Characteristics and serotype distribution of childhood cases of invasive pneumococcal disease following pneumococcal conjugate vaccination in England and Wales, 2006-14

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Short title: Pneumococcal conjugate vaccine failure

Key words: Invasive pneumococcal disease, vaccine failure, pneumococcal conjugate vaccine, epidemiology, risk factors, outcome

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Total word count: 2,998 words

Key Points: We compared children with PCV13 and PCV7 vaccine failure in the UK. Vaccine failure was rare and, compared to PCV7 serotypes, the additional PCV13 serotypes are more likely to cause lower respiratory tract infections and empyema in healthy vaccinated children.

ABSTRACT

Background The 7-valent (PCV7) and 13-valent (PCV13) pneumococcal conjugate vaccines are highly effective in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes. Vaccine failure (vaccine-type IPD after age-appropriate immunisation) is rare. Little is known about the risk, clinical characteristics or outcomes of PCV13 compared to PCV7 vaccine failure.

Methods Public Health England conducts IPD surveillance and provides a national reference service for serotyping pneumococcal isolates in England and Wales. We compared the epidemiology, rates, risk factors, serotype distribution, clinical characteristics, and outcomes of IPD in children with PCV13 and PCV7 vaccine failure.

Results A total of 163 episodes of PCV failure were confirmed in 161 children over eight years (04 September 2006 to 03 September 2014) in ten birth cohorts. After three vaccine doses, PCV7 and PCV13 failure rates were 0.19/100,000 (95% CI, 0.10-0.33; 57 cases) and 0.66/100,000 (95% CI, 0.44-0.99; 104 cases) vaccinated person-years, respectively. Children with PCV13 failure were more likely to be healthy (87/105 [82.9%] vs. 37/56 [66.1%]; *P*=0.02), present with bacteremic lower respiratory tract infection (61/105 [58.1%] vs. 11/56 [19.6%]; *P*<0.001) and develop empyema (41/61 [67.2%] vs. 1/11 [9.1%]; *P*<0.001) compared to PCV7 failures. Serotypes 3 (n=38, 36.2%) and 19A (n=30, 28.6%) were responsible for most PCV13 failures. Five children died (3.1%; 95% CI, 1.0-7.1%), including four with co-morbidities.

Conclusions PCV failure is rare and, compared to PCV7 serotypes, the additional PCV13 serotypes are more likely to cause bacteremic lower respiratory tract infection and empyema in healthy vaccinated children.

INTRODUCTION

In the United Kingdom, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in September 2006 as a 2+1 schedule for all infants at 2, 4 and 12 months alongside a 12-month limited catch-up for <2 year-olds [1]. The programme led to a rapid decline in invasive pneumococcal disease (IPD) and, since young children are the main carriers of *S. pneumoniae* and PCV7 reduces carriage acquisition [2], significant reductions in PCV7-type IPD were observed across all age-groups, with overall IPD rates falling by 34% [3]. From April 2010, PCV7 was replaced by a 13-valent PCV (PCV13) without any catch-up and, by 2013/14, IPD incidence had fallen by a further 32% because of continued reduction in PCV7-type IPD and a 69% reduction in PCV13-type IPD [4].

The development of vaccine-serotype IPD in a PCV-immunised child (i.e. vaccine failure) is rare [5]. Although a number of studies have described children with PCV7 failure, little is known about PCV13 failure. Since individual pneumococcal serotypes have different propensities for invasiveness and disease, and since vaccine immunogenicity varies for the different serotypes, it is likely that the characteristics of children with PCV13 failure are different to those with PCV7 failure. This study aimed to describe the rate, vaccination status, serotype distribution, clinical characteristics and outcomes of children aged <5 years with PCV7 and PCV13 failure in England and Wales over an eight-year period.

METHODS

Public Health England (PHE) conducts enhanced national surveillance of IPD in England and Wales and, since PCV7 introduction, collected clinical and epidemiological information for all laboratory-confirmed IPD cases in <5 year-olds [3]. Briefly, hospital laboratories routinely report clinically significant infections to PHE electronically and submit invasive pneumococcal isolates to the national PHE Reference Laboratory for confirmation and serotyping. As part of enhanced national surveillance, general practitioners (GPs) and hospital paediatricians for <5 year-olds with laboratory-confirmed IPD completed a short questionnaire on vaccination history, known co-morbidities at the time of IPD, complications and outcomes. In the UK, children are actively called and immunised by their GPs, and their vaccinations documented in their individual electronic records. For this study, all children born since 04 September 2004 (i.e. including <2 year-olds eligible for the initial catch-up) with PCV failure diagnosed during 04 September 2006 to 03 September 2014 (i.e. 8-year period) were included.

