Pneumococcal Conjugate Vaccine Failure in Children: a systematic review of the literature

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ABSTRACT

Background

Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing pneumococcal invasive disease (IPD) due to serotypes included in the vaccines. The risk of vaccine-type IPD in immunised children (i.e. vaccine failure) has not been systematically assessed in countries with established PCV programmes.

Methods

We undertook a systematic review of the English literature published from January 2000 to April 2016 to evaluate the vaccine schedule, risk factors, serotype distribution, clinical presentation and outcomes of vaccine failure in children vaccinated with the 7-valent (PCV7), 10-valent (PCV10), and 13-valent (PCV13) vaccines. Data sources included MEDLINE, EMBASE, Cochrane library, and references within identified articles.

Results

We identified 1,742 potential studies and included 20 publications involving 7,584 participants in children aged ≤5 year-olds: 5,202 received 2 doses followed by a booster in 10 studies, (68.6%), 64 (0.8%) received 3 doses without a booster in 2 studies, and 2,318 received a 3+1 schedule (30.6%) in 8 studies. A total of 159 vaccine failure cases were identified, representing 2.1% [95% CI: 1.8%-2.4%] of the reported IPD cases. Most studies did not report clinical characteristics or outcomes. Among eight studies reporting comorbidities, 33/77 patients (42.9%) had an underlying condition. The main serotypes associated with vaccine failure were 19F (51/128 cases with known serotype; 39.8%), 6B (33/128; 25.8%), and 4 (10/128; 7.8%). Only five studies reported patient outcomes, with a crude case fatality rate of 2.4% (2/85; 95%CI: 0.3%-8.5%).

Conclusion

Pneumococcal conjugate vaccines have been implemented in national immunisation programmes for more than a decade, yet there are only a few studies reporting vaccine failure. PCV failure is rare, irrespective of vaccine or schedule. Co-morbidity prevalence was high amongst vaccine failure cases but case fatality rate was relatively low. There is a need for more systematic reporting vaccine failure cases in countries with established pneumococcal vaccination programmes.

Introduction

Pneumococcal conjugate vaccines (PCVs) have been widely introduced into childhood immunisation programmes in most industrialised countries. In 2000, the 7-valent vaccine (PCV7) that protects against the seven most prevalent pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) causing invasive pneumococcal disease (IPD) in children was licensed. In 2010, PCV7 was replaced with a 13-valent vaccine (PCV13) that aimed to protect against six additional serotypes (1,3, 5, 6A, 7F, and 19A). Another licensed PCV formulation, PCV10, that protects against serotypes 1, 5, and 7F in addition to PCV7 serotypes was also licensed at around the same time. Introduction of these vaccines into national childhood immunisation programmes has led to rapid and sustained declines in invasive pneumococcal disease (IPD) caused by the vaccine serotypes.[1]

Little is known about the risk of vaccine-type IPD (VT-IPD) after completing the recommended course of PCV immunisation (i.e. vaccine failure). In children with *Haemophilus influenzae* type b (Hib) conjugate vaccine failure, 20% of those immunised before 12 months of age had a clinical risk factor for vaccine failure (prematurity, malignancy, dysmorphic or developmental delay, Down syndrome or neutropenia), 30% had immunological deficiency (total immunoglobulin and/or immunoglobulin subclass deficiency) and 44% had one or both risk factors.[2] Moreover, children who were vaccinated after 12 months of age were more likely to have one or both factors (67%). In contrast, the vast majority of children with group C meningococcal (MenC) conjugate vaccine failure were healthy prior to becoming unwell.[3] A number of clinical, immunological and other chronic conditions are reported with an increased risk of IPD.[4] Whether these conditions also increase the risk of PCV failure is not known. We, therefore, conducted a systematic review of published studies to evaluate the clinical presentation, co-morbidity status, serotype distribution and outcomes of PCV failure in children. It is hoped that the findings of this systematic review will provide clinicians with a robust evidence base to investigate and manage children suspected with pneumococcal vaccine failure.

