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Effects of PCV10 and PCV13 on pneumococcal serotype 6C disease, carriage, and antimicrobial resistance

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ABSTRACT

Background: The cross-protection of pneumococcal conjugate vaccines (PCV) against serotype 6C is not clearly documented, although 6C represents a substantial burden of pneumococcal disease in recent years. A systematic review by the World Health Organization that covered studies through 2016 concluded that available data were insufficient to determine if either PCV10 (which contains serotype 6B but not 6A) or PCV13 (containing serotype 6A and 6B) conferred protection against 6C.

Methods: We performed a systematic review of randomized controlled trials and observational studies published between January 2010 – August 2022 (Medline/Embase), covering the direct, indirect, and overall effect of PCV10 and PCV13 against 6C invasive pneumococcal disease (IPD), non-IPD, nasopharyngeal carriage (NPC), and antimicrobial resistance (AMR).

Results: Of 2548 publications identified, 112 were included. Direct vaccine effectiveness against 6C IPD in children ranged between 70 and 85 % for ≥ 1 dose PCV13 (n = 3 studies), was 94 % in fully PCV13 vaccinated children (n = 2), and −14 % for ≥ 1 dose of PCV10 (n = 1). Compared to PCV7, PCV13 efficacy against 6C NPC in children was 66 % (n = 1). Serotype 6C IPD rates or NPC prevalence declined post-PCV13 in most studies in children (n = 5/6) and almost half of studies in adults (n = 5/11), while it increased post-PCV10 for IPD and non-IPD in all studies (n = 6/6). Changes in AMR prevalence were inconsistent.

Conclusions: In contrast to PCV10, PCV13 vaccination consistently protected against 6C IPD and NPC in children, and provided some level of indirect protection to adults, supporting that serotype 6A but not 6B provides cross-protection to 6C. Vaccine policy makers and regulators should consider the effects of serotype 6A-containing PCVs against serotype 6C disease in their decisions.

1. Introduction

Streptococcus pneumoniae serogroup 6 was initially considered to include only serotypes 6A and 6B, which were distinguished using specific antiserum factors in the Quellung reaction [1]. In 2007, a new serotype within the serotype 6 group, named 6C, was discovered using monoclonal antibodies [2]. Serotype 6C differs in its genetic capsular locus and carbohydrate structure from serotype 6A, i.e., by one variation in the *wciN* gene and by the orientation of a single hydroxyl group of one of the repeating unit monosaccharide building blocks [1,3]. The antisera used at the time for the Quellung reaction could not distinguish serotype 6C from 6A, leading to historic misclassification of serotype 6C isolates as 6A [3]. Retrospective laboratory studies have revealed that serotype 6C has circulated since at least 1979 [1,2]. Nowadays, serotype 6C is identified by specific polymerase chain reaction (PCR) or by an antiserum specific for serotype 6C (factor antiserum 6d) [1].

Pneumococcal conjugate vaccines (PCV) differ in which serogroup 6 serotypes they contain: PCV7 and PCV10 contain only serotype 6B while

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PCV13, PCV15 and PCV20 include both serotypes 6A and 6B. Based on minor antigenic differences between serotype 6A and 6B polysaccharides, it was anticipated that antibodies raised against 6B could provide cross-protection against 6A [2,4]. Post-authorization studies confirmed that PCV7 provided cross-protection against serotype 6A, but also demonstrated no cross-protection against 6C [3,5,6]. On the contrary, following PCV7 introduction, serotype 6C became one of the most frequent serotypes causing invasive pneumococcal disease (IPD), pneumococcal pneumonia, otitis media (OM)[7], and was commonly identified in the nasopharyngeal carriage from children and adults of many countries [1,8–16]. Pneumococcal isolates with a serotype 6C capsule are often non-susceptible to multiple antibiotics including penicillin, erythromycin, clindamycin, tetracycline, among others, with increasing occurrence of non-susceptibility post-PCV7 introduction in the US, France, Spain, and Portugal [1,14,17,18].

Despite the demonstrated ability of the 6B conjugate in PCV7 to cross-protect against serotype 6A, a 6A conjugate was included in the second generation PCV, PCV13, and post-authorization studies for PCV13 demonstrated protection against both serotypes [19,20]. Given that serotype 6A showed a high degree of antigenic relatedness to 6C, it was anticipated that immune responses elicited against this serotype could generate cross-reactive antibodies against serotype 6C [1]. Indeed, vaccination with PCV13 induced high levels of IgG and functional opsonic antibodies (OPA) against serotype 6C strains [21,22]. In contrast, PCV7 vaccination did not induce cross-reactive antibody and OPA response against 6C in the same studies [21,22]. Similar to the PCV7 experience, countries using PCV10 have documented increases in serotype 6C IPD, suggesting that the serotype 6B conjugate does not cross-protect against serotype 6C [23].

Through 2022, no randomized head-to-head studies have been conducted to evaluate the immune responses elicited by PCV10 and PCV13 against serotype 6C [24]. A systematic literature review from the World Health Organization (WHO) covered clinical trials and observational studies reporting pre- and post-introduction data published as of December 31, 2016, to assess the effects of pediatric use of PCV10 and PCV13 against serotype-specific disease (IPD and pneumonia) and colonization. At that time, the included studies presented data at most for the 3–4 years after PCV10 or PCV13 introduction, and the evidence for both PCV10 and PCV13 effects against serotype 6C was limited for IPD (for both children and adults), unavailable for pneumonia, and inconclusive for carriage. The evaluation did not include an assessment of PCV10 or PCV13 effects against serotype 6C OM. Consequently, the report concluded that the available data were insufficient to determine if either PCV10 or PCV13 conferred protection against serotype 6C [25].

In the analysis reported here, we re-evaluated the evidence on PCV10 and PCV13 effects against 6C disease up to mid-2022, allowing for additional evidence to accrue and time to pass since PCV10 and PCV13 introduction among children. We conducted a systematic literature review of the direct, indirect, and overall effects of PCV10 and PCV13 against serotype 6C invasive and non-invasive disease, nasopharyngeal carriage, and antimicrobial susceptibility.

2. Methods

This systematic literature review follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and is registered in the PROSPERO database (CRD42021225558). We included randomized controlled trials (RCT) and observational studies that provided data on the effect of PCV10 or PCV13 against serotype 6C invasive and non-invasive disease, carriage, and antimicrobial susceptibility. Direct vaccine effect was defined as the effect of the vaccine in vaccinated individuals and estimated by comparing disease occurrence in vaccinated and unvaccinated individuals exposed to the same vaccination program. Direct effect comprises vaccine efficacy (measured in RCT) and vaccine effectiveness (measured in observational studies) [26,27]. Indirect effect was defined as the population-level effects of reduced transmission due to widespread vaccination, and is measured by comparing disease occurrence in unvaccinated individuals from the population with a vaccination program to those unvaccinated in a population without a vaccination program [26,27]. Overall effect, often referred to as vaccine impact, is the effect of the vaccination program in the entire population, including vaccinated and unvaccinated individuals, and is estimated by assessing the occurrence of disease in populations with and without a vaccination program (most often measured before and after a vaccination program) [27]. We also included the changes in serotype 6C proportions before and after vaccine introduction, as a qualitative estimate of vaccination impact proposed by WHO [28].

2.1. Search methodology

We searched MEDLINE via PubMed and EMBASE for relevant articles published between 01 January 2010 (before the introduction of PCV10 and PCV13) and 31 May 2022. Reference lists from eligible articles and systematic reviews were also searched to identify other relevant studies. We used the Population-Intervention-Comparator-Outcomes-Time Frame-Setting (PICOTS) framework to define search terms, which covered PCV10 and PCV13 vaccines, *S. pneumoniae*, serotype, disease outcome and epidemiological indicator reported. Studies in English, French, Spanish, Portuguese, Dutch, German, and Italian were included. Details of the search strategy, inclusion and exclusion criteria are provided in the Supplements 1 and 2.

2.2. Study selection and data extraction

Retrieved articles were screened independently by two reviewers based on titles and abstracts, and discrepancies were solved by a third reviewer. Full-text screening was performed by one reviewer and a quality check of the screened articles was done by a second reviewer.