Definitions

IPD was defined as *S. pneumoniae* cultured from a normally sterile site or pneumococcal DNA detected in cerebrospinal fluid (CSF) or pleural fluid. Meningitis was defined as *S. pneumoniae* identified (culture/PCR) in the CSF or *S. pneumoniae* cultured from blood with radiological and/or clinical features of meningitis. Lower respiratory tract (LRTI) was defined as *S. pneumoniae* identified in pleural/empyema fluid or in blood with a radiological and/or clinical diagnosis of pneumonia. Septicaemia was defined as *S. pneumoniae* cultured in blood with no clear focus of infection. Co-morbidity was defined as presence of a high-risk condition as defined in the Green Book on Immunisation [6]. For children with >1 IPD episode, only the first episode was included in the primary analysis; subsequent episodes are described separately.

Of the cases eligible for PCV7 only, the vaccine failure group was composed of three cohorts aged <5 years at diagnosis: PCV7-type IPD in a child (i) ≥14 days after two doses in <12 month-olds (PCV7-PCV7), (ii) ≥7 days after a single PCV7 dose in ≥12 month-olds (PCV7 catch-up); or (iii) ≥7

days after three PCV7 doses including the 12-month booster (PCV7-PCV7-PCV7). By definition, these cohorts could still be diagnosed even after PCV13 introduction if they only received PCV7, were diagnosed with PCV7-type IPD and were aged <5 years at diagnosis. The vaccine failure group that was eligible for ≥1 PCV13 dose also included three cohorts aged <5 years at diagnosis: IPD caused by the additional PCV13 serotypes (1, 3, 5, 6A, 7F and 19A) (i) ≥14 days after two doses in <12 month-olds (PCV13-PCV13); (ii) ≥7 days after PCV7 in infancy with a 12-month PCV13 booster (PCV13 catch-up); and (iii) ≥7 days after three PCV13 doses including the 12-month booster (PCV13-PCV13-PCV13).

Data Analysis

Data were analysed using Stata™ v.11.0 (Statcorp, Texas) and are mainly descriptive. The denominator for the vaccine failure rate was calculated by multiplying the number of children aged <5 years who were eligible for a specific vaccine schedule nationally (www.statistics.gov.uk) with the vaccine coverage and the eligible time-period for that schedule. Childhood vaccine coverage for both PCV7 and PCV13 has remained consistently high (>90%) over the years (https://www.gov.uk/government/collections/immunisation) [7]. Categorical variables were described as percentages with binomial 95% confidence intervals (95% CI) and compared using the chi-squared test or two-tailed Fisher's Exact test. Continuous variables that did not follow a normal distribution were described as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test. Multivariable logistic regression was used to investigate relationships between variables using the largest group as the baseline and adjusting for age as a continuous variable, gender and co-morbidity status. The serotype distribution among vaccine failure cases were compared to overall laboratory-confirmed IPD cases in the same age group in the nearest complete epidemiological year before the introduction of the relevant PCV (i.e. 2005/06 for PCV7 failures and 2009/10 for PCV13 failures). A p value of <0.05 was considered statistically significant; in Table 2, the Bonferroni correction was applied for multiple comparisons among PCV7 and PCV13 serotypes.

RESULTS

Over the eight-year surveillance period (04 September 2006 to 03 September 2014), 163 PCV failure episodes were confirmed in 161 children aged <5 years from ten birth cohorts. Complete clinical questionnaires and responsible serotypes were available for all children.

Types of failure

Of the 161 children, one third (n=57, 35.4%) were exclusively PCV7 failures, including 12 after completing the 2+1 schedule (**Table 1**). After PCV13 introduction, there were 104 additional failures, including 28 after three PCV13 doses. Compared to PCV7 serotypes responsible for IPD prior to PCV7 introduction (2005/06 epidemiological year), serotypes 6B and 19F were significantly over-represented while serotypes 4 and 14 were under-represented among PCV7 vaccine failures (**Table 2**). Following PCV13 introduction, serotype 3 was significantly over-represented and serotype 7F under-represented among PCV13 vaccine failures when compared to PCV13 serotypes responsible for IPD during 2009/10 (**Table 2**). In 2013/14, eight serotypes contributed to 23 vaccine failure cases, including nine (39%) due to serotype 3, four (17%) serotype 1 and three each (13%) of serotypes 19A and 19F (**Figure 1**).

Following the 2+0 schedule, although there were very few cases, serotype 19A failures clustered during the three months prior to the 12-month booster (**Figure 2**). This was not observed for any of the other PCV13 serotypes, including serotype 3. Additionally, of the 18 serotype 19A IPD cases diagnosed after 12 months of age, only two were in fully immunised children; the others were either in the PCV7-PCV7-PCV13 group (n=9) or developed IPD after their first birthday (5 of 7 cases diagnosed at 12-14 months of age) following a delay in receiving their 12-month booster. In contrast, 12/33 (36%) serotype 3 IPD cases after 12 months of age occurred in fully-immunised children, 16 in the PCV7-PCV7-PCV13 group and five in those with delayed 12-month booster.

