Title: Invasive pneumococcal disease in UK children under 1 year of age in the post-PCV13 era: what are the risks now?

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Summary: Whilst the incidence of invasive pneumococcal disease (IPD) in infants in England remains low, the risk of IPD is significantly higher in premature infants compared to term infants. Changes to the infant pneumococcal immunisation schedule may disproportionally affect premature infants.

Abstract

Background: Invasive pneumococcal disease (IPD) has declined significantly since the introduction of pneumococcal conjugate vaccines (PCV). It is not known whether certain infant populations remain at higher risk of IPD in countries with established PCV13 programmes. We aimed to describe the epidemiology, clinical characteristics, serotype distribution and outcomes of IPD in infants, and to estimate the relative risk of PCV13-type, non-PCV13 type and overall IPD in premature infants compared to term infants during a four-year period after the PCV13 programme was established.

Methods:

Prospective, enhanced national surveillance of laboratory-confirmed IPD in England in infants aged <1 year diagnosed during 2013-16

Results

There were 517 cases of IPD (incidence: 19/100,000 infants). Incidence was significantly higher in premature infants compared with those born at term (49/100,000 vs 17/100,000; incidence rate ratio (IRR) 2.87; p<0.001) with infants born below 28 weeks gestation having the highest incidence (150/100,000; IRR 8.8; p<0.001). Of the 454 IPD cases with serotyped isolates, most were caused by non-PCV13 serotypes (369 cases, 71.4%), with 85 cases (16.4%) due to PCV13 serotypes. There were 31 deaths (case fatality rate 6.2%; 95% CI, 4.3-8.6%). Premature infants did not have a higher CFR than term infants (p=0.62).

Conclusion & relevance

IPD incidence in infants remains lower than rates reported prior to PCV7 introduction in England. The risk of IPD remains significantly higher in premature infants compared to infants born at term, for both PCV13 and non-PCV13 serotypes. Any changes to the infant PCV13 immunisation schedule may disproportionally affect premature infants.

Keywords: Invasive pneumococcal disease; Infant; Pneumococcal conjugate vaccines; Infant, premature

Background

Streptococcus pneumoniae is a major cause of meningitis, septicaemia and pneumonia worldwide and is associated with significant morbidity and mortality, especially in young children, the elderly and those with underlying health conditions [1–3]. There are currently 92 distinct pneumococcal serotypes based on polysaccharide capsular differences [4–6]. Pneumococcal conjugate vaccines (PCVs) have been part of the UK infant immunisation programme since 2006, initially using a vaccine covering the 7 most prevalent pneumococcal serotypes causing invasive pneumococcal disease (IPD) in children (PCV7, Prevenar®, Pfizer, New York). Infants received a 2 dose priming schedule at 8 and 16 weeks, followed by a booster at 12 months. This programme led to a rapid reduction in vaccine-type and overall IPD across all age groups, both directly and indirectly through a reduction in nasopharyngeal carriage of vaccine serotypes[7]. A small and steady increase in IPD due to non-PCV7 serotypes (serotype replacement) was observed in children and adults after PCV7 introduction [8].

In April 2010, this vaccine was replaced by a 13-valent vaccine (PCV13, Prevenar13®, Pfizer), which provided additional protection against some of the major replacing serotypes, including 7F and 19A [9]. This programme led to further reductions in vaccine-type and overall IPD, and was also associated with an increase in replacement disease due to non-PCV13 serotypes [9]. Because of the current low rates of PCV13-type IPD, the UK vaccination advisory committee (the Joint Committee on Vaccination and Immunisation, JCVI) have recently recommended reducing the number of infant priming doses to a single dose at 3 months of age [10].

During the PCV7 era, 23% of infants with IPD in the first 3 months of life had been born prematurely compared to a background rate of 7% [11]. Among 3-59 month-olds, 10% of children with IPD had been born prematurely and 15% had an underlying co-morbidity [12]. Premature infants have reduced antibody responses to pneumococcal conjugate vaccination compared with those born at term [13], and these responses are dependent on the primary vaccination schedule received [14].