Methods

Search Strategy

A search strategy was designed to identify observational studies (cohort study, case-control study, case series) reporting pneumococcal conjugate vaccine failure in children aged ≤ 5 year-olds who were immunised with PCVs in regions with established PCV immunisation programmes. We searched MEDLINE, EMBASE, and the Cochrane library from 1st January 2000 to 30th April 2016. We also searched the papers using the ISI web of knowledge, to identify relevant articles and conference proceedings. The medical subject headings (MeSH) terms used included "pneumococcal conjugate vaccines", "pneumococcal conjugate vaccine failure", "invasive pneumococcal disease", "*Streptococcus pneumoniae*", "pneumococcus", "pneumococcal infection", "child", "infant", "toddler", "PCV7, "13vPCV", "PCV9", "PCV10", "comorbidity", and "risk factors". The full search strategies have shown in Appendix 1. We only included studies published in English language in our review. In addition, we screened reference lists of selected papers to retrieve relevant studies.

Study selection

Studies were eligible for inclusion if they reported vaccine-type IPD in immunised children (i.e. vaccine failure) from observational studies and surveillance databases. Vaccine failure was defined as reported in the original articles; in general, the definition included cases of vaccine-type IPD after the primary course of immunisation (two or three doses) and/or after completing the full immunisation course, including the booster. Breakthrough cases with vaccine-type IPD in partially immunised children were not included in our study. Studies were excluded if they were case reports, laboratory or experimental studies, or not original research. Two independent reviewers (G.O. and S.L.) screened the title and abstract of papers identified by the electronic searches, evaluating inclusion and exclusion criteria for all papers. We retrieved full articles of included publications and each publication was then independently reviewed for eligibility. Discrepancies were resolved by discussion with a third author (Y. H.).

Quality assessment and data extraction

Two reviewers (G.O. and S.L.) independently reviewed the methodological quality of included studies, comparability of case and controls, and outcomes. The explanatory

variables extracted included: study design, country, description of study subjects, vaccine schedule, serotype, underlying co-morbidity, clinical presentation and outcome of infection. The study quality assessment was undertaken according to the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the conduct and reporting of systematic reviews.[5]

Data analysis

Included studies were summarised using descriptive analyses to provide an overview of the information on vaccine schedule, reported clinical presentations, underlying co-morbidity, serotype distribution, and vaccine failure outcomes. We calculated the crude vaccine failure rate as the total number of vaccination failure cases divided by total number of reported IPD cases over the same period. We calculated the percentage with exact binomial 95% confidence interval (CI) for the outcome of interest where data were available.

Results

Study characteristics

We identified 1,742 potential studies, of which 1,563 were excluded on the basis of title and abstracts (Figure 1). A further 106 duplicate studies and 53 additional studies did not meet eligibility criteria. One recent French study was excluded because it only evaluated vaccine failure among pneumococcal meningitis cases.[6] The remaining 20 studies were eligible and the full text was assessed for inclusion in the final review.[7-26] Five of the studies included older children, adults and the elderly population,[20-24] but we were able to extract data for aged ≤5 year-olds. Most studies involved PCV7 (70.0%; 14/20), one PCV10 (5.0%; 1/20), and one involved both PCV7 and PCV10 (5.0; 1/20). There was only one study reporting PCV13 failure (5.0%; 1/20). Most studies identified vaccine-type IPD cases through national and/or regional surveillance of IPD. Two Spanish studies identified IPD cases and vaccine failures among children admitted to the local paediatric hospitals.[8,26] A summary of the study design, data collection method, study subjects, and definition of vaccine failure is presented in Table 1 and Table 2. The majority of studies did not report the ethnicity. A total of 7,584 participants aged ≤ 5 years who had received PCV in 20 studies were included in the final analysis (Table 2): 5,202 (68.6%) children in 10 studies received

a two-dose priming schedule followed by a booster (2+1), 64 children (0.8%) children received three-dose priming schedule without a booster (3+0), and 2,318 (30.6%) children in 8 studies received three-dose priming schedule followed by a booster (3+1). One UK study reported vaccine failures after two priming doses as well as after the booster dose at 12-13 months of age.[17] Two of the studies were case-control design. Ten studies (50.0%) were performed in Europe, 8 (40.0%) in North America, and 2 (10.0%) in Australia. There were no studies from developing countries.