PCV7 failure rate after three doses was 0.19/100,000 person-years (95% CI, 0.10-0.33) and 0.66/100,000 person-years (95% CI, 0.44-0.95) after three PCV13 doses (**Table 1**). The annual incidence of vaccine failure cases declined with time since PCV7 introduction, but this was less marked after PCV13 introduction (**Figure 1**). The increase in vaccine failure rates from 2010/11 was due to the inclusion of the additional PCV13 serotypes. Children with PCV13 failure were more likely to have been healthy (85% vs. 67%; a*OR*=2.8*;* 95% CI*,* 1.3-5.9; *P*=0.01), present with LRTI (58% vs. 21%; aOR, 4.6; 95% CI, 2.2-9.9; *P*<0.001) and develop empyema following LRTI (67% vs. 8%; aOR=20.7; 95% CI, 2.4-175.2; *P*=0.005) compared to PCV7 failures (**Table 3**). PCV7 failures had increased odds of presenting with septicaemia compared to PCV13 failures (47% vs. 19%; aOR=3.2, 95% CI, 1.5-6.7; P=0.002).

Clinical Presentation

Overall, LRTI (n=72; 45%) was the most common clinical presentation (**Table 3**). Serotypes 3 (n=28/72; 39%), 19A (n=15; 21%) and 1 (n=9; 13%) were responsible for most cases. Notably, 28/38 (74%) serotype 3, 15/30 (50%) serotype 19A and 9/13 (69%) serotype 1 cases presented with LRTI. Forty-one of the 72 children (57%) with LRTI developed empyema, including 22/28 (79%), 8/15 (53%) and 6/9 (67%) due to serotypes 3, 19A and 1, respectively. These same three serotypes were more likely to cause vaccine failure in healthy children than those with co-morbidity (**Figure 3**).

Septicaemia was the second most common clinical presentation (n=47; 29%) and serotypes19F and 6B (11/47 each; 23%) were mainly responsible. Meningitis was diagnosed in 36 children (22%); of these, five (14%) had co-morbidities and 19A (7/36, 19%), 19F (6/36; 17%) and 6B (5/36; 14%) were the main responsible serotypes.

IPD by Comorbidity status

Overall, 35 (22%) cases had underlying co-morbidity, mainly malignancy/immunosuppression (16/161, 10%) or cardiac abnormalities (8/161, 5%); five children (3%) had >1 comorbidities. Children with co-morbidity were likely to be older (median age, 28 [IQR, 18-39] vs. 19 [IQR, 11-28] months; *P*=0.007) and present with septicaemia (20/35 [57%] vs. 27/126 [21%]; aOR=5.5, 95% CI, 2.4-12.7; P<0.0001), but less likely to present with LRTI (9/35 [26%] vs. 63/126 [50%]; aOR=0.24, 95% CI, 0.10-0.60; P=0.002). Serotype 6B (n=7; 20%), 23F (n=6; 17%) and 3 (n=5, 14%) were the main serotypes responsible; 6/10 (60%) serotype 23F and 3/6 (50%) serotype 18C, but only 5/38 (13%) serotype 3, IPD cases occurred in children with co-morbidity. Conversely, only 3/30 (10%) serotype 19A, 1/13 (8%) serotype 1 and 1/5 (20%) serotype 7F occurred in children with comorbidity.

Repeat episodes and case fatality

One toddler with congenital hydrocephalus and a VP shunt suffered two episodes of serotype 6B meningitis, with the first episode occurring five months after a PCV7 catch-up dose. A second toddler with congenital deafness developed two episodes of serotype 4 meningitis after three PCV7 doses, with the first episode occurring two weeks after cochlear implantation [2, 8]. CFR among vaccine failure cases was 4% (n=6; 95% CI, 1-8%) (**Table 3**). Five children had underlying co-morbidity and one was healthy (5/35 [14%] vs. 1/126 [1%]; p<0.001).

DISCUSSION

In England and Wales, PCV failure was rare, with only 161 children diagnosed in ten birth cohorts diagnosed over eight years (<1/100,000 vaccinated person-years). Vaccine failure rates were higher after two PCV doses in infancy and lowest after completion of the recommended 3-dose schedule, most likely because of a combination of factors, including higher VE after 3 doses, lower incidence in older ages and more time for herd immunity effects after PCV introduction. PCV13-failure cases were more likely to be healthy and develop LRTI, while those with PCV7-failure were more likely to have co-morbidities and develop septicaemia. Only a third of PCV13-failure cases had co-morbidity, mainly immunosuppression and cardiac abnormality. Recurrent IPD was rare (two children) and case fatality rate was low (six children), both associated with underlying co-morbidity.