The impact of PCV13 on IPD following a reduced 2-dose priming schedule in infants and, especially in premature infants is not known. Using national surveillance data, we aimed to describe the epidemiology, clinical characteristics, serotype distribution and outcomes of IPD in infants, and to

estimate the relative risk of PCV13-type, non-PCV13 type and overall IPD in premature infants compared to term infants during a four-year period after the PCV13 programme was established in England.

Methods

Identification of cases

Public Health England (PHE) conducts enhanced surveillance for IPD in England. PHE provides a national reference laboratory service for serotyping and characterisation of invasive pneumococcal isolates. PHE routinely receives electronic reports of invasive pneumococcal isolates from National Health Service (NHS) hospital laboratories across England, and actively requests referral of invasive isolates to the reference laboratory if not already done. For confirmed cases, additional clinical details including vaccination history, comorbidities, clinical presentations and outcomes are obtained from the child's general practitioner using standard surveillance questionnaires. In order to accurately assign outcomes of IPD and cause of death in fatal cases, all confirmed cases are cross-checked with the Personal Demographic Service (https://digital.nhs.uk/Demographics) and electronic death registration records provided by the Office for National Statistics (www.statistics.gov.uk) to PHE.

Ethical approval

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process confidential patient information for national surveillance of communicable diseases (http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made). This includes PHE's responsibility to monitor the safety and effectiveness of vaccines.

Definitions

An IPD case was defined as culture of *S. pneumoniae* from a normally sterile site or detection of pneumococcal DNA via PCR in the cerebrospinal (CSF), pleural or joint fluid. For clinical presentations with multiple manifestations, the following hierarchy was applied for analysis: meningitis, pneumonia, other sites and bacteraemia. Meningitis was defined as *S. pneumoniae* isolated from the CSF, or clinical, radiological or laboratory features of meningitis with *S. pneumoniae* isolated from the blood culture. Pneumonia was defined as *S. pneumoniae* isolated from empyema fluid or the blood with radiological or clinical evidence of pneumonia. Bacteraemia

was defined as *S. pneumoniae* cultured from the blood without a distinctive clinical syndrome. Multiple samples collected in a 30 day time period from the same individual were regarded as the same episode of infection. In addition to prematurity (birth gestation below 37 weeks), underlying conditions associated with IPD were pre-defined as: chronic renal, hepatic, respiratory and cardiac disease, diabetes mellitus, CSF leak or cochlear implants, and asplenia or splenic dysfunction [15]. PCV13 serotypes include: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. PCV13 breakthrough cases were defined as IPD caused by a PCV13 serotype at least 14 days after receiving a PCV13 dose.

Data analysis

All confirmed IPD cases diagnosed in infants (aged <1 year) between 01 January 2013 and 31 December 2016 were included in the analysis. Data were analysed using Stata 13 (StataCorp, Texas, USA). Population estimates, including data on premature births, were obtained from the Office of National Statistics [16]. In cases where the serotype was not known, it was assumed that they had the same PCV13/non-PCV13 serotype distribution as the serotyped cases. Incidence rate ratios (IRR) were calculated with exact 95% confidence intervals (CI) using binomial probabilities. Non-parametric data are described using medians and interquartile ranges (IQR). Proportions were compared using the X^2 or Fisher exact test, as appropriate.

Results

Study Population

During the four year period, there were 517 cases of IPD in infants, and 291 (56.3%) were male. The overall IPD incidence was 19/100,000 infants. There was an increase in the incidence of all-serotype IPD from 17/100,000 infants in 2013 to 23/100,000 infants in 2016 (IRR 1.35, 95% CI 1.04-1.71, p=0.019). The median age at presentation was 165 days (IQR 63-269), with 49 cases (9.5%) occurring in the first 7 days and 158 (30.6%) in the first three months of life. IPD incidence in infants aged <90 days was 16/100,000 live births. Overall, 99 (19.1%) infants had been born prematurely, 67 (13.0%) had clinical risk factors (excluding prematurity) for IPD and 148 (28.6%) had been born prematurely and/or had risk factors for IPD (Table 1).