Overall, 159 vaccine failure cases were reported. None of the studies reported vaccine failure rates in the population (i.e using the total number of vaccinated children as the denominator). Of the children who developed IPD over a defined time period, 2.1% (95% CI: 1.8%-2.4%) were vaccine failures. Nine studies reported an underlying co-morbidity in 33 of 77 (42.9%) vaccine failure cases. Two studies reported detailed co-morbidities among vaccine failure cases.[11,27] Of the eight studies that reported clinical presentation, 25 (43.1%; 25/58) cases had bacteraemia, 24 (41.4%; 24/58) had pneumonia, and 5 (8.6%; 5/58) had meningitis. Only five studies reported patient outcomes, with a hospitalisation rate of 24.7% (21/85 patients) and a crude case fatality rate of 2.4% (2/85 patients; 95%CI: 0.3%-8.5%). The major serotypes associated with vaccine failure were 19F (39.8%; 51/128 cases with known serotype), followed by 6B (25.8%; 33/128), and 4 (7.8%; 10/128). The only study on PCV13 failure from Spain reported 3 children who developed PCV13-type IPD after a complete 4-dose immunisation schedule among 84 children aged 3-59 months diagnosed with IPD during 2012 and 2013.[26] Notably, all three presented with complicated pneumonia and empyema; serotype 3 was responsible for two cases and serotype 19A for the third. A formal statistical analysis comparing the different vaccines and schedules was not performed because of small numbers of cases with limited information.

Discussion

A thorough systematic review of the literature identified a very low rate of childhood PCV failure in industrialised countries with established national immunisation programmes, irrespective of the conjugate vaccine or priming or boosting schedule used. Children with vaccine failure accounted for around 2% of total IPD cases and almost half had significant underlying comorbidities. Bacteraemia was the most

common clinical presentation and the crude case-fatality rate among vaccine failure cases was very low at 2.4%.

These findings confirm the high effectiveness of PCVs in preventing vaccine-type IPD in young children, who have a very high risk of serious bacterial infections. Moreover, conjugate vaccines can also induce herd protection by preventing carriage and onward transmission of vaccine serotypes to both vaccinated and unvaccinated children as well as adults and older adults.[27] Over time, therefore, vaccine failure should become even less common as vaccine serotypes stop circulating in highly immunised populations. Serotypes 19F and 6B were responsible for more than two-thirds of vaccine failure cases, perhaps because these two serotypes are the least immunogenic of the vaccine serotypes in infants and toddlers.[4, 11]

Co-morbidity prevalence in children with conjugate vaccine failure varies, depending on the disease responsible. In children with Hib vaccine failure, almost half had co-morbidity and/or immunoglobulin deficiency.[2] In contrast, the vast majority of children with MenC vaccine failure were previously healthy. Of the few published studies that reported comorbidity status in children with PCV7 or PCV10 vaccine failure, a third had co-morbidity. Only 2 of the studies listed the co-morbidities, with immunodeficiency and prematurity being the most prevalent.[7, 11] These are known risk factors for IPD, irrespective of vaccination status and, therefore, it is not surprising that such children are also at increased risk of vaccine failure. In children with PCV failure and no comorbidities, we were unable to identify any study that systematically assessed their immunological status and, therefore, a potential as yet undiagnosed underlying immune deficiency cannot be excluded in this group. Recurrent IPD is rare, especially among vaccinated children, and most have an identifiable risk factor, such as asplenia, immunosuppression or cochlear implants,[17, 28-31] which is reassuring; however, children with recurrent IPD and no obvious risk factors are more likely to have an underlying immune deficiency, irrespective of their previous pneumococcal vaccination status.[32-34] Such children, therefore, should be subjected to a thorough immunological assessment and investigation.