Data extracted included study description, population, vaccine effect measured, PCV exposure (PCV type, vaccine schedule, vaccine status or PCV period), pneumococcal outcome, laboratory methods for pneumococcus detection and serotyping, comparison (unvaccinated) group, and epidemiological indicator of vaccine effect. PCV program information of the target population was collected as well for impact studies. As quality check, re-extraction of 10 % of the papers was done by a second reviewer. All data were also individually checked for missing values and outliers (e.g., very low or very high frequency), study design, PCV type and vaccine effect by comparing to the original paper.

Five specific tools were developed according to the study design of the included studies, based on the Rob 2 Tool for RCT, the Newcastle-Ottawa Scale for cohort and case-control studies and the National Institute of Health (NIH) checklist for before-after and cross-sectional studies.

2.3. Data analysis

Data were summarized descriptively and stratified by type of PCV (PCV10 or PCV13), age group (overall defined as <18 years for children and ≥ 18 years for adults), type of vaccine effect (direct, indirect, overall/impact) and pneumococcal outcome. Outcomes were defined according to the authors and classified into IPD, non-IPD and any pneumococcal disease. IPD included overall IPD, meningitis, non-meningitis IPD, invasive pneumonia, empyema and bacteremia. Non-invasive disease included overall non-IPD, non-invasive pneumococcal pneumonia, acute otitis media (AOM), sinusitis and conjunctivitis. Invasive and non-invasive disease included overall pneumococcal disease, any pneumococcal pneumonia and any lower respiratory tract infections (LRTI).

For the direct effect, the adjusted VE was reported unless only crude VE was provided. The following measures were calculated when not provided by the study, when applicable:

- For the measure of direct effect, vaccine efficacy or vaccine effectiveness (VE) and the corresponding 95 % confidence interval (CI) were calculated using the relative risk (RR), odd ratio (OR) or hazard ratio (HR) reported in the articles as follows: VE = (1 − ratio) × 100.
- For the measure of indirect and overall effect, incidence rate ratio (IRR) and the corresponding CI 95 % were calculated from the incidence rates (IR) provided per period, as follows: IRR = IR post-PCV/IR pre-PCV.
- Serotype 6C serotype proportions were calculated by using the number of serotyped isolates as the denominator.

The temporal trends of serotype 6C IRR were calculated per year after PCV10 or PCV13 introduction, when more than one estimate post-introduction was available, and plotted over time. Statistical analyses were conducted using R.

3. Results

3.1. Study description

Of 2548 articles identified, 112 were eligible (Fig. 1, Supplement 3 and 4), including 7 studies on direct effect (3 on PCV10, 5 on PCV13, one on both), 20 studies on overall effect (6 on PCV10, 15 on PCV13, one on both), and 79 studies compared proportions before and after PCV10 or PCV13 introduction. A number of studies covered several age groups and pneumococcal outcomes, therefore the sum of studies per subgroup exceeds the total of 112. Studies were conducted in children (n = 97), adults (n = 56), and in subjects of any age (n = 41). Pneumococcal outcomes included invasive pneumococcal disease (IPD, n = 63), non-invasive disease (n = 12), invasive and non-invasive disease (not differentiated, n = 8), nasopharyngeal carriage (n = 40) and antimicrobial non-susceptibility (n = 21).

The assessment of study quality identified 77 of 112 studies (68 %) as having at least one risk of bias (Supplement 5), including studies with a high risk of bias in at least one domain (n = 53) and at least one

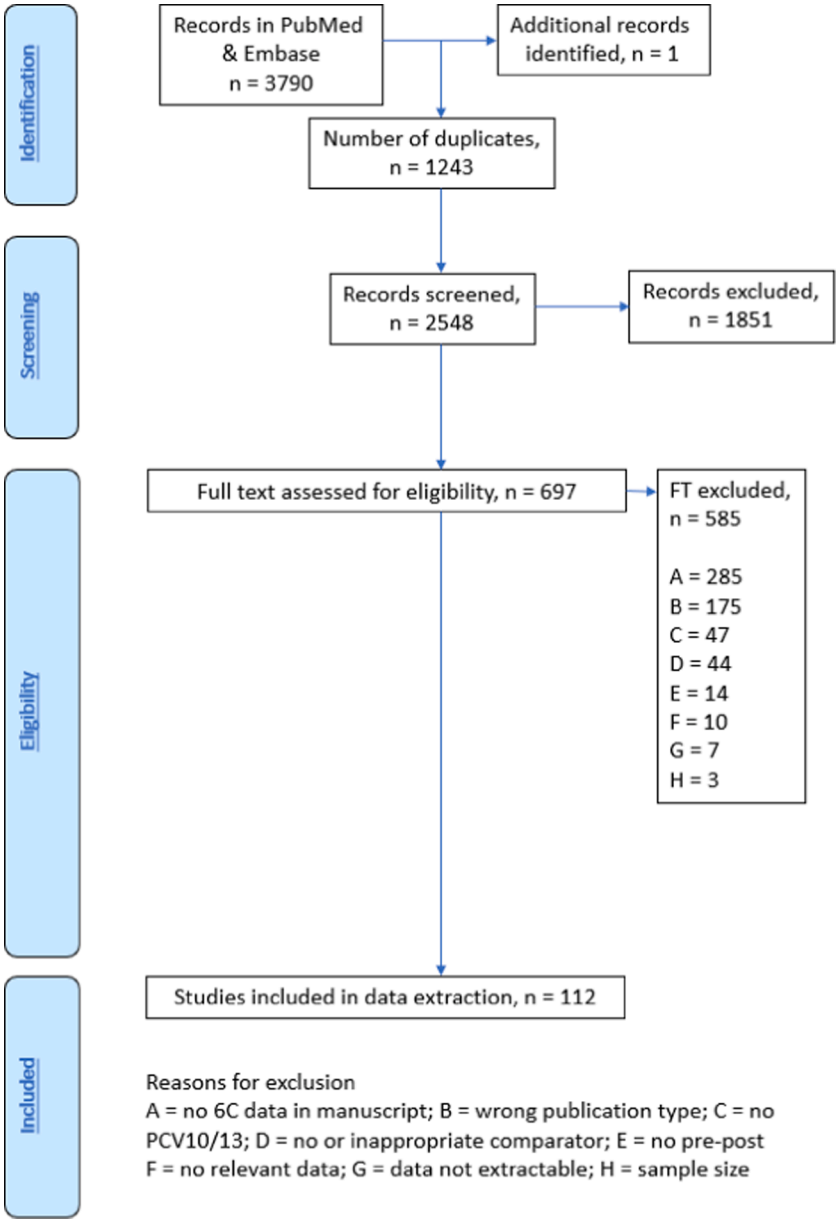

Fig. 1. PRISMA flow chart.

uncertainty (n = 24). Studies on direct effect, overall effect, AMR and 6C proportions presented at least one risk of bias in 43 %, 52 %, 69 % and 70 % of studies, respectively. No risk of bias was identified in all direct effect studies with IPD as outcome, regardless of the PCV assessed. At least one potential risk of bias was identified in all PCV10 overall effect studies, around half of PCV13 overall effect studies and in all nasopharyngeal carriage studies, regardless of vaccine and type of effect.

3.2. Direct PCV effect against serotype 6C disease and carriage

All studies measuring the direct effect of PCV10 and PCV13 against serotype 6C outcomes (n = 7) were conducted in children < 10 years of age.

3.2.1. PCV13

Among the studies estimating PCV13 direct effect (n = 5) against serotype 6C, one was an RCT, and all were conducted in children and three studies (Table 1A) reported consistent VE estimates ranging from 70 to 85 % for ≥ 1 dose to 94 % for full vaccination (either 2 or 3 infant doses followed by a toddler booster dose) [19,29,30]. We did not identify studies of direct effect against non-invasive disease. With regard to the effect against nasopharyngeal carriage of serotype 6C, one RCT in Israel showed that PCV13 vaccination provided an additional 66 % protection compared to PCV7 [31] and a cohort study comparing PCV13 and PCV10 vaccinees provided inconclusive point estimates with wide 95 % Cis [32].

3.2.2. PCV10

Among the studies estimating PCV10 direct effect (n = 3), two PCV10 effectiveness studies (Table 1B) reported no protection afforded by PCV10 against serotype 6C IPD (n = 1, [30]) or carriage (n = 1, [33]). One RCT reported that no additional protection against carriage was provided by PCV10 compared to PCV7 vaccination [34]. All point estimates were negative.

Table 1B
Direct efficacy/effectiveness of PCV10 vaccination against serotype 6C disease and carriage.