Following three infant doses of the *Haemophilus influenzae* type b (Hib) conjugate vaccine, the vaccine failure rate was 2.2/100,000 UK children over six years and five months [9]. For the meningococcal group C (MenC) conjugate vaccine, only 53 vaccine failure cases were identified among <18 year-olds during the first four years after vaccine introduction [10]. Potential explanations for vaccine failure include the presence of underlying co-morbidities and waning antibodies after vaccination, which has been described for both Hib and MenC vaccine failures [9, 10].

In the UK, PCV7 introduction rapidly achieved high vaccine coverage, resulting in 98% and 93% lower IPD rates in PCV7-type IPD within four years in <2 year-olds and 2-4 year-olds, respectively [3]. Compared to serotypes causing IPD in the pre-PCV7 period, serotypes 6B and 19F were over-represented among vaccine failure cases. These two serotypes had the lower antibody responses after infant immunisation [11], and the lowest serotype-specific vaccine effectiveness after PCV7 introduction (49% and 70%, respectively) [12]. Others have also reported a predominance of these two serotypes among PCV7 failure cases, which were responsible for 59% of PCV7 failures in our cohort [13]. Co-morbidity prevalence in the published literature, relating almost exclusively to PCV7 failures, ranged between 10-36%, which is in keeping with 15% in our cohort [5], with

immunosuppression – mainly malignancy – and cardiac conditions predominating.

After PCV13 introduction, serotype 3 was over-represented among vaccine failures. Low vaccine effectiveness for this serotype has been reported in England and Wales [14], although some protection was observed in the United States [15]. In infants, serotype 3 elicited the lowest post-primary and post-booster antibody responses of the additional PCV13 serotypes [16]. It is estimated that very higher serum IgG concentrations (>2.83 µg/mL) are required for protect against disease compared to the internationally-accepted threshold of 0.35 µg/mL [14], which are rarely attained after vaccination [16]. On the other hand, although serotype 19A is immunogenic in infants [16], vaccine effectiveness against this serotype has been poor (62% after two infant doses, 67% after three doses including the 12-month booster). A higher correlate for protection (>1.0 µg/mL) has also been estimated for this serotype [14].

In our cohort, the clustering of serotype 19A vaccine failure cases around the first birthday may indicate waning immunity after two infant priming doses, but this was not observed for any other serotype. Whether a three-dose priming schedule might reduce vaccine failure rates before the 12-month booster by inducing higher post-primary immunisation antibody concentrations is questionable, but this would involve an additional ~700,000 doses to prevent around eight vaccine failure cases, annually.

On the other hand, the vaccine failure cases diagnosed after 12 months of age in this same group highlights the importance of timely immunisation, especially for the booster dose. This dose is critical not only for individual protection but also to maintain herd protection through reduction in carriage.

Another contributing factor was the single PCV dose from 12-months of age in the initial PCV7 catch-up campaign and among those who received PCV7-PCV7-PCV13, when the latter vaccine was introduced. Here, two PCV doses from 12 months of age doses might have reduced vaccine failure rates but would have involved additional vaccination and immunisation visits during the catch-up campaign to prevent very few vaccine failure cases annually.

Comparison of PCV7 with PCV13 vaccine failure cases identified several important differences. Children with PCV13 failure were more likely to be healthy and develop LRTI. During 2006-2010 (after PCV7 introduction and before replacement with PCV13), we reported higher co-morbidity prevalence among children with PCV7-failure compared with cases in unvaccinated children due to the same serotypes. Moreover, IPD due to the additional PCV13 serotypes was associated with lower comorbidity (17% vs. 40%) and higher LRTI (58% vs. 20%) prevalence when compared to children with PCV7-type IPD [5]. This pattern was also observed for serotype 3 only, which is responsible for a third of vaccine failure cases in our PCV13 cohort. After PCV13 introduction, 19% of our PCV13 failure cases had comorbidity, compared to 9% among unvaccinated children with PCV13-type IPD prior to PCV13 introduction.[5] Any additional benefit of offering extra PCV13 doses to children with comorbidities (e.g. using a 3+1 schedule) is are likely to be negligible given the small numbers of PCV13-failures overall (23 cases) and in those with co-morbidities (6 cases, including five in fully-immunised children) in 2013/14. Children with co-morbidities are also benefiting from the continuing indirect (herd) protection offered by the current programme