The low overall hospitalisation rate of around 25% reported in five studies must be interpreted with caution. In countries such as the UK, blood cultures are usually only

taken in patients presenting to hospital and, therefore, hospitalisation rates for IPD are always near 100%. In contrast, taking blood cultures in primary care is a common practice in the United States and, often, the children are treated with antibiotics as outpatients (68% of those younger than 5 years in 1998–99),[35] hence the higher IPD incidence of 98.7/100,000 in the US compared with 31.8/100,000 population in England.[21] It is possible that vaccinated children who develop vaccine-type IPD may have milder disease and better outcomes than unvaccinated children, but none of the published studies provided sufficient information to support this hypothesis

Our results demonstrate the potential strengths of combining outcomes of rare events through a systematic review of the literature. However, the lack of information on vaccine failure cases in the observational studies was a significant limitation; consequently, we were unable to conduct any meta-analyses to compare differences in dosing schedules or calculate risks associated with clinical outcomes. Moreover, several publications utilised the same population-based surveillance to identify and report vaccine failure cases; this could potentially lead to double counting of the same cases. Given that PCV13 replaced PCV7 as far back as 2010, more data are needed on clinical characteristics, risk factors and outcomes of PCV13-type and non-vaccine type IPD in PCV13-immunised children. It is also important that future studies report vaccine failure rates using the total number of vaccinated children and their at-risk time period so that different vaccines, immunisation schedules and populations can be compared.

Our study has identified a clear need to establish national and international registers for rare outcomes such as vaccine failure, as part of post-vaccine implementation surveillance in countries with established immunisation programmes. Standardising the collection and reporting for individual cases across regions and countries would further allow meaning analysis of the data collected, enabling valid comparison between different vaccines and schedules and to monitor trends over time.

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Figure 1: Identification and selection of eligible studies in the systematic review