Country (region)	Study (author, year [reference])	Age	N PCV doses	Study design	VE in % (95 % CI)
Invasive pneumococcal disease (compared to non-vaccinated)					
Czech Republic, Netherlands, Spain (Catalonia), Finland.	Savulescu, 2022 [30]	2–19 mo	≥1 dose (s)	Indirect cohort method	−14 (−527 to 79)
Nasopharyngeal carriage (compared to non-vaccinated)					
Pakistan	Nisar, 2022 [33] ◊	0–2 y	3 doses	Cohort	−14
Nasopharyngeal carriage (compared to PCV7 or PCV10)[$]					
South Africa	Nunes, 2020 [34] ◊	6 wks – 27 mo	3 doses	Randomized controlled trial	−163

VE: Vaccine efficacy (RCT) or effectiveness (observational studies); 95% CI: 95% confidence interval; PCV10, and PCV7: 10-valent, and 7-valent pneumococcal conjugate vaccines, respectively; mo: months; wks: weeks; y: years. ◊: Crude VE calculated from prevalence provided by the publication; [$]: additional protection afforded by PCV10 compared to PCV7 vaccination, by comparing outcomes between PCV10 and PCV7 vaccinees.

3.3. PCV impact against serotype 6C disease and carriage

The PCV overall effect or impact in the population was measured in studies (n = 21) comparing disease incidence rates or carriage prevalence before and after PCV10 or PCV13 introduction. Table 2 describes incidence rates and IRRs comparing the last pre-PCV10 or PCV13 period to the last post-PCV10 or PCV13 period, per age and outcome.

Table 1A
Direct efficacy/effectiveness of PCV13 against serotype 6C disease and carriage.

Country (region)	Study (author, year [reference])	Age	N PCV doses	Study design	VE in % (95 % CI)
Invasive pneumococcal disease (compared to unvaccinated)					
United Kingdom (England)	Andrews, 2019 [19]	2.5 mo-9 y	≥1 dose(s)	Indirect cohort method	70 (2 to 92)
		4–12 mo	2 doses		82 (−103 to 98)
		4 mo-9 y	≥2 doses		78 (24 to 94)
		13 mo-9 y	2 + 1 doses		94 (65 to 99)
Australia	Jayasinghe, 2018 [29]	2–42 mo	≥1 dose(s)	Case control	80 (−100 to 98)
Czech Republic, Denmark, France, Ireland, Norway, Spain (Catalonia, Madrid, Navarra), United Kingdom (Scotland, England)	Savulescu, 2022 [30]	2–19 mo	≥1 dose(s) Fully vaccinated	Indirect cohort method	85 (62–94) 94 (68–99)
Nasopharyngeal carriage (compared to PCV7 or PCV10)[$]					
Israel	Dagan, 2013 [31] ∘	7–24 mo	3 doses (2, 4, 6 mo)	Randomized controlled trial	66 (29 to 73)*
Cyprus	Hadjipanayis, 2016 [32] ■	6–36 mo	≥1 dose	Cohort	41 (−56 to 77) **
			Partially vaccinated†		77 (−88 to 97) **
			Fully vaccinated		−22 (−345 to 67)**

VE: Vaccine efficacy (RCT) or effectiveness (observational studies); 95% CI: 95% confidence interval; PCV13, PCV10, and PCV7: 13-valent, 10-valent, and 7-valent pneumococcal conjugate vaccines, respectively; mo: months; y: years; [$]: additional protection afforded by PCV13 compared to PCV7 or PCV10 vaccination, by comparing outcomes between PCV13 and PCV7/PCV10 vaccinees; ∘ Crude VE calculated from incidence rate ratios provided by the publication; ■ Crude VE calculated from odds ratios provided by the publication; † Children were considered partially vaccinated for age if they had not completed the schedule for age according to the US Center of Disease and Control guidelines; * PCV13 vs. PCV7; ** PCV13 vs. PCV10.

3.3.1. PCV13

PCV13 impact differed across age and settings (n = 15). In studies involving children (n = 6), IRRs were mostly below 1, indicating a decline in serotype 6C IPD incidence rates or carriage prevalence [35–40], except in 2–4-year-olds in Australia (Table 2A). In IPD studies among adults (any adults or older adults, n = 10), 6C incidence rates showed diverging trends after PCV13 introduction. It mostly decreased in Australia [38], England and Wales [39], and the US (IRR < 1) [41], and increased in Spain [35,42,43], Israel [44], and Ireland [45]. In one US study, prevalence of serotype 6C carriage declined in all age groups [40]. In studies involving participants of any age, IRRs were mostly above 1 [35,37,38,46–50].

3.3.2. PCV10

Serotype 6C incidence rates increased post-PCV10 for all outcomes in all studies including for any IPD (n = 3, [37,51,52]), meningitis (n = 1, [53]), and pneumococcal LRTI cases (n = 1, [54]); no cases were detected in some age groups in Finland at any time point (Table 2B). IRRs of serotype 6C incidence ranged from 2 to 24 (or infinity where pre-PCV10 or PCV13 incidence was null). In Iceland, the point prevalence of nasopharyngeal carriage in children 1–6 years rose from 6.5 per 1000 before to 49.0 after PCV10 introduction [55].

3.3.3. PCV10 vs. PCV13

Fig. 2 shows the annual trends of serotype 6C IRR after PCV10 (dotted lines) and PCV13 introduction (full lines) from eight studies that

Table 2A
Serotype 6C disease incidence rates and carriage prevalence before and after PCV13 vaccination.

Country (region)	Study (author, year [reference])	Age	Pre-PCV period	IR (95 %CI)*	Post-PCV period	IR (95 %CI)*	IRR (95 %CI)
Children							
- Invasive pneumococcal disease							
Spain (Madrid)	Latasa, 2018 [35]	0–4 y	2008–2010	0.3	2013–2015	0.2	0.7
Spain, Catalonia	Martínez-Osorio, 2022 [36]	0–4 y	2007–2009	0.0	2012–2016	0.2	NC
Sweden	Naucler, 2017 [37]	0–4 y	2007–2009	0.2 (0.0, 1.7)	2013–2016	0.0 (0.0, 0.5)	0.0 (0.0, 13.0)
Australia	Jayasinghe, 2017 [38]	<2 y	2004–2011	0.9	2014	0.4	0.4 (0.0, 1.7)
Australia	Jayasinghe, 2017 [38]	2–4 y	2004–2011	0.4	2014	0.7	1.8 (0.5, 5.9)
Australia	Jayasinghe, 2017 [38]	5–14 y	2004–2011	0.2	2014	0.0	0.0 (0.0, 0.7)
UK (England and Wales)	Ladhani, 2018 [39]	0–4 y	2008–2010	NR	2016–2017	NR	0.8 (0.1, 4.0)
- Pneumococcal carriage							
US	Grant, 2016 [40]	0–4 y	2006–2007	NR	2011–2012	NR	0.3 (0.2, 0.6)∘
US	Grant, 2016 [40]	5–7 y	2006–2007	NR	2011–2012	NR	0.7 (0.2, 2.0)∘
Adults†							
- Invasive pneumococcal disease							
Israel	Regev, 2017 [44]	≥18 y	2009–2010	0.1	2014–2015	0.2	2.1
Spain	Camara, 2017 [42]	≥18 y	2008–2009	0.1	2012–2013	0.5	3.8
Spain	González-Díaz, 2020 [43]^||	≥18 y	2008–2009	0.1	2015–2016	0.2	1.2 (0.5, 2.8)
Spain (Madrid)	Latasa, 2018 [35]	5–59 y	2008–2010	0.1	2013–2015	0.1	0.7
Sweden	Naucler, 2017 [37]	5–64 y	2007–2009	0.0 (0, 0.1)	2013–2016	0.1 (0.0, 0.2)	∞ (0.7, ∞)
Australia	Jayasinghe, 2017 [38]	15–49 y	2004–2011	0.1	2014	0.1	0.7 (0.2, 1.5)
Australia	Jayasinghe, 2017 [38]	50–64 y	2004–2011	0.3	2014	0.3	0.9 (0.4, 1.7)
UK (England and Wales)	Ladhani, 2018 [39]	5–64 y	2008–2010	NR	2016–2017	NR	0.5 (0.2, 0.9)
- Pneumococcal carriage							
US	Grant, 2016 [40]	≥18 y	2006–2007	NR	2011–2012	NR	0.2 (0.1, 0.8)∘
Older adults							
- Invasive pneumococcal disease							
US	Baxter, 2020 [41]	≥50 y	2008–2010	1.4	2011–2018	0.7	0.5 (0.3, 0.7)
Spain (Madrid)	Latasa, 2018 [35]	≥59 y	2008–2010	0.5	2013–2015	0.7	1.2
Sweden	Naucler, 2017 [37]	≥65 y	2007–2009	0.5 (0.2, 1.3)	2013–2016	1.3 (0.9, 2.0)	2.7 (0.9, 8.3)
Ireland	Corcoran, 2017 [45]	≥65 y	2009–2010	0.4	2015–2016	1.3	3.3
Australia	Jayasinghe, 2017 [38]	≥65 y	2004–2011	1.7	2014	1.1	0.7 (0.4, 0.9)
UK (England and Wales)	Ladhani, 2018 [39]	≥65 y	2008–2010	NR	2016–2017	NR	0.5 (0.3, 0.7)
Any age							
- Invasive pneumococcal disease							
Canada	Vadlamudi, 2020 [46]	Any	2004–2010	0.0	2011–2015	0.2	6.1 (3.4, 11.9)
US	Bruce, 2015 [47]	Any	2005–2008	0.3	2010–2013	0.7	2.3
Spain (Catalonia)	Ciruela, 2018 [48]	Any	2006–2009	0.2	2010–2014	0.4	1.9 (1.4, 2.5)
Spain (Madrid)	Latasa, 2018 [35]	Any	2008–2010	0.2	2013–2015	0.2	1.1
Sweden	Galanis, 2016 [49]	Any	2009–2010	NR	2011–2014	NR	0.9 (0.4, 1.6)
Sweden	Naucler, 2017 [37]	Any	2007–2009	0.1 (0.0, 0.2)	2013–2016	0.3 (0.2, 0.4)	2.8 (1.0, 8.0)
Switzerland	Oyewole, 2021 [50]	Any	2008–2010	0.2	2017–2019	0.3	1.7
Australia	Jayasinghe, 2017 [38]	Any	2004–2011	0.4	2014	0.3	0.7 (0.5, 1)