Prematurity

The overall incidence of IPD was significantly higher in premature infants compared with those born at term (49/100,000 vs 17/100,000, incidence rate ratio 2.87; 95% CI, 2.28-3.59, p<0.001) with

infants born at below 28 weeks having the highest incidence (incidence rate 150/100 000, IRR 8.77; CI 4.63-15.16, p<0.001 compared with term infants). In premature infants, a higher proportion of cases occurred in the first month (27/97 [27.8%] vs. 38/420 [9.0%]; p<0.001) and particularly in the first two days of life (23/97 [23.7%) vs. 18/420 [4.3%]; p<0.001) compared to term infants. The median age (IQR) was 119 (17-234) days for premature infants compared to 177 (74-277) days in infants born at term (p<0.001). Premature infants had a higher incidence of both PCV13 and non-PCV13 IPD compared with term infants (Table 2) and both the absolute incidence and the relative risk declined with age (Table 3).

Clinical Presentation

Meningitis was the most common clinical presentation (222 cases, 42.6%), followed by septicaemia (164 cases, 31.7%), pneumonia (122 cases, 23.6%) and other sites (11 cases, 2.1%), including joint (n=10) and soft tissue (n=1) infections. Meningitis cases were diagnosed from birth and declined after 7 months of age; this trend was observed among both PCV13 and non-PCV13 serotypes causing meningitis. The majority of meningitis cases occurred in healthy infants born at term (185 cases, 84.1%). Of the 418 term infants with IPD, 49 (11.7%) had comorbidities. Infants with underlying conditions were more likely to have bacteraemia or pneumonia while previously healthy infants were likely to develop meningitis (p=0.004).

Serotypes

Of the 454 IPD cases with serotyped isolates, most were caused by non-PCV13 serotypes (369 cases, 71.4%) with 85 cases (16.4%) due to PCV13 serotypes. The most common non-PCV13 serotypes causing IPD were serotypes 12F and 8 (43 cases each, 9.5%) and 10A (40 cases, 8.8%) (Figure 1). Of PCV13 serotypes, serotype 3 dominated among premature (13/23, 56.5%) and term (21/62, 33.9%) infants, as well as serotypes 19A and 7F in the latter.

Whilst the total number of IPD cases increased over the study period (from 115 in 2013 to 153 in 2016), the proportion of PCV13-serotype cases dropped from 31.3% (36 cases) in 2013 to 18.3% in 2016 (28 cases) (p=0.023). The serotype distribution varied during the first year of life (Figure 2). Overall, 50/143 (35.0%) cases in the first two months of life (pre-vaccination) were due to PCV13 serotypes compared to 35/311 (11.8%) in older infants (p<0.001). Non-PCV13 serotypes were

responsible for 51/60 (85%) IPD cases in infants with underlying conditions and 318/394 (80.7%) cases in healthy children (p=0.42).

PCV13-type IPD after vaccination

There were 85 PCV13-serotype cases in our cohort, 24 (28%) in preterm infants and 61 (72%) in term infants. In preterm infants, 15 were too young for vaccination, both infants who were eligible for one dose were unvaccinated prior to developing IPD (serotypes 3, 19A); of those who were eligible for 2 doses (7 infants), one was unvaccinated (serotype 7F), three had received one dose (all serotype 3) and the three appropriately vaccinated infants developed IPD (two serotype 3 and one 19A). In term infants, 26 were too young to be vaccinated, 3/12 who were eligible for the first dose were unvaccinated prior to developing IPD (serotypes 3, 7F, 19F) and the remaining 9 developed IPD due to serotypes 7F (8 cases) and 19A. Of the 23 eligible for 2 doses, 2 were unvaccinated (serotypes 7F, 19F), 3 had received a single dose only (two serotypes 7F, one serotype 3) and the 18 appropriately vaccinated infants developed IPD due to serotypes 3 (6), 19A (5), 1 (2) and one case each of serotypes 6B, 7F, 18C, 19F and 23F. Therefore, 6/9 (67%) preterm infants and 8/35 (23%) term infants were under-vaccinated prior to developing PCV13-type IPD (P=0.012).