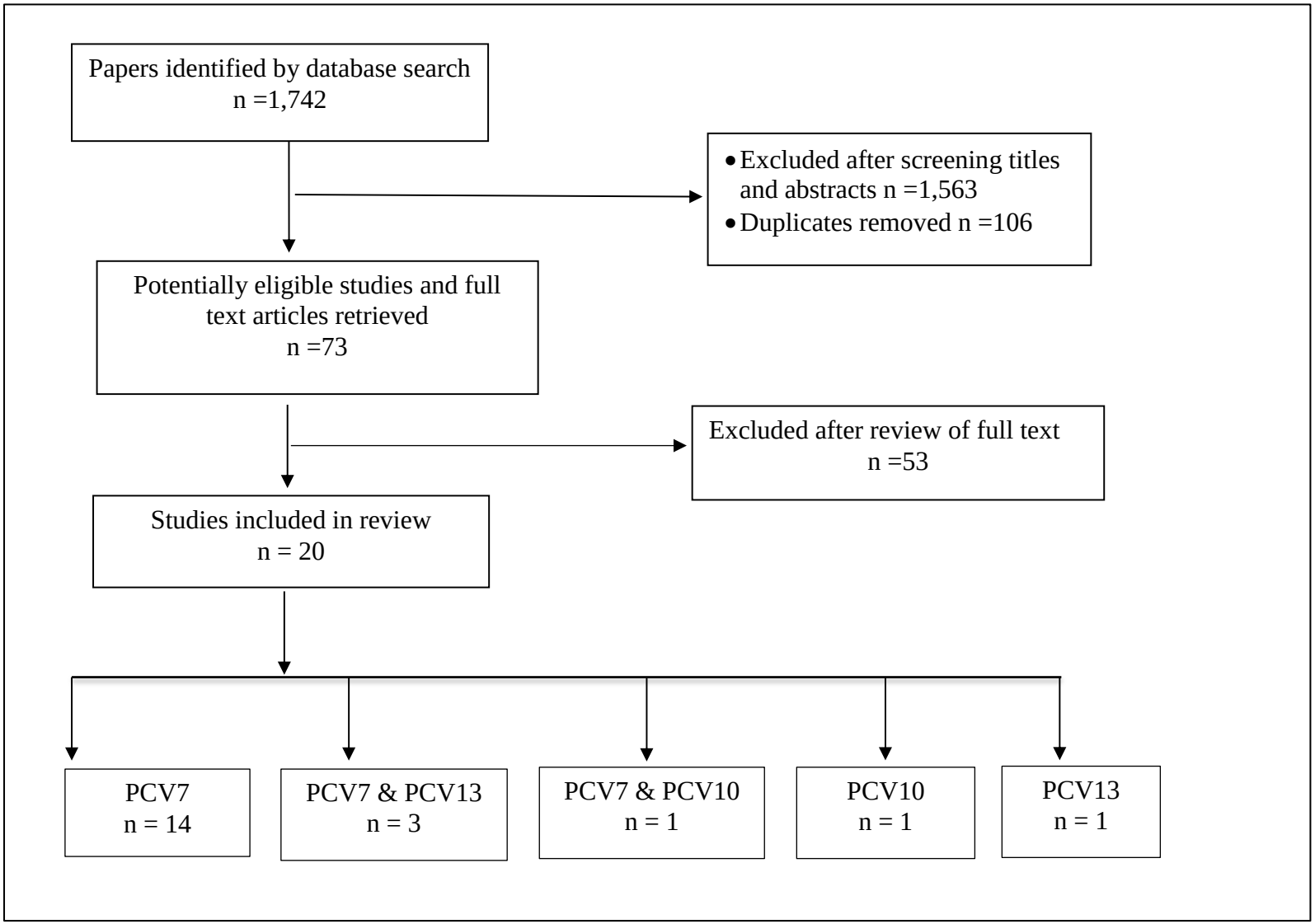

Table 1. Description of study design and reported vaccine failure definition

Study	Country	Study design	Data collection	Ethnicity	Vaccine schedule	VF definition
Dosing schedule 3+1						
Hsu et al. 2005	US	Population- and laboratory-based surveillance	Laboratories in Massachusetts send all *S. pneumoniae* to Department of Public Health	White, Black, Hispanic, and Asian/Pacific islander	2,4,6, and 12-15 mo	Vaccine-related serotype IPD in a fully-vaccinated case
Whitney et al. 2006	US	Population- and laboratory-based surveillance; matched case-control study	CDC-ABCs	White, Black, and Hispanic	2,4,6, and 12-15 mo	Fully vaccinated cases who developed vaccine-serotype IPD
Callbo et al. 2006	Spain	Retrospective study	Local hospitals in Barcelona	Not reported	2,4,6, and 12-15 mo	IPD caused by a vaccine serotype in a vaccinated patient
Black et al. 2007	US	Laboratory-based surveillance	Northern California Kaiser Permanente Healthcare System	White, Black, Asian, Hispanic, Native American, and Eskimo	2,4,6, and 12-15 mo	Fully vaccinated cases who developed vaccine-serotype IPD
Park et al. 2009	US	Population-based surveillance	CDC-ABCs	White, Black, Asian, Native American/Alaska Native	2,4,6, and 12-15 mo	Vaccine-type IPD in a child who completed age-appropriate PCV7 vaccination schedule as recommended by ACIP
Ruckinger et al. 2009	Germany	Population-based surveillance	Hospital- and laboratory based surveillance system	Not reported	2,3,4, and 12-15 mo	Fully vaccinated IPD caused by vaccine serotype
Kellner et al. 2009	Canada	Prospective, population-based surveillance	Population-based surveillance in Calgary region	Not reported	2,4,6, and 12-15 mo	Fully vaccinated cases who developed vaccine-serotype IPD
Moraga et al. 2016	Spain	Prospective study	Local paediatric hospitals in Barcelona area	Not reported	2,4,6, and 12-15 mo	IPD due to a PCV13 serotype in a fully-vaccinated child. IPD should have occurred 2 weeks or longer after the last dose of PCV13.
Dosing schedule 3+0						
Hanna et al. 2010	Australia	Laboratory-based surveillance	Diagnostic laboratories are required to notify all cases to their local public health units	Non-Indigenous children	2, 4, and 6 mo	Vaccine-type IPD in fully immunised child; IPD defined as isolation of *S. pneumoniae* from sterile body site
Lehmann et al. 2010	Australia	Hospital-based surveillance & laboratory-based surveillance	Surveillance involving all public and private hospitals in Western Australia	3.5% Aboriginal vs 96.5% of non-Aboriginal	2, 4, and 6 mo	Vaccine-type IPD case in fully immunised children
Dosing schedule 2+1						
Bettinger et al. 2010	Canada	Surveillance study	Canadian immunization monitoring program, Active (IMPACT)	Not reported	2,4, and 12 mo	Invasive disease with a PCV7 isolate in a healthy child completely immunized according to national guidelines
Deceunick et al. 2010	Canada	Population-based study	IPD cases reported by physicians and laboratories to public health authority in Quebec	Not reported	2,4, and 12 mo	Children who developed vaccine-serotype IPD
Hanquet et al. 2011	Belgium	Laboratory-based surveillance	National reference laboratory	Not reported	Not reported	Vaccine-type IPD in fully immunised child; IPD defined as *S. pneumoniae* isolated from a sterile site in children aged <5 years
de Wals et al. 2012	Canada	Population-based ecological study	Laboratory-based surveillance data	Not reported	2+1 for low-risk infants (2, 4, and 12 mo) 3+1 for high-risk (2, 4, 6, and 12 mo)	Vaccine-type IPD in fully immunised child;
Martinelli et al. 2013	Italy	Hospital-based surveillance	Computerized Immunization Registry (vaccination coverage) Prospective laboratory-confirmed surveillance (IPD cases among hospitalised children)	Not reported	3, 5, and 12 mo	Vaccine-type IPD in fully immunised child; IPD defined as a child with isolation of *S. pneumoniae* by PCR positive sample from a sterile body site
Steens et al. 2013	Norway	Observational retrospective population-based cohort study	National Institute of Public Health; Norwegian Surveillance System for Communicable Diseases	Not reported	3, 5, and 12 mo	Vaccine-type IPD in fully immunised child; IPD case defined as isolation of *S. pneumoniae* from a sterile body site