IR: incidence rate; IRR: Incidence rate ratio; NC: non-computable; NR: not reported; PCV: pneumococcal conjugate vaccines; UK: United Kingdom; US: United States of America; y: years; 95 % CI: 95 % confidence interval. * Incidence reported as per 100,000 person years; ∘ prevalence ratio (not IRR). † We categorized as adults any age group starting from 5 years and above and including subjects 18–49 years of age.^The 6 hospitals reported are from 3 regions (Madrid, Catalonia, and Basque country), with PCV13 uptake ranging from 50 to 92 % in 2012–13. ||Reported results from the same study population as Camara et al., 2017 but post-PCV13 is reported at a later time period.

Table 2B
Serotype 6C disease incidence rates and carriage before and after PCV10 vaccination.

Country	Study (author, year [reference])	Age	pre-PCV Period	IR (95 %CI)*	Post-PCV Period	IR (95 %CI)*	IRR (95 %CI)
Children							
- Invasive pneumococcal disease							
Sweden	Naucler, 2017 [37]	0–4 y	2007–2009	0.0 (0.0, 0.2)	2013–2016	0.9 (0.3, 2.4)	∞ (0.6, ∞)
Finland	Polkowska, 2021 [53] ■	0–4 y	2004–2010	0.0	2011–2017	0.1	NC
Finland	Polkowska, 2021 [53] ■	5–17 y	2004–2010	0.0	2011–2017	0.0	NC
Netherlands	Peckeu, 2020 [51]	0–4 y	2009–2011	0.1	2018–2019	0.2	2
- Pneumococcal carriage							
Iceland	Quirk, 2018 [55]	1–6 y	2009–2011	650	2012–2017	4900	7.5 ∘
Adults†							
- Invasive pneumococcal disease							
Sweden	Naucler, 2017 [37]	5–64 y	2007–2009	0.0 (0, 0.1)	2013–2016	0.3 (0.2, 0.4)	∞ (2.6, ∞)
Finland	Polkowska, 2021 [53] ■	18–49 y	2004–2010	0.0	2011–2017	0.0	NC
Finland	Polkowska, 2021 [53] ■	50–64 y	2004–2010	0.02	2011–2017	0.04	3.0 (0.4, 60.6)
- Invasive and non-invasive pneumococcal disease							
Iceland	Quirk, 2019 [54] #	≥18 y	2009–2011	0.6	2015–2017	7.5	12.5
Iceland	Quirk, 2019 [54] #	18–64 y	2009–2011	0.0	2015–2017	4.5	NC
Older adults							
- Invasive pneumococcal disease							
Sweden	Naucler, 2017 [37]	≥65 y	2007–2009	0.2 (0.0, 1.0)	2013–2016	4.6 (3.6, 5.7)	22.3 (4.7, 105.4)
Finland	Polkowska, 2021 [53] ■	≥65 y	2004–2010	0.0	2011–2017	0.1	2.4 (0.6, 16.7)
- Invasive and non-invasive pneumococcal disease							
Iceland	Quirk, 2019 [54] #	≥65 y	2009–2011	3.8	2015–2017	21.6	5.7
Any age							
- Invasive pneumococcal disease							
Sweden	Naucler, 2017 [37]	Any	2007–2009	0.1 (0.0, 0.2)	2013–2016	1.2 (1.0, 1.5)	24.1 (5.0, 115)
Finland	Polkowska, 2021 [53] ■	Any	2004–2010	0.0	2011–2017	0.1	4.9 (1.6, 20.9)
Netherlands	Vestjens, 2019 [52]	Any	2009–2011	0.2	2016–2018	0.5	2.5

IR: incidence rate; IRR: Incidence rate ratio; NC: non-computable; PCV: pneumococcal conjugate vaccines; y: years; 95% CI: 95% confidence interval.
*Meningitis, incidence reported per 100,000 person years; ∘ prevalence ratio (not IRR); †: we categorize as adults any age group starting from 5 years and above and including subjects 18–49 years of age. # LRTI: lower respiratory tract infection

provided estimates for more than one post-introduction period, including IPD (n = 7) and pneumococcal LRTI (n = 1). In children, serotype 6C IRR declined in Australia (PCV13) and increased in the Netherlands (PCV10). In adults and in the total population (any age), serotype 6C IRR declined in Australia and England (PCV13), fluctuated over time in Spain, Israel, and Switzerland (PCV13) and increased in Ireland (PCV13) and Iceland (PCV10).

3.4. Changes in serotype 6C proportions

Changes in the proportion of serotype 6C (among all typed strains) before and after PCV10 or PCV13 introduction were reported or could be calculated from 79 studies (Supplement 6).

3.4.1. PCV13

No consistent trend could be identified among the 87 studies describing the proportion of different outcomes due to serotype 6C before and after PCV13 introduction (Supplement 6A) among IPD (n = 44), non-IPD (n = 15), any pneumococcal disease (n = 4), and carriage (n = 24). For instance, in children, the proportion of IPD due to serotype 6C tended to decline after PCV13 introduction in Australia, Israel, and Japan and to increase in Spain. In France, England and Wales, and the US, the 6C proportion increased in some studies or analyses and declined in others. Diverging trends were also observed for any pneumococcal diseases and carriage, and in adults.

3.4.2. PCV10

In the 14 studies comparing changes in the proportion of different outcomes due to serotype 6C before and after PCV10 introduction (Supplement 6B) for IPD (n = 7), non-IPD (n = 2) and carriage (5), the proportion of 6C increased in all studies and age groups with two exceptions (carriage in Israel and IPD in Brazil, any age).

3.5. Changes in serotype 6C antimicrobial non-susceptibility

Changes in the proportion of serotype 6C strains that were non-susceptible before and after PCV10 or PCV13 introduction were reported in 12 studies. Non-susceptibility to penicillin and macrolides are described in Table 3.

3.5.1. PCV13

The proportion of penicillin and macrolide non-susceptible strains among 6C isolates (Table 3A) did not show consistent changes pre- and post-PCV13 in the studies on IPD (n = 6, [45,56,5713,5815]), non-IPD (n = 4, [15,59–61]), any pneumococcal disease (n = 1, [62]) and carriage (n = 2, [13,63]) in any of the age groups, as it declined in some studies and increased in others. Multidrug resistance of serotype 6C tended to decline between pre-PCV13 and post-PCV13 periods from 38 % to 18 % in France [13], similar proportions were reported from the US (36 % versus 33 %) [62].