Clinical Implications

An important consideration for children with conjugate vaccine failure, especially those without known co-morbidities, is the possibility of an undiagnosed underlying immune deficiency. In addition to clinical risk factors, immunoglobulin deficiency has been described in those with Hib [17], but not MenC, vaccine failure [10]. In the UK, 11% of 172 children with IPD had transient IgG deficiency, which was only marginally below the lower limit for age [18]. We recently reported that, although a significant proportion of vaccinated children with vaccine-type IPD did not achieve protective antibody thresholds against the infecting serotype even after vaccination post-IPD, their IgG responses to the other vaccine serotypes remained intact, indicating that an underlying antibody deficiency was unlikely [19]. In a recent French study, however, 26/163 (16%) children with IPD had abnormal immunological investigations and 17 (10%) had a primary immunodeficiency, including MyD88 deficiency (n=1), complement C2/C3 deficiency (n=1), congenital asplenia (n=1) and Bruton's disease (X-linked agammaglobulinaemia; n=1) [20]. In addition to MyD88, a number of rare

primary immunodeficiencies associated with mutations in toll-like receptors (TLR), interleukin pathways (e.g. IRAK4) and NEMO genes have been associated with (often recurrent) invasive bacterial infections in early childhood, mostly due to *S. pneumoniae* [21]. The extent of immunological investigations for individual children with conjugate vaccine failure is likely to require careful clinical assessment, taking into account the family and past history of serious infections as well as the severity of IPD. An underlying immune deficiency is more likely in children who develop IPD after two years of age [20], and those with recurrent IPD [22], but has not been reported for children with PCV failure, possibly because this is such a rare event.

In England and Wales, follow-up investigations in children with IPD were at the discretion of the attending clinician but, since the surveillance questionnaire was completed several weeks after the IPD episode, any immune deficiency identified after IPD would have been reported. It is also reassuring that second episodes and deaths among vaccine failure cases were rare.

This study has strengths and limitations. The established IPD surveillance spanning more than two decades alongside a national reference laboratory service has ensured high case ascertainment and near-complete follow-up of laboratory-confirmed cases. We did not include children diagnosed by urinary pneumococcal antigen or blood pneumococcal PCR; neither test is offered by local hospital laboratories or the national reference laboratory because nasopharyngeal carriage can give false-positive results in young children colonised with *Streptococcus pneumoniae* [23]. We also do not collect detailed information on IPD cases in children after their fifth birthday. If PCV13-type IPD cases do start appearing in older children because of waning immunity, for example, these would be identified through the on-going national IPD surveillance. Finally, it was also not possible to compare vaccine failure rates between the two PCVs for several reasons, including non-contemporaneous introduction of the two vaccines, differences in circulating serotypes prior to vaccine introduction, differential serotype-specific carriage rates, invasiveness of individual serotypes, serotype-specific vaccine immunogenicity and a catch-up programme for PCV7 only. Each vaccine, however, has been used for approximately four years and these results suggest that vaccine failure is more common for the additional PCV13 serotypes, especially serotype 3.

CONCLUSIONS

Most children with PCV13 failure were healthy, developed LRTI and survived their infection without long-term complications. The low prevalence of PCV7 failures after PCV13 introduction is reassuring and it is likely that PCV13 failures will also decline in the coming years. Given that most IPD cases are now due to non-PCV13 serotypes, there is an urgent need for serotype-independent subunit or whole-cell vaccines to control this devastating disease [24].

ACKNOWLEDGMENTS

GO, SC and SNL reviewed the literature, analysed the data, wrote the first draft, and co-ordinated the production of the manuscript. SC and SLN had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the interpretation of the data and writing the report; all authors approved the final version.

Additional Contributions

The authors would like to thank Mrs Rashmi Malkani and Ms Melissa Kephalas for her assistance with the clinical follow-up of cases and data entry. The authors are grateful to the general practitioners and clinicians who took the time to complete the surveillance questionnaires and provide additional information when requested. We also thank Dr Derrick Crook and David Griffiths of the John Radcliffe Hospital Oxford for reporting IPD cases in Southern England serotyped by their laboratory.

Ethical Approval

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential 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.

Funding/Support

No external funding was received for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest

No external funding was received for this piece of work. SC, NA and SNL have provided vaccine manufactures with post-marketing surveillance reports which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. In accordance with PHE policy a cost recovery charge is made for these reports payable to the Immunisation department. Public Health England has received payment for lectures given by and RB from GSK, Baxter, SPMSD, and Novartis. MPES has received funding from Pfizer and Sanofi Pasteur for participation in Advisory Boards and from GSK and Astra Zeneca for participation in Symposia at International Scientific Meetings. RB and SNL perform contract research on behalf of Public Health England for GSK, Novartis, Pfizer and Sanofi Pasteur.

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LIST OF FIGURES

Table 1. Characteristics of children with vaccine failure in the cohort eligible for PCV7 and PCV13, England and Wales.