Ladhani et al. 2013	UK	National Surveillance	Health Protection Agency	Not reported	2, 4, and 12-13 mo	PCV7 vaccine failure defined as PCV7-type IPD at least 14 days after 2 doses in <12 month-olds or after 1 dose in ≥12 month-olds.
Harboe et al. 2013	Denmark	Nationwide cohort study	Laboratory surveillance data linked to the Danish Childhood Vaccination Registry	Not reported	3, 5, and 12 mo	Vaccine-type IPD as follows: (1) any child <13 mo and received 2 doses PCV7 or PCV13; (2) any child aged at least 12 months and completed the vaccination schedule; (3) any child at least 6 months of age and received 2 doses of PCV7
Harboe et al. 2014	Denmark	Population-based cohort study	Laboratory surveillance data linked to the Danish Civil Registration System	Not reported	3, 5, and 12 mo	Vaccine-type IPD in fully immunised child; IPD defined as *S. pneumoniae* was isolated from sterile body site
Jokinen et al. 2015	Finland	Population-based, observational follow-up study	National Infectious Disease Register	Not reported	3, 5, and 12 mo	Vaccine-type IPD in fully immunised child; IPD defined as isolation of *S. pneumoniae* by culture from blood or CSF and reported to the National Infectious Disease Register

Abbreviations: IPD, invasive pneumococcal disease; mo, month; yr, year; CDC, the Centers for Disease Control and Prevention; ABCs, Active Bacterial Core Surveillance; CSF, Cerebrospinal fluid; ACIP, Advisory Committee on Immunization Practices; US, United State; UK, United Kingdom.