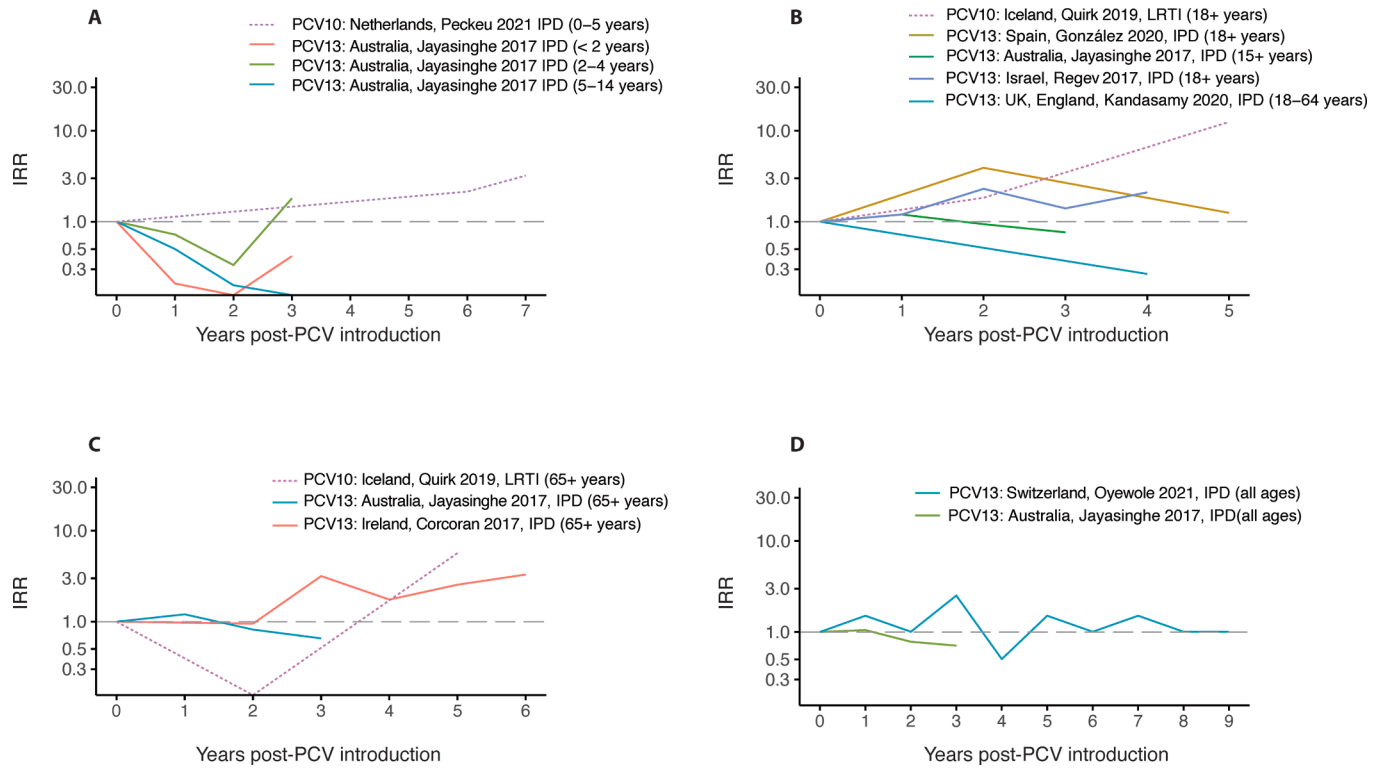

Fig. 2. Incidence rate ratios of serotype 6C (log_{10} vertical axis) comparing incidence before and after introduction of PCV10 and PCV13, over time after introduction. IRR: incidence rate ratios. Based on studies reporting more than one post-PCV10 or PCV13 period estimate. For periods including several years, the mid-period point is used for x-axis. A: PCV10 or PCV13 vaccination in children aged < 14 years. B: PCV10 or PCV13 vaccination in adults aged 15 + years. C: PCV10 or PCV13 vaccination in adults aged 65 + years. D: PCV13 vaccination among all ages.

3.5.2. PCV10

The two studies comparing pre- and post-PCV10 non-susceptibility among 6C isolates were both from Iceland (Table 3B) and did not report macrolide non-susceptibility. The proportion of serotype 6C carriage strains that were penicillin non-susceptible (PNSP) and multidrug resistant remained stable [55]. In LRTI [54] and AOM [55] studies, only one isolate was reported in the pre-PCV10 period for each. The proportions of PNSP and multidrug resistant 6C reached high levels in the post-PCV10 period (36–46 % and 64–73 %, respectively).

4. Discussion

Our systematic review found a consistent high direct effectiveness of PCV13 vaccination of children against serotype 6C IPD and efficacy against 6C carriage compared to PCV7 vaccination. By contrast, studies of PCV10 provided no evidence for effectiveness against serotype 6C IPD and carriage. Serotype 6C disease and carriage rates consistently declined in children after PCV13 introduction, had diverging trends in adults, and consistently increased after PCV10 introduction in all age groups. No consistent changes were observed in the proportion of different outcomes due to serotype 6C or the prevalence of antimicrobial resistance associated with serotype 6C after either PCV10 or PCV13 introduction.

This review, mostly based on observational studies, fills a gap in the knowledge on PCV13 protection against serotype 6C that could not be assessed at the time of the WHO systematic literature review. This serotype was not included as a separate clinical outcome in the pre-licensure trials, and at that time, the potential cross-protection from PCV13 against disease was unclear. The WHO systematic literature review stated that data were insufficient to conclude that either PCV10 or PCV13 has an effect on serotype 6C disease, based on available data up to May 2017 [25]. Yet the WHO recommendation on PCV choice stated that countries with a substantial occurrence of serotype 6C disease might achieve some incremental benefit through the use of PCV13 rather than PCV10 [64]. In our review, we show that PCV13 effectiveness against serotype 6C IPD is as at least as high as the effectiveness against IPD due to the aggregate vaccine serotypes: PCV13 effectiveness of full vaccination against PCV13 serotypes was 63 % (-6 to 87 %) in England and 89 % (83 to 93 %) in a multicenter EU study, as compared to 94 % (65 to 99 %) and 94 % (68 to 99 %) against serotype 6C, respectively [19,30]. Similarly, effectiveness of at least one PCV13 dose against serotype 6A was 72 % (-24 to 94 %) in England, as compared to 70 % (2 to 92 %) against 6C in the same study.

PCV13 direct protection against serotype 6C and PCV13 impact in children, the majority of whom were vaccinated, were consistent across studies. However, evidence for indirect PCV13 protection (estimated by the impact in non-vaccinated groups) in adults was not consistent across studies, as 6C disease incidence rates and carriage prevalence decreased post-PCV13 in some countries and increased in others. However, greater heterogeneity of indirect effects may be expected, as disease rates in unvaccinated populations are not only dependent on vaccine effectiveness but also other factors related to vaccine use (such as vaccine uptake, catch up-campaigns); factors related to disease transmission (contact patterns, selection pressure from antimicrobial use); and changes in population characteristics (prevalence of at risk conditions, average age increasing within an age strata such as 65 years and older). Consequently, true indirect effects due to PCV13 likely are best evaluated for adults in countries with rapid transition from PCV7 to PCV13 programs as well as higher uptake such as England and Australia than in countries with later or slow transition from PCV7 to PCV13 or a lower uptake (Spain, Israel, and Ireland). The former countries have shown consistent declines in serotype 6C among unvaccinated age cohorts [27,28]. Indirect effects of PCV13 vaccination against 6C are also supported by reductions in carriage acquisition in children. An RCT from Israel that randomized children to either PCV13 or PCV7 demonstrated a PCV13 efficacy of 66 % against 6C nasopharyngeal carriage acquisition [31].

Table 3A
Proportions of serotype 6C isolates that are non-susceptible to penicillin or macrolides, by PCV13 vaccination period.

