of data concerning patients' immunization status and past antibiotics intake [78].

The IPD case definition, the length of IPD surveillance in relation to the introduction of PCV-10/13, and the number of the reported IPD isolates that underwent penicillin susceptibility testing are important factors that condition the quality of the reported findings. In the included study from Mozambique (PCV-10), the implemented sentinel surveillance only reports cases of pediatric pneumococcal meningitis at two regional referral hospitals [67]. IPD surveillance in Mozambique started only when PCV-10 was introduced; therefore, PNSP rates prior to the introduction of PCV-10 were not available. These factors combined with the limited number of collected isolates may affect the estimation of real PNSP rates [67]. For example, in Morocco (PCV-13 then PCV-10), a regional laboratory-based surveillance is implemented in the city of Casablanca since 1994, the gathered data give insight on the epidemiological impact of PCVs on the decline of PNSP strains in Casablanca, nonetheless, these findings cannot be extrapolated to the whole Moroccan pediatric populations aged under 5 years [59]. The study from South Korea (PCV-13), on the other hand, did not publish any data related to IPD surveillance, which makes the evaluation of the impact of PCVs on penicillin resistance incomplete [68]. Thereby, it is highly desirable that future studies comprehensively describe the implemented surveillance system and the methodology used in the extraction of data.

The aforementioned limitations in IPD surveillance depict the need of IPD surveillance and antibiotic resistance monitoring strengthening. Key to the improvement of IPD surveillance is to make IPD notification mandatory by law. Additionally, a common electronic database that encompasses clinical data, laboratory findings, immunization status, and demographic information could help inform immunization-related decisions

and make official clinical treatment guidelines drafting more efficient, all in consideration of the IPD epidemiological context. Ideally, a population-based IPD surveillance system that pools data from several surveillance sites at the national level could provide with more reliable estimates of the effect of PCVs on the evolution of the resistance of PNSP strains over time [78–80]. Furthermore, conclusions relating to the published data on PNSP rates in children should be drawn with caution given the discrepancies in antimicrobial resistance surveillance guidelines and the lack of globally agreed laboratory standards— currently, different terminologies are used when referring to antibiotic resistance.

Our findings provide insights into the importance of IPD PNSP surveillance before and after routine immunization with PCV-10/13 to assess pneumococcal conjugate vaccines potential impact on PNSP rates in children under the age of five. The present review has several potential limitations due to the lack of relevant data regarding the determinants of antibiotics resistance. Indeed, while comparing penicillin resistance reported by each surveillance site, we did not find information regarding the level of antibiotic consumption nor the prescription practices in both community and hospital settings, which might affect estimation of the effect of PCV-10/-13 on PNSP rates. In addition, comparing the results of antimicrobial resistance between countries should be done with caution while taking into consideration the heterogeneity in laboratory methods and guidelines used to evaluate the level of penicillin non-susceptibility in pneumococcal isolates. Moreover, low and middle income (LMIC) countries were underrepresented in this study as the number of published articles from these settings was limited [81]. Of particular note, 50% of the included studies did not publish resistance levels prior to the implementation PCV-10/13 in children aged <5 years, which makes the estimation of the effect of PCVs on penicillin resistance more biased. Finally, as all the studies included in this systematic review presented various vaccination schedules and different resistance breakpoints, we were not able to conduct a meta-analysis and pool indicators linked to penicillin resistance.

To our knowledge, this is probably the first systematic review to assess the impact of PCV-10 and PCV-13 on PNSP IPD rates. We included surveillance-based studies that met our pre-defined inclusion criteria, which may have provided a relevant update on the epidemiological evolution of the course of *S. pneumoniae*'s penicillin resistance in children aged under 5 years.

5. Conclusion

The efficacy of PCVs currently used in children under 5 years of age is threatened by the emergence of invasive and resistant non-vaccine serotypes worldwide. Further studies on the epidemiological evolution of PNSP strains are much needed in order to assess the benefits of PCVs on the occurrence of penicillin resistance in IPD in children under the age of five.

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Author's contributions

HS designed the study and wrote all the versions of the manuscript. IJ led the study protocol, revised each draft, and approved the final manuscript. MBG did a critical revision of the article and approved the final version of the manuscript. CM revised the final version of the manuscript and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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