Table 2: Characteristics of studies included in the systematic review

	Country	Age	No. of study participants	Vaccine	VT-IPD* No. of cases	Serotypes No. of cases	Comorbidities[§] No. of cases	Clinical presentations & complications No. of cases	Clinical Outcomes
Schedule 3+1 dosing									
Hsu et al. 2005	US	<18yr	138 (aged <5yr)	PCV7	11	6B: 2 18C: 1 19F: 5 23F: 3	3	Bacteraemia: 7 URTI with bacteraemia: 1 Peritonitis with bacteraemia: 1 Abscess: 1	Not reported
Whitney et al. 2006	US	3 to 59 mo	782	PCV7	27	19F: 16 4: 6 Unknown: 5	Not reported	Not reported	Not reported
Callbo et al. 2006	Spain	≤ 5yr	121	PCV7	1	6A: 1	0	AOM with bacteraemia:1	Reported favourable outcomes without detailed description
Black et al. 2007	US	<5 yr	131	PCV7	3	19F: 1 9V: 1 4: 1	Not reported	Meningitis: 1 Pneumonia with bacteraemia: 2	Not reported
Park et al. 2009	US	< 5 yr	753	PCV7	27	6B: 9 19F: 6 9V: 4 23F: 3 14: 2 4: 2 18C: 1	10	Pneumonia: 11 Bacteraemia: 10 Meningitis: 2 Otitis: 2 Endocarditis: 1 Deep thigh abscess: 1	Hospitalised: 18 Died: 1 (with endocarditis)
Ruckinger et al. 2009	Germany	0 to 15 yr	166 (aged <5yr)	PCV7	4	19F: 2 23F: 1 4: 1	Not reported	Not reported	Not reported
Kellner et al. 2009	Canada	all ages	143 (aged <5yr)	PCV7	2	14: 1 6B: 1	2	Meningitis: 1 Pneumonia: 1	Not reported
Moraga et al. 2016[†]	Spain	3 to 59 mo	84	PCV13	9	3: 6 6B: 1 19A: 2	Not reported	Complicated pneumonia: 8 Empyema: 8 Pneumothorax: 3 Bronchoalveolar fistula: 2 Bacteraemic mastoiditis: 1 Septic shock: 1 Epidural abscess & sigmoid sinus thrombosis: 1	Not reported
Schedule 3+0 dosing									
Lehmann et al. 2010	Australia	All ages	40 (aged <5yr)	PCV7	3	14: 1 18C: 1 19F: 1	Not reported	Not reported	Not reported
Hanna et al. 2010	Australia	All ages	24 (aged <5yr)	PCV7	1	6B: 1	Not reported	Not reported	Not reported
Schedule 2+1 dosing									
Bettinger et al. 2010	Canada	<16 yr	1,138 (aged <5)	PCV7	4	Unknown	0	Not reported	Not reported
Deceunick et al. 2010	Canada	2 to 59 mo	180	PCV7	2	Unknown	1	Not reported	Not reported
Hanquet et al. 2011	Belgium	<5 yr	1,317	PCV7	1	18C: 1	1	Not reported	Died: 0
De Wals et al. 2012	Canada	<5 yr	265	PCV7& PCV10	2	19F: 2	Not reported	Not reported	Not reported
Martinelli et al. 2013	Italy	0 to 60 mo	159	PCV7	2	9V: 2	Not reported	Pneumonia with bacteraemia: 2	Not reported
Steens et al. 2013	Norway	All ages	307	PCV7	2	6B: 1 9V: 1	Not reported	Not reported	Not reported
Ladhani et al. 2013	UK	3 to 59 mo	1,342	PCV7	53	6B: 18 19F: 16	15	Not reported	Died: 1 (with meningitis, immunodeficiency)
Harboe et al. 2013	Denmark	<5 yr	191	PCV7& PCV13	3	14: 1 19F: 1 23F: 1	1	Bacteraemia: 1 Meningitis: 1	Hospitalised: 3 Died: 0
Harboe et al. 2014	Denmark	All ages	260 (aged <5yr)	PCV7&PCV 13	1	Unknown	Not reported	Not reported	Not reported
Jokinen et al. 2015	Finland	0 to 5 yr	43	PCV10	1	19F: 1	Not reported	Not reported	Not reported

Abbreviations: PCV: pneumococcal conjugate vaccine; US: United State; UK: United Kingdom; IPD, invasive pneumococcal disease; AOM: acute otitis media; URTI, upper respiratory tract infection. * VT-IPD: vaccine-type IPD. [§]co-morbidities in patients with treatment failure. [†]1 patient was administrated 2+1 schedule in a foreign country (Andorra); 1 patient received 3 dose of PCV7 at aged 3,5, and 7 months before receiving PCV13.