Country, author, year [reference]	Age	Clinical presentation	Pre-PCV period	Post-PCV period	Penicillin (%)		Macrolides (%)*	
					Pre	Post	Pre	Post
Children								
- Pneumococcal carriage								
France, Janoir, 2014 [13] ◊	6–23 mo	Any	2008–2009	2010–2011	37.8	33.0	57.8	76.1
Adults								
- Non-invasive pneumococcal disease								
US, Mendes, 2015 [59] ■¥	≥18 y	Overall	2009	2012	0.0	0.0	53.3	50.0
Japan, Shoji, 2015 [60] ¥	Adults	LRTI	2006	2012	25.0	23.1	NR	NR
Older adults								
- Invasive pneumococcal disease								
France, Alari, 2016 [56]	≥65 y	Meningitis	2007–2009	2012–2014	33.3	40.0	NR	NR
Ireland, Corcoran, 2017 [45] ¥	≥65 y	Overall	2009–2010	2015–2016	0.0	0.0	NR	NR
Spain, Fernandez-Chavez, 2021 [57] °◊	≥59 y	Overall	2007–2009	2011–2016	5.4	1.4	NR	NR
Any age								
- Invasive pneumococcal disease								
France, Janoir, 2014 [13] ◊	Any	Overall	2008–2009	2010–2011	50.9	23.1	78	78.0
US, Mendes, 2014 [58] ◊¥	Any	Overall	2008	2011–2012	NR	1.5	66.7	56.1
US, Richter, 2013 [15] ¥	Any	Overall	2008–2009	2010–2011	35.1■	40.0 ■	NR	NR
- Non-invasive pneumococcal disease								
US, Richter, 2013 [15] ¥	Any	Overall	2008–2009	2010–2011	58.7	55.8	NR	NR
Taiwan, Su, 2015 [61] ¥	Any	Overall	2012	2014	80.0	100.0	NR	NR
- Any pneumococcal disease (invasive and non-invasive)								
US, Richter, 2014 [62] ¥	Any	Overall	2008–2009	2012–2013	52.5	53.2	NR	NR
- Pneumococcal carriage								
US, Plumb, 2020 [63] ¥	Any	Any	2008–2011	2012–2015	22.3	37.8	NR	NR

CLSI: Clinical and Laboratory Standards Institute, EUCAST: European Committee on Antimicrobial Susceptibility Testing; NR: not reported; NS: non-suspectible; PNSP: penicillin non-susceptible pneumococci; mo: months; y: years; PCV: pneumococcal conjugate vaccines; RTI: respiratory tract infections; * Erythromycin/clarithromycin; ■ Pneumococcus serotype 6C resistant to Ceftriaxone: 3.1%; ◊ EUCAST guideline; ¥ CLSI guideline.

Table 3B
Proportions of serotype 6C isolates that are non-susceptible before and after PCV10 vaccination.

Country, name, year [reference]	Age	Clinical presentation	Pre-PCV period	Post-PCV period	PNSP pre-PCV10 (%)	PNSP post-PCV10 (%)
Children						
Iceland, Quirk, 2018 [55]	0–6 y	Carriage	2009–2011	2012–2017	33.3	30.5
Iceland, Quirk, 2018 [55]	0–6 y	Acute otitis media	2009–2011	2012–2017	0.0	46.3
Adults						
Iceland, Quirk, 2019 [54]	≥18 y	LRTI	2009–2011	2015–2017	0.0	35.7

All studies followed the EUCAST guideline thresholds. y: years; LRTI: lower respiratory tract infections; PCV: pneumococcal conjugate vaccines; PNSP: penicillin non-susceptible pneumococci.

In the US, declines of serotype 6C IPD among adults are likely to be a combination of direct and indirect effects since routine PCV13 vaccination of all individuals age ≥ 65 years was recommended since 2014. Australia and some Spanish regions have also recently recommended the use of PCV13 in older adults but its direct effects against serotype 6C have not yet been reported.

Protection by PCV13 against serotype 6C was hypothesized due to the inclusion of 6A antigen, the structural and immunologic similarities between serotypes 6A and 6C and the induction of cross-reactive functional antibody by PCV13 vaccination [1]. In one US study, sera of PCV13 vaccinated children showed strong OPA responses to serotype 6C (96 % responders), while responses of PCV7 immune sera were low (22 % responders) [21]. Another study among American Indian children showed high levels of 6C OPA after PCV13 but not after PCV7 [22]. Consistent with the low titers of opsonic antibody induced by PCV7 vaccination, trends of increasing serotype 6C disease after the introduction of PCV7 suggest that antibodies raised against the serotype 6B antigen are not cross-protective. Moreover, serotype 6C acted as a replacement serotype in countries with PCV7 infant vaccination [1,3].

In contrast to what has been observed with PCV13, our study found that PCV10 childhood immunization had no effect on serotype 6C disease. In fact, countries that introduced these vaccines reported increases of pneumococcal disease caused by serotype 6C thereafter; similar to what was observed after PCV7 introduction [1]. As PCV10 was used during the same time period as PCV13, assessing the direct and overall effects of both PCVs helps to better understand the potential incremental protection offered by the addition of serotype 6A to the PCV13 formulation. For example, the effectiveness of ≥ 1 dose of PCV10 against 6C

was estimated at −14 % (-527 % to 79 %) by a multicenter EU study, as compared to 85 % (62 % to 94 %) for ≥ 1 dose PCV13 [30]. In older adults of Sweden, where the choice between PCV10 and PCV13 vaccination was made at the county level, serotype 6C IPD rates increased more in PCV10 counties (IRR = 23.4) than in PCV13 counties (IRR = 2.7) between 2007 and 2009 and 2013–2016 [37].

A strength of our systematic review is the inclusion of 112 primary studies describing PCV10 or PCV13 effect against serotype 6C, various clinical outcomes (invasive and non-invasive disease, antibiotic non-susceptibility and carriage) and the analysis of different vaccine effects (direct, indirect, and overall). Another strength is that the manuscript was drafted with the critical domains of the AMSTAR2 guidelines in mind to facilitate quality appraisal of this SLR [65]. However, some limitations should be considered when interpreting our results. Most included studies were observational and therefore prone to biases and confounding factors, including ecological biases for impact studies. We attempted to limit this problem by providing adjusted VE values and IRRs when available. Study populations may also have differed in the level of antimicrobial resistance and antibiotic use, which may exert a differential selection pressure on serotype 6C, regardless of vaccination programs. Heterogeneity in baseline 6C epidemiology across studies, PCV7 history, and PCV13 programs may also make interpretation of trends difficult. A high proportion of studies presented a risk of bias. However, no risk of bias was identified in studies measuring PCV10 and PCV13 direct effect studies against IPD, which were adjusted for the main confounding factors, and represent a stronger level of evidence. Studies on overall effect presented a higher risk of bias, in particular for PCV10. Finally, 6C proportions of pneumococcal disease was the most frequently reported measure; however, these data should be interpreted cautiously. Indeed, PCVs could provide direct, indirect, or overall protection against serotype 6C and yet the proportion of an outcome due to serotype 6C could increase before and after vaccine introduction if protection was greater against non-6C serotypes. Nevertheless, WHO suggests including this metric as a qualitative estimate of vaccine impact [28]. Finally, data from low- and middle-income countries (LMIC) were scarce and restricted to the effect of PCV10 vaccination on nasopharyngeal carriage (Table 1B, [33,34]). Although it can be assumed that data from LMIC would lead to the same conclusion as data from high-income countries, it would be useful to see these findings confirmed in LMIC studies.

PCV13 provides a high level of protection against serotype 6C disease and carriage in children, which is similar to the protection afforded against the aggregate PCV13 serotypes and serotype 6A in particular. A degree of indirect protection in unvaccinated adults was shown in some countries but not in others, possibly due to different increasing serotype 6C trends after PCV7 introduction. Given the strength of evidence from immunological studies reported elsewhere [21,22], and the evidence around vaccine efficacy and impact summarized in this review, regulatory authorities could consider whether protection against serotype 6C could be included in the label indication of pneumococcal conjugate vaccine formulations that include serotype 6A. Furthermore, vaccine policy makers should consider the effects of serotype 6A containing PCVs against serotype 6C disease in their decision-making processes and economic evaluations, as serotype 6C still contributes a substantial burden of pneumococcal disease, especially among older adults [9,10,15]. Clinical trials and observational studies on higher valency PCVs should include serotype 6C, whenever feasible, as a separate outcome to further confirm our findings.