Case Fatality Rate (CFR)

There were 31 deaths (CFR 6.2%; 95% CI, 4.3-8.6%), including 7 in children with comorbidities. CFR in previously healthy infants was 5.3% (24/450 cases) compared to 10.4% in infants with co-morbidities (7/67 cases; p=0.10). There were 7 deaths in infants born prematurely (CFR 7.1%) compared with 24 (5.7%) in infants born at term (p=0.62). Twelve infants with bacteraemia died (12/164, 7.3%), 8 with meningitis (8/222, 3.6%) and 11 with pneumonia (11/122, 9.0%). Of the 23 deaths with known serotypes, 5 were associated with PCV13 serotypes (Supplementary Table 1).

Discussion

Our study focused on infants in their first year of life with IPD in the post-PCV13 era. We found that infants born prematurely continue to have an increased risk of IPD compared with infants born at term for both PCV13 and non-PCV13 serotypes, and that this risk was highest in the first month of life. Currently, in infants, most PCV13-type IPD cases occur either before PCV13 vaccination or in those partially-immunised.

The successes of both the PCV7 and PCV13 programmes in the UK are remarkable [9] with near elimination of IPD due to the vaccine serotypes. The few cases of PCV13-type IPD, however, indicate that some of these serotypes, especially 3 and 19A, continue to circulate in the community and highlight the importance of timely immunisation for infants, including those born prematurely.

IPD in premature infants

In our cohort, premature infants had a higher risk of both PCV13 and non-PCV13 type IPD compared to those born at term; this risk increased with increasing prematurity and decreased with postnatal age. Premature infants are known to have an increased risk of infectious diseases, including vaccine-preventable infections [17–19]. A study of 6,000 low birth weight and premature infants in the USA prior to PCV introduction revealed a 1.6-2.6 fold increase in IPD compared with normal weight, term infants [19]. There have been few studies looking at PCV impact in term and premature infants. Ruckinger *et al* compared IPD rates before and after the introduction of PCV7 into the German national immunisation schedule. They included all cases in children up to 15 years of age and, although they identified only 22 children born prematurely, they noted a comparable reduction in IPD rates in those born at term (15.0 to 8.5/100,000; 43% reduction) and those born prematurely (26.1 to 16.7/100,000; 36% reduction) between 2000 and 2007. The IPD incidence in premature infants remained nearly twice as high as children who had been born at term [17]. This increased risk of IPD and other vaccine-preventable diseases is likely to be due to a combination of reasons, including an immature immune system, reduced transplacental transfer of maternal antibodies, delayed immunisation, prolonged hospitalisation and ongoing medical conditions [20–23]. Previous studies have shown reduced immunogenicity of pneumococcal conjugate vaccines in infants born prematurely, particularly those receiving reduced primary immunisation schedules [14,20]. Our findings confirm an ongoing increased risk of vaccine preventable IPD in premature infants in the post-PCV13 era. Differences in clinical presentation and serotype distribution may be due to premature infants developing early-onset IPD, most likely through vertical transmission, and presenting with septicaemia, while term infants are more likely to acquire the infection through horizontal transmission, develop IPD at a later age and present with meningitis and other focal infections [11].