		PCV7				**PCV13**			
	All cases (%)	PCV7 catch-up	PCV7-PCV7	PCV7-PCV7-PCV7	**All PCV7 Cases**	PCV13 catch-up	PCV13-PCV13	PCV13-PCV13-PCV13	**All PCV13 Cases**
Immunised Cohort		1 dose >12m only (catch-up)	2 doses <12m only	1 or 2 doses <12m + 12m booster		2 doses PCV7 <12m + 12m PCV13 booster	2 doses <12m only	2 doses <12m + 12m booster	
Total (%)	**161**	20 (12%)	25 (16%) *15**	12 (7%)	**57**	35 (22%)	41 (25%) *28**	28 (17%)	**104** ***91****
Immunised person-years at risk	**17,513,442**	1,747,843	1,390,792	6,364,742	**9,503,378**	2,085,286	1,656,249	4,268,529	**8,010,064**
Vaccine failure rate per 100,000 person-years at risk	**0.92 (0.78-1.07)**	1.14 (0.70-1.77)	1.80 (1.16-2.65) *1.08 (0.60-1.78)**	0.19 (0.10-0.33)	**0.60 (0.45-0.78)**	1.68 (1.17-2.33)	2.48 (1.78-3.36) *1.69 (1.12-2.44)**	0.66 (0.44-0.95)	**1.30 (1.06-1.57)**
Male Cases	**90 (55%)**	12 (60%)	17 (68%)	8 (67%)	**37 (65%)**	23 (66%)	18 (44%)	12 (43%)	**53 (51%)**
Median age in months (IQR)	**20.0 (11.3-30.9)**	25.6 (22.2-39.3)	10.0 (6.3-12.7)	38.3 (32.1-43.1)	**21.0 (11.3-37.0)**	29.7 (20.1-41.4)	10.0 (8.6-12.2)	23.9 (19.9-30.4)	**19.9 (11.2-29.6)**

** In infants receiving two priming doses (2+0 schedule), only those vaccine failure cases diagnosed before 12 months of age were included in this analysis*

Table 2. Distribution of vaccine failure serotypes compared to the pre-vaccine baseline. Proportions of individual serotypes causing IPD in England and Wales during the epidemiological year prior to PCV introduction were compared using the χ2-test against the proportion of IPD cases caused by the same serotypes in vaccinated children after PCV introduction. After applying the Bonferroni correction for multiple comparisons, p<0.007 was considered statistically significant for the PCV7 serotypes and p<0.003 for the PCV13 serotypes.

Serotype	Total cases by serotype	Pre-PCV7 serotypes among IPD cases 2005/06	PCV7				Pre-PCV13 serotypes among IPD cases 2009/10	PCV13			
			Total PCV7	1 dose >12m only (catch up)	2 doses < 12m only	1 or 2 doses <12m + 12m booster		Total PCV13	2 doses PCV7 <12m + 12m PCV13 booster	2 doses <12m only	2 doses <12m + 12m booster
	N=161	N=2,122	N=57	N=20	N=25	N=12	N=2,651	N=104	N=35	N=41	N=28
4	2 (1%)	298 (14%)	2 (4%)	-	-	2	70 (3%)	-	-	-	-
6B	**23 (14%)**	**219 (10%)**	**19 (33%), *P<0.001***	9	9	1	72 (3%)	4 (4%)	2	-	2
9V	5 (3%)	323 (15%)	5 (9%),	2	2	1	72 (3%)	-	-	-	-
14	5 (3%)	646 (30%)	3 (5%),	1	2	-	72 (3%)	2 (2%)	-	1	1
18C	6 (4%)	145 (7%)	4 (7%)	-	1	3	59 (3%)	2 (2%)	-	1	1
19F	**22 (14%)**	**195 (9%)**	**15 (26%), *P<0.001***	4	9	2	**69 (3%)**	**7 (7%)**	-	4	3
23F	10 (6%)	296 (14%)	9 (16%)	4	2	3	70 (3%)	1 (1%)	-	-	1
1	13 (8%)						457 (17%)	13 (11%)	7	2	4
3	38 (24%)						**376 (14%)**	**38 (37%), *P*<0.001**	16	10	12
5	1 (0.6)						9 (0.3%)	1 (1%)	1	-	-
6A	1 (0.6)						99 (4%)	1 (1%)	-	1	-
7F	5 (3%)						**621 (23%)**	**5 (5%), *P*<0.001**	-	3	2
19A	30 (19%)						605 (23%)	30 (29%)	9	19	2

Table 3. Characteristics of children with vaccine failure in the cohort eligible for PCV7 and PCV13, England and Wales.