CRediT authorship contribution statement

Lindsay R. Grant: Conceptualization, Data curation, Methodology, Resources, Supervision, Writing – review & editing. **Germaine Hanquet:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Ingrid T. Sepúlveda-Pachón:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Christian Theilacker:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Marc Baay:** Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Mary P.E. Slack:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **Luis Jodar:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **Bradford D. Gessner:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GH, IS, and MB are employees of P95 Epidemiology & Pharmacovigilance, which was contracted by Pfizer to conduct the research described in this manuscript. GH has also received personal fees from MSD, Sanofi Pasteur, Janssens, SNB, and Pfizer as speaker at international meetings and as a member of advisory boards, outside the scope of the submitted work. LRG, CT, LJ, and BDG are employees of Pfizer, Inc. and may hold stocks or stock options. MS has received personal fees from GSK, Pfizer, AstraZeneca, and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). She has also worked as a contractor for Pfizer.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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References

[1] McEllistrem MC, Nahm MH. Novel pneumococcal serotypes 6C and 6D: anomaly or harbinger. Clin Infect Dis 2012;55:1379–86.
[2] Park IH, Pritchard DG, Cartee R, Brandao A, Brandileone MC, Nahm MH. Discovery of a new capsular serotype (6C) within serogroup 6 of Streptococcus pneumoniae. J Clin Microbiol 2007;45:1225–33.
[3] Park IH, Moore MR, Treanor JJ, Pelton SI, Pilishvili T, Beall B, et al. Differential effects of pneumococcal vaccines against serotypes 6A and 6C. J Infect Dis 2008; 198:1818–22.
[4] Park IH, Park S, Hollingshead SK, Nahm MH. Genetic basis for the new pneumococcal serotype, 6C. Infect Immun 2007;75:4482–9.
[5] Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006;368:1495–502.
[6] Palmu AA, Kaijalainen T, Jokinen J, Kilpi TM. Efficacy of the 7-valent pneumococcal conjugate vaccine against acute otitis media caused by serotype 6C pneumococcus. Pediatr Infect Dis J 2015;34:796–7.
[7] Kaplan SL, Center KJ, Barson WJ, Ling-Lin P, Romero JR, Bradley JS, et al. Multicenter surveillance of Streptococcus pneumoniae isolates from middle ear and mastoid cultures in the 13-valent pneumococcal conjugate vaccine era. Clin Infect Dis 2015;60:1339–45.

[8] Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. PLoS One 2017;12:e0177113.

[9] Tin Tin Htar M, Morato Martinez J, Theilacker C, Schmitt HJ, Swerdlow D. Serotype evolution in Western Europe: perspectives on invasive pneumococcal diseases (IPD). Expert Rev Vaccines 2019;18:1145–55.

[10] Benfield T, Skovgaard M, Schonheyder HC, Knudsen JD, Bangsborg J, Ostergaard C, et al. Serotype distribution in non-bacteremic pneumococcal pneumonia: association with disease severity and implications for pneumococcal conjugate vaccines. PLoS One 2013;8:e72743.

[11] Porat N, Benisty R, Givon-Lavi N, Trefler R, Dagan R. The impact of pneumococcal conjugate vaccines on carriage of and disease caused by Streptococcus pneumoniae serotypes 6C and 6D in southern Israel. Vaccine 2016;34:2806–12.

[12] Cohen R, Varon E, Doit C, Schlemmer C, Romain O, Thollot F, et al. A 13-year survey of pneumococcal nasopharyngeal carriage in children with acute otitis media following PCV7 and PCV13 implementation. Vaccine 2015;33:5118–26.

[13] Janoir C, Cohen R, Levy C, Bingen E, Lepoutre A, Gutmann L, et al. Clonal expansion of the macrolide resistant ST386 within pneumococcal serotype 6C in France. PLoS One 2014;9:e90935.

[14] Nunes S, Valente C, Sá-Leão R, de Lencastre H. Temporal trends and molecular epidemiology of recently described serotype 6C of Streptococcus pneumoniae. J Clin Microbiol 2009;47:472–4.

[15] Richter SS, Heilmann KP, Dohrn CL, Riahi F, Diekema DJ, Doern GV. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999-2011(1.). Emerg Infect Dis 2013; 19: 1074–83.

[16] Agudelo CI, Castaneda-Orjuela C, Brandileone MCC, Echaniz-Aviles G, Almeida SCG, Carnalla-Barajas MN, et al. The direct effect of pneumococcal conjugate vaccines on invasive pneumococcal disease in children in the Latin American and Caribbean region (SIREVA 2006–17): a multicentre, retrospective observational study. Lancet Infect Dis 2021;21:405–17.

[17] Carvalho Mda G, Pimenta FC, Gertz Jr RE, Joshi HH, Trujillo AA, Keys LE, et al. PCR-based quantitation and clonal diversity of the current prevalent invasive serogroup 6 pneumococcal serotype, 6C, in the United States in 1999 and 2006 to 2007. J Clin Microbiol 2009;47:554–9.

[18] Rolo D, Fenoll A, Ardanuy C, Calatayud L, Cubero M, de la Campa AG, et al. Trends of invasive serotype 6C pneumococci in Spain: emergence of a new lineage. J Antimicrob Chemother 2011;66:1712–8.

[19] Andrews N, Kent A, Amin-Chowdhury Z, Sheppard C, Fry N, Ramsay M, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: the indirect cohort design, 2006–2018. Vaccine 2019;37:4491–8.

[20] van der Linden M, Falkenhorst G, Perniciaro S, Fitzner C, Imöhl M. Effectiveness of pneumococcal conjugate vaccines (PCV7 and PCV13) against invasive pneumococcal disease among children under two Years of age in Germany. PLoS One 2016;11:e0161257.

[21] Cooper D, Yu X, Sidhu M, Nahm MH, Fernsten P, Jansen KU. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to Streptococcus pneumoniae serotypes 6C and 7A. Vaccine 2011;29:7207–11.

[22] Grant LR, O'Brien SE, Burbidge P, Haston M, Zancolli M, Cowell L, et al. Comparative immunogenicity of 7 and 13-valent pneumococcal conjugate vaccines and the development of functional antibodies to cross-reactive serotypes. PLoS One 2013;8:e74906.

[23] Garcia Quesada M, Yang Y, Bennett JC, Hayford K, Zeger SL, Feikin DR, et al. Serotype Distribution of Remaining Pneumococcal Meningitis in the Mature PCV10/13 Period: Findings from the PSERENADE Project. Microorganisms 2021; 9.

[24] Izurieta P, Nieto GJ. Exploring the evidence behind the comparable impact of the pneumococcal conjugate vaccines PHiD-CV and PCV13 on overall pneumococcal disease. Hum Vaccin Immunother 2022;18:1872341.

[25] International Vaccine Access Center. Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME). Summary of Findings from Systematic Review. Available from: https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2017/9_session_PCV/Oct2019_session9_PCV_PRIMEsummary.pdf.

[26] Halloran ME. Overview of vaccine field studies: types of effects and designs. J Biopharm Stat 2006;16:415–27.

[27] Hanquet G, Valenciano M, Simondon F, Moren A. Vaccine effects and impact of vaccination programmes in post-licensure studies. Vaccine 2013;31:5634–42.

[28] World Health Organization = Organisation mondiale de la S. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 — Vaccins antipneumococciques conjugués chez les nourrissons et les enfants de moins de 5 ans: note de synthèse de l'OMS – février 2019. Weekly Epidemiol Record = Relevé épidémiologique hebdomadaire 2019; 94: 85–103.

[29] Jayasinghe S, Chiu C, Quinn H, Menzies R, Gilmour R, McIntyre P. Effectiveness of 7- and 13-valent pneumococcal conjugate vaccines in a schedule without a booster dose: a 10-Year observational study. Clin Infect Dis 2018;67:367–74.

[30] Savulescu C, Krizova P, Valentiner-Branth P, Ladhani S, Rinta-Kokko H, Levy C, et al. Effectiveness of 10 and 13-valent pneumococcal conjugate vaccines against invasive pneumococcal disease in European children: SpIDnet observational multicentre study. Vaccine 2022;40:3963–74.

[31] Dagan R, Patterson S, Juergens C, Greenberg D, Givon-Lavi N, Porat N, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. Clin Infect Dis 2013;57:952–62.

[32] Hadjipanayis A, Efstathiou E, Alexandrou M, Panayiotou L, Zachariadou C, Petrou P, et al. Nasopharyngeal pneumococcal Carriage among healthy children in Cyprus post widespread simultaneous implementation of PCV10 and PCV13 vaccines. PLoS One 2016;11:e0163269.