PCV13 serotype IPD

We found a significant proportion of infants who developed PCV13-type IPD were delayed with their

pneumococcal vaccinations, emphasising the importance of timely immunisation in this vulnerable group [13,14,24]. Of the PCV13 serotypes causing IPD, serotypes 19A and 3 were overrepresented in term and preterm infants. The estimated vaccine effectiveness against these serotypes – even after completion of the nationally recommended schedule – is lower compared to the other PCV13 serotypes [25] and these two serotypes are the most common cause of vaccine failure in UK children [26].

In October 2017, the JCVI recommended a reduction in the UK infant PCV13 schedule to a single priming dose at 3 months of age [10]. The success of the current vaccination programme means that PCV13 disease is at very low levels in the UK and modelling suggests that the 12 month dose is the most important for the reduction of carriage and, therefore, maintaining population (herd) protection across all age groups. In a recent clinical trial, although a single PCV13 priming in term infants was less immunogenic than two priming doses, antibody concentrations and proportion of infants protected after the 12-month booster for the PCV13 serotypes were similar across both groups [27]. Therefore, the continuing population protection offered by the 12-month booster should limit exposure of PCV13 serotypes during the vulnerable period between the priming and booster vaccinations, even with a reduced PCV13 priming schedule. This could potentially save the health service around 800,000 vaccine doses annually and reduce the number of injections to only two per primary immunisation.

However, given the increased incidence of IPD in premature infants, any reductions in the priming schedule will require careful monitoring in this vulnerable group. In a previous study a two-dose infant priming schedule in premature infants resulted in significantly lower geometric mean concentrations for 12 of the PCV13 serotypes compared with infants receiving 3 doses and, prior to the 12-month booster, very few infants had protective antibody concentrations against more than half the PCV13 serotypes [14]. No clinical trial has been undertaken to assess a single priming dose in premature infants.

IPD in infants with underlying health problems

Individuals with specific conditions are known to have a significantly higher risk of IPD compared to their healthy peers [28]. We found a similar prevalence of these co-morbidities in our cohort

compared with a comparable cohort in the PCV7 period (both 13%) [12]. Other studies have reported similar rates of co-morbidities in children with IPD following PCV13 introduction, with a higher prevalence of IPD due to non-PCV13 serotypes in those with underlying health conditions compared to healthy infants [29]. Unfortunately, we do not have accurate denominator data on at-risk conditions in infants to calculate relative incidence and compare relative risks of IPD.

Meningitis is the most severe of all IPD presentations, being responsible for 43% of cases in our cohort, and is responsible for significant morbidity and mortality, with high rates of long-term neurodevelopmental sequelae among survivors [3]. CFR in our cohort was 6.2% and 4.4% in a previous PCV7 cohort; we do not, however, routinely collect data on neurodevelopmental sequelae. This is worthy of further study, especially given that most cases are now due to novel, replacing serotypes that are not preventable with current pneumococcal conjugate vaccines.

Strengths and limitations

The strength of this study lies in the established long-term national surveillance for IPD, alongside a national reference laboratory to serotype nearly 95% of all invasive pneumococcal isolates across England, which also allows us to compare rates over time. Since 2010, there is a statutory requirement for laboratories to report clinically significant infections to PHE; this process is now automated through electronic reporting. One limitation is the limited data collected in the surveillance questionnaire which is completed by the patient's general practitioner rather than hospital clinician. Detailed clinical information on presenting symptoms and signs, laboratory investigations, treatment and supportive management, sequelae and long-term follow-up are lacking. It is also possible that the prematurity status of some infants may not be readily identified in the general practice electronic database; however, identifying any additional IPD cases in infants born prematurely would only serve to increase the estimated incidence in this vulnerable group. Our rates should, therefore, be considered a minimum estimate.

Conclusions

The incidence of IPD in infants remains far lower than rates reported prior to PCV7 introduction in England, despite a small increase in disease due to non-PCV13 serotypes. The risk of IPD remains significantly higher in infants born prematurely compared to infant born at term, for both PCV13 and

non-PCV13 serotypes. The recent recommendation to reduce the UK 2+1 pneumococcal immunisation schedule (2 priming doses plus a booster) to a 1+1 schedule (single priming dose plus a booster) will need careful monitoring, especially in premature infants, who may be disproportionately affected by this change.