		PCV7				PCV13			
		PCV7 catch-up	PCV7-PCV7	PCV7-PCV7-PCV7		PCV13 catch-up	PCV13-PCV13	PCV13-PCV13-PCV13	
	All cases	1 dose >12m only (catch up)	2 doses < 12m only	1 or 2 doses <12m + 12m booster	**All PCV7 cases**	2 doses PCV7 <12m + 12m PCV13 booster	2 doses <12m only	2 doses <12m + 12m booster	**All PCV13 cases**
Total cases	**161**	20	25	12	**57**	35	41	28	**104**
Prematurity	**15 (9%)**	1 (5%)	4 (16%)	1 (8%)	**6 (11%)**	5 (14%)	3 (7%)	1 (4%)	**9 (9%)**
Any co-morbidity	**35 (22%)**	8 (40%)	5 (20%)	6 (50%)	**19 (33%)**	5 (14%)	4 (10%)	7 (25%)	**16 (15%) ***
Clinical Presentation									
Meningitis	**36 (22%)**	5 (25%)	7 (28%)	4 (33%)	**16 (28%)**	2 (6%)	15 (37%)	3 (11%)	**20 (19%)**
LRTI	**72 (45%)**	5 (25%)	5 (20%)	2 (17%)	**12 (21%)**	28 (80%)	13 (32%)	19 (68%)	**60 (58%) ***
Septicaemia	**47 (29%)**	9 (45%)	12 (48%)	6 (50%)	**27 (47%)**	4 (11%)	11 (27%)	5 (18%)	**20 (19%) ***
Other	**6 (4%)**	1 (5%)	1 (4%)	-	**2 4%)**	1 (3%)	2 (5%)	1 (4%)	**4 (4%)**
2nd episode	**2 (1%)**	-	-	1 (8.3)	**1 (2%)**	-	-	1 (4%)	**1 (1%)**
Died	**6 (4%)**	1 (5%)	1 (4%)	-	**2 (4%)**	2 (6%)	1 (2%)	1 (4%)	**4 (4%)**

** P<0.01 (proportions were compared using the χ2-test between cases eligible for PCV7 only and those eligible for ≥1 PCV13)*

Figure 1

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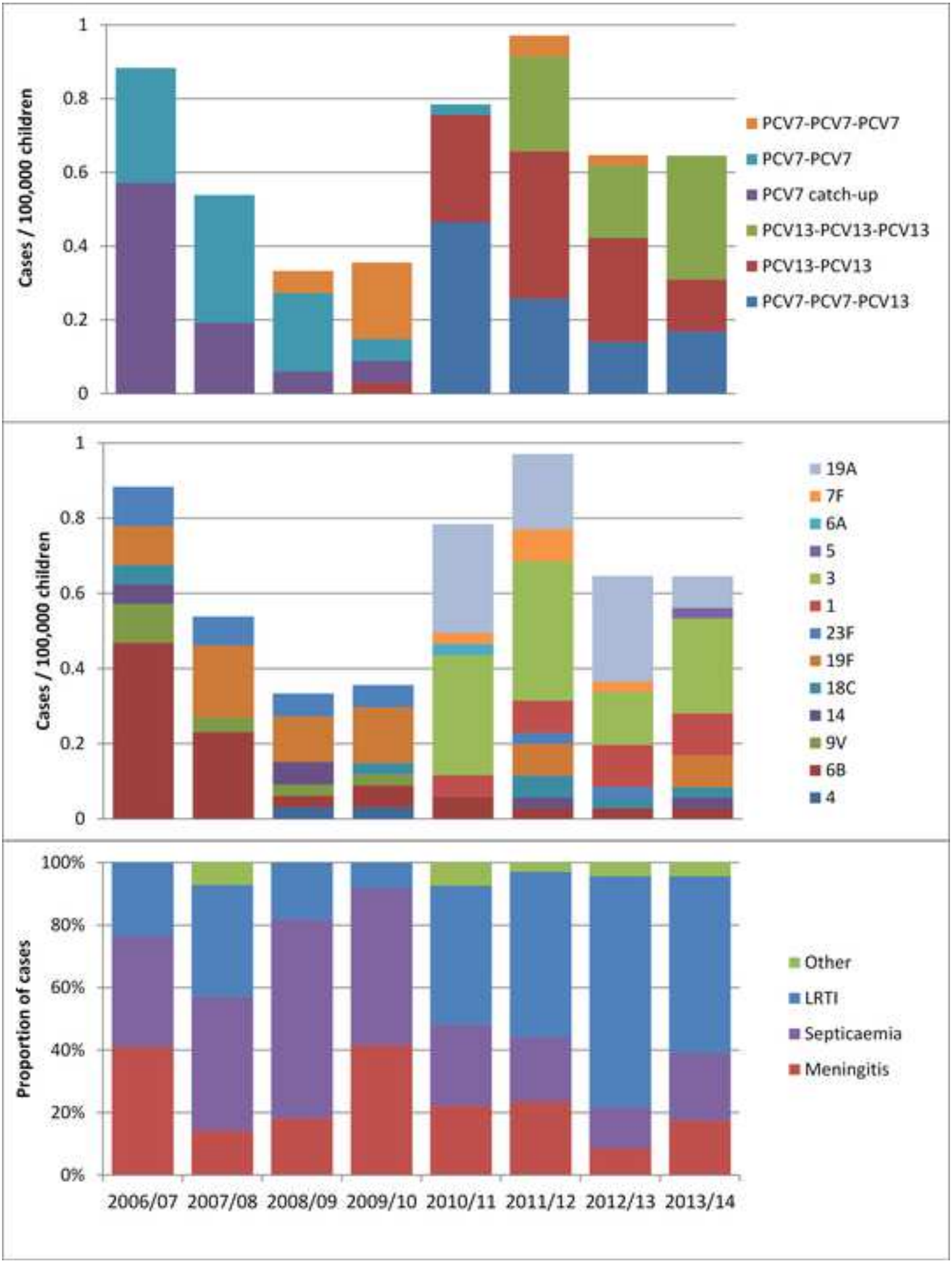