[33] Nisar MI, Jehan F, Shahid S, Ahmed S, Shakoor S, Kabir F, et al. Serotype-specific effectiveness against pneumococcal carriage and serotype replacement after ten-valent pneumococcal conjugate vaccine (PCV10) introduction in Pakistan. PLoS One 2022;17:e0262466.

[34] Nunes MC, Moreira M, Koen A, van Niekerk N, Jose L, Cutland CL, et al. Bacterial nasopharyngeal carriage following infant immunization with pneumococcal conjugate vaccines according to a 2+1 schedule in children in South Africa: an exploratory analysis of two clinical trials. Expert Rev Vaccines 2020;19:1177–89.

[35] Latasa Zamalloa P, Sanz Moreno JC, Ordobás Gavín M, Barranco Ordoñez MD, Insúa Marisquerena E, Gil de Miguel Á, et al. Trends of invasive pneumococcal disease and its serotypes in the Autonomous Community of Madrid. Enferm Infecc Microbiol Clin (Engl Ed) 2018; 36: 612–20.

[36] Martínez-Osorio J, García-García JJ, Moraga-Llop F, Díaz A, Hernández S, Solé-Ribalta A, et al. Invasive pneumococcal disease in children under 60 months before and after availability of 13-valent conjugate vaccine. An Pediatr (Engl Ed) 2022;96:501–10.

[37] Naucler P, Galanis I, Morfeldt E, Darenberg J, Ortqvist A, Henriques-Normark B. Comparison of the impact of pneumococcal conjugate vaccine 10 or pneumococcal conjugate vaccine 13 on invasive pneumococcal disease in equivalent populations. Clin Infect Dis 2017;65:1780–9.

[38] Jayasinghe S, Menzies R, Chiu C, Toms C, Blyth CC, Krause V, et al. Long-term impact of a "3 + 0" schedule for 7- and 13-valent pneumococcal conjugate vaccines on invasive pneumococcal disease in Australia, 2002–2014. Clin Infect Dis 2017;64:175–83.

[39] Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis 2018;18:441–51.

[40] Grant LR, Hammitt LL, O'Brien SE, Jacobs MR, Donaldson C, Weatherholtz RC, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal Carriage among American Indians. Pediatr Infect Dis J 2016;35:907–14.

[41] Baxter R, Aukes L, Pelton SI, Yee A, Klein NP, Gruber WC, et al. Impact of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease after introduction into routine pediatric use. J Pediatric Infect Dis Soc 2021;10:141–50.

[42] Càmara J, Marimón JM, Cercenado E, Larrosa N, Quesada MD, Fontanals D, et al. Decrease of invasive pneumococcal disease (IPD) in adults after introduction of pneumococcal 13-valent conjugate vaccine in Spain. PLoS One 2017;12:e0175224.

[43] González-Díaz A, Càmara J, Ercibengoa M, Cercenado E, Larrosa N, Quesada MD, et al. Emerging non-13-valent pneumococcal conjugate vaccine (PCV13) serotypes causing adult invasive pneumococcal disease in the late-PCV13 period in Spain. Clin Microbiol Infect 2020;26:753–9.

[44] Regev-Yochay G, Katzir M, Strahilevitz J, Rahav G, Finn T, Miron D, et al. The herd effects of infant PCV7/PCV13 sequential implementation on adult invasive pneumococcal disease, six years post implementation; a nationwide study in Israel. Vaccine 2017;35:2449–56.

[45] Corcoran M, Vickers I, Mereckiene J, Murchan S, Cotter S, Fitzgerald M, et al. The epidemiology of invasive pneumococcal disease in older adults in the post-PCV era. Has there been a herd effect? Epidemiol Infect 2017;145:2390–9.

[46] Vadlamudi NK, Patrick DM, Hoang L, Sadarangani M, Marra F. Incidence of invasive pneumococcal disease after introduction of the 13-valent conjugate pneumococcal vaccine in British Columbia: a retrospective cohort study. PLoS One 2020;15:e0239848.

[47] Bruce MG, Singleton R, Bulkow L, Rudolph K, Zulz T, Gounder P, et al. Impact of the 13-valent pneumococcal conjugate vaccine (pcv13) on invasive pneumococcal disease and carriage in Alaska. Vaccine 2015;33:4813–9.

[48] Ciruela P, Izquierdo C, Broner S, Muñoz-Almagro C, Hernández S, Ardanuy C, et al. The changing epidemiology of invasive pneumococcal disease after PCV13 vaccination in a country with intermediate vaccination coverage. Vaccine 2018;36:7744–52.

[49] Galanis I, Lindstrand A, Darenberg J, Browall S, Nannapaneni P, Sjöström K, et al. Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm. Sweden Eur Respir J 2016;47:1208–18.

[50] Oyewole OR, Lang P, Albrich WC, Wissel K, Leib SL, Casanova C, et al. The impact of Pneumococcal Conjugate Vaccine (PCV) coverage heterogeneities on the changing epidemiology of invasive pneumococcal disease in Switzerland, 2005-2019. Microorganisms 2021; 9.

[51] Peckeu L, van der Ende A, de Melker HE, Sanders EAM, Knol MJ. Impact and effectiveness of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease among children under 5 years of age in the Netherlands. Vaccine 2021;39:431–7.

[52] 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.

[53] Polkowska A, Rinta-Kokko H, Toropainen M, Palmu AA, Nuorti JP. Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland. Vaccine 2021;39:3216–24.

[54] Quirk SJ, Haraldsson G, Hjálmarsdóttir M, van Tonder AJ, Hrafnkelsson B, Bentley SD, et al. Vaccination of Icelandic children with the 10-valent pneumococcal vaccine leads to a significant herd effect among adults in Iceland. J Clin Microbiol 2019;57.

[55] Quirk SJ, Haraldsson G, Erlendsdóttir H, Hjálmarsdóttir M, van Tonder AJ, Hrafnkelsson B, et al. Effect of vaccination on pneumococci isolated from the Nasopharynx of healthy children and the middle Ear of children with otitis Media in Iceland. J Clin Microbiol 2018;56.
[56] Alari A, Chaussade H, Domenech De Cellès M, Le Fouler L, Varon E, Opatowski L, et al. Impact of pneumococcal conjugate vaccines on pneumococcal meningitis cases in France between 2001 and 2014: a time series analysis. BMC Med 2016;14:211.
[57] Chávez AF, Comas LG, Moreno JCS, Moreno RC, de Provens OCP, Andrés JMA. Effect of childhood pneumococcal vaccination and beta-lactam antibiotic use on the incidence of invasive pneumococcal disease in the adult population. Eur J Clin Microbiol Infect Dis 2021;40:1529–38.
[58] Mendes RE, Costello AJ, Jacobs MR, Biek D, Critchley IA, Jones RN. Serotype distribution and antimicrobial susceptibility of USA Streptococcus pneumoniae isolates collected prior to and post introduction of 13-valent pneumococcal conjugate vaccine. Diagn Microbiol Infect Dis 2014;80:19–25.
[59] Mendes RE, Hollingsworth RC, Costello A, Jones RN, Isturiz RE, Hewlett Jr D, et al. Noninvasive Streptococcus pneumoniae serotypes recovered from hospitalized adult patients in the United States in 2009 to 2012. Antimicrob Agents Chemother 2015;59:5595–601.
[60] Shoji H, Maeda M, Shirakura T, Takuma T, Hanaki H, Niki Y. Changes in the distribution of Capsular serotypes of Streptococcus pneumoniae isolated from adult respiratory specimens in Japan. Intern Med 2015;54:1337–41.
[61] Su LH, Kuo AJ, Chia JH, Li HC, Wu TL, Feng Y, et al. Evolving pneumococcal serotypes and sequence types in relation to high antibiotic stress and conditional pneumococcal immunization. Sci Rep 2015;5:15843.
[62] Richter SS, Diekema DJ, Heilmann KP, Dohrn CL, Riahi F, Doern GV. Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. Antimicrob Agents Chemother 2014;58:6484–9.
[63] Plumb ID, Gounder PP, Bruden DJT, Bulkow LR, Rudolph KM, Singleton RJ, et al. Increasing non-susceptibility to antibiotics within carried pneumococcal serotypes - Alaska, 2008–2015. Vaccine 2020;38:4273–80.
[64] Strategic Advisory Group of Experts (SAGE) Evidence to recommendation framework: Pneumococcal Conjugate Vaccine PICO 2: Product Choice. Impact 2017.
[65] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.