Notes

Conflicts of Interest: The Immunisation Department at Public Health England provides vaccine manufacturers (including GSK, MSD, and Pfizer) with post-marketing surveillance reports on vaccine preventable diseases, including pneumococcal infections, which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. CLS and NKF as employees of the Respiratory and Vaccine Preventable Bacteria Reference Unit have received research funding from Pfizer and GlaxoSmithKline but receive no personal remuneration. The PHE Respiratory and Vaccine Preventable Bacteria Reference Unit has provided pneumococcal serotyping surveillance reports to Affinivax. A cost recovery charge is made for these reports. PTH & SNL perform contract research for vaccine manufacturers (including GSK, Pfizer, and Sanofi Pasteur) on behalf of St George's University of London and Public Health England (London, UK), respectively, but receive no personal remuneration. All other authors declare no competing interests.

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Tables

Table 1: Characteristic of infants with IPD

	Term	Preterm	<28 weeks gestation	28-<32 weeks gestation	32-<37 weeks gestation
Number of IPD cases	419 (81)	99 (19)	13 (3)	21 (4)	64 (12)
Population	2437959	199100	8646	21121	169333
Incidence (per 100 000)	17	49[a]	15 [a]	99 [a]	38 [a]
Age at IPD					
<7 days	25 (6)	24 (24)	5 (38)	9 (43)	10 (16)
7-89 days	94 (22)	15 (15)	1 (7)	4 (19)	9 (14)
≥90 days	299 (72)	60 (60)	7 (54)	8 (38)	45 (70)
Risk factors					
Any	49 (12)	18 (18)	3 (23)	5 (24)	10 (16)
Chronic heart disease	23 (5)	5 (5)	0 (0)	1 (5)	4 (6)
Chronic respiratory condition	10 (2)	6 (6)	1 (7)	4 (2)	1 (1)
Asplenia or dysfunction	5 (1)	3 (3)	0 (0)	0 (0)	3 (5)
Cochlear implant	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
CSF leak	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Chronic liver disease	2 (<1)	1 (1)	0 (0)	0 (0)	1 (1)
Chronic renal disease	2 (<1)	1 (1)	1 (7)	0 (0)	0 (0)
Immunosuppression	1 (<1)	2 (2)	1 (7)	0 (0)	1 (1)
Diabetes	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
Presentation					
Bacteraemia	119 (28)	46 (46)	7 (54)	12 (57)	26 (41)
Meningitis	196 (47)	24 (24)	0 (0)	6 (29)	18 (28)
Pneumonia	93 (22)	29 (29)	6 (46)	3 (14)	20 (31)
Other	11 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Serotype group					
PCV13	61 (15)	24 (24)	4 (31)	9 (43)	11 (17)
Non-PCV13	302 (72)	68 (69)	9 (69)	10 (48)	48 (75)
Not serotyped	56 (13)	7 (7)	0 (0)	2 (10)	5 (8)
Died	24 (6)	7 (7)	0 (0)	3 (14)	4 (6)

Cases (%). [a] Statistically significant difference compared to term infants (p-value<0.05).
One premature infant had unknown gestation.