Figure 2

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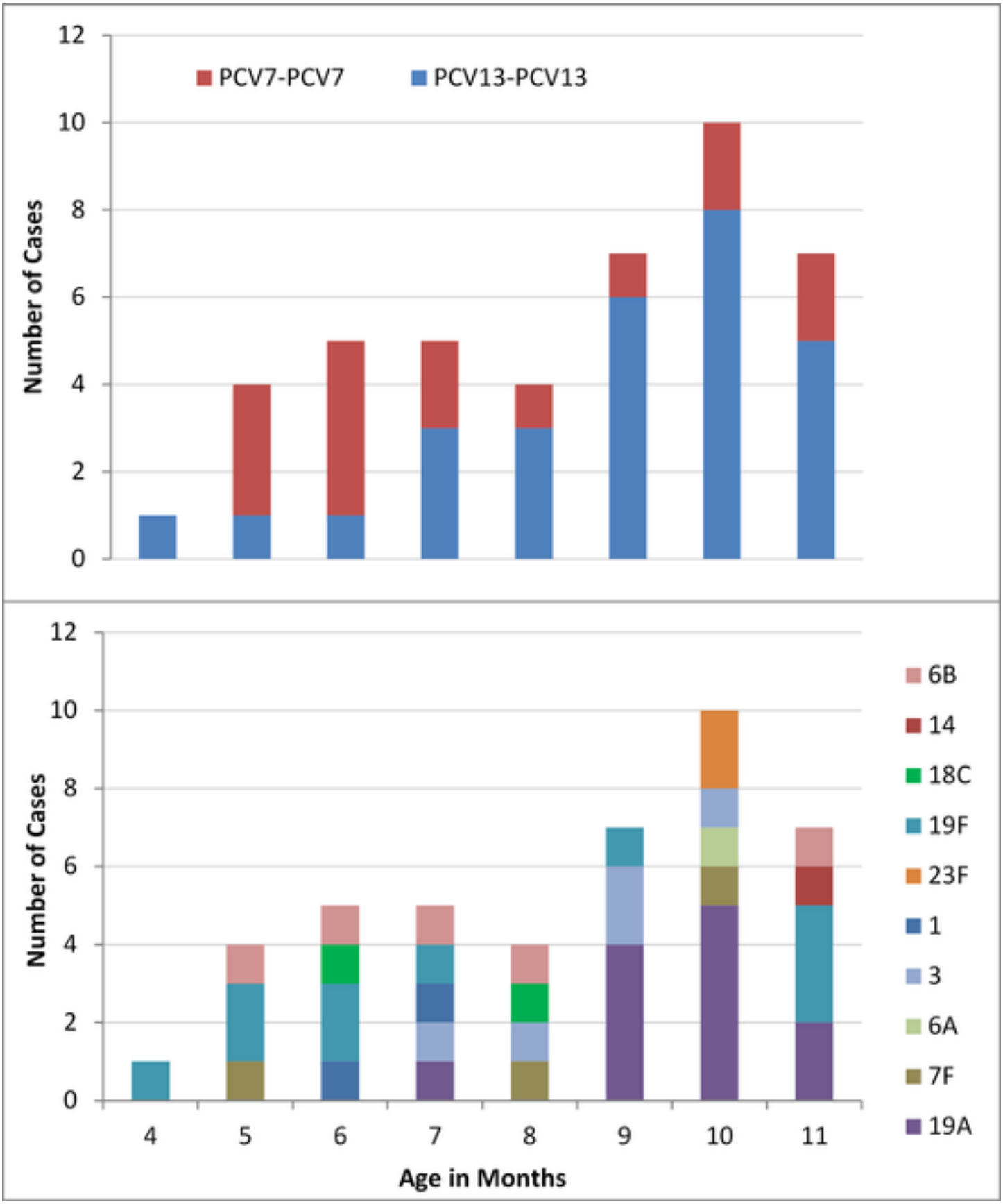

Figure 3

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