Table 2: Incidence rates and ratios for preterm infants

	Incidence rate (premature)	Incidence rate (term)	IRR (95% CI)	p-value
All serotypes				
<28 weeks	150/100 000	17/100 000	8.77 (4.63-15.16)	<0.001
28-32 weeks	99/100 000		5.80 (3.55-8.98)	<0.001
32-37 weeks	38/100 000		2.20 (1.67-2.87)	<0.001
All <37	49/100 000		2.87 (2.28-3.59)	<0.001
PCV13 serotypes only				
<28 weeks	46/100 000	3/100 000	16.11 (4.3-43.1)	<0.001
28-32 weeks	47/100 000		16.5 (7.6-32.2)	<0.001
32-37 weeks	7/100 000		2.5 (1.2-4.6)	0.009
All <37	13/100 000		4.5 (2.8-7.2)	<0.001
Non-PCV13 serotypes only				
<28 weeks	104/100 000	14/100 000	7.3 (3.3-14.0)	<0.001
28-32 weeks	52/100 000		3.6 (1.8-6.6)	<0.001
32-37 weeks	31/100 000		2.1 (1.6-2.9)	<0.001
All <37	36/100 000		2.5 (1.9-3.3)	<0.001

IRR: Incidence rate ratio, CI: confidence interval

Table 3: Incidence rates and ratios for age of IPD in preterm and term infants

	Incidence rate (premature)	Incidence rate (term)	IRR (95% CI)	p-value
All serotypes				
<1 month	162/100 000	19/100 000	8.70 (5.1-14.6)	<0.001
<3 months	80/100 000	19/100 000	3.95 (2.68-5.71)	<0.001
3-11 months	30/100 000	12/100 000	2.47 (1.84-3.27)	<0.001
PCV13 serotypes only				
<1 month	66/100 000	8/100 000	8.41 (3.53-19.30)	<0.001
<3 months	30/100 000	7/100 000	4.59 (2.35-8.50)	<0.001
3-11 months	5/100 000	1/100 000	4.08 (1.78-8.58)	<0.001
Non-PCV13 serotypes only				
<1 month	96/100 000	11/100 000	8.91 (4.37-17.8)	<0.001
<3 months	48/100 000	13/100 000	3.63 (2.20-5.78)	<0.001
3-11 months	25/100 000	11/100 000	2.29 (1.66-3.11)	<0.001

IRR: Incidence rate ratio, CI: confidence interval

Figures

Figure 1: IPD serotypes.

Legend: 6C included as a PCV13 related serotype.

Figure 2: PCV7, PCV13 and non-PCV7/13 serotypes over the first year of life

Figure 1

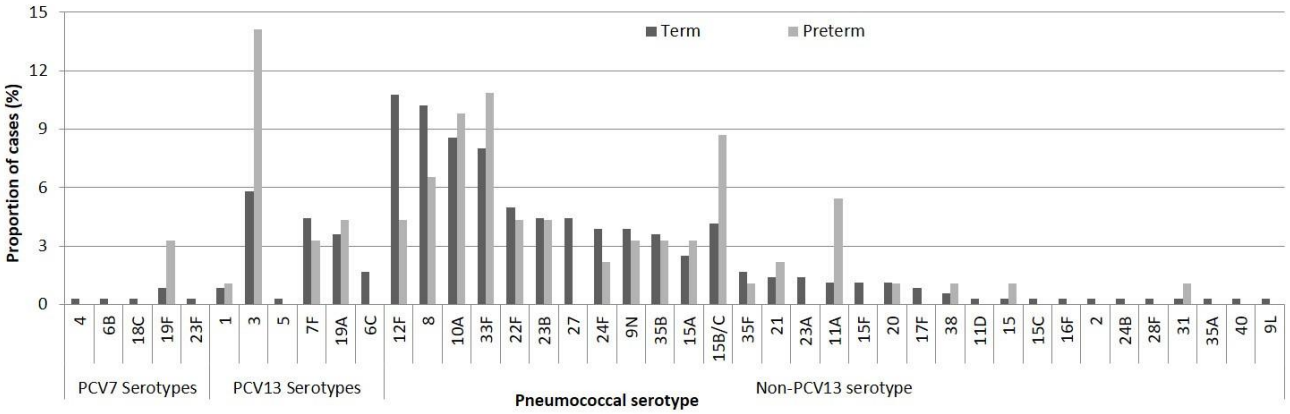

Figure 2