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Recurrent invasive pneumococcal disease in children: A retrospective cohort study, England, 2006/07-2017/18

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SUMMARY

Background: Recurrent invasive pneumococcal disease (IPD) is rare in children and usually associated with underlying comorbidities. We aimed to assess the risk and describe the characteristics of children with recurrent IPD over a 12-year period covering the introduction of the 7-valent (PCV7), followed by the 13-valent (PCV13) pneumococcal conjugate vaccine (PCV) in the national childhood immunisation programme in England.
Methods: We used enhanced national surveillance data for England and included all laboratory-confirmed IPD cases in children (< 15 years) during 2006/07–2017/18. We assessed the risk and rate of recurrent IPD, the serotypes responsible and the demographics, comorbidity status and prevalence, vaccination status, clinical presentation and outcomes in children with recurrent IPD compared to those with a single IPD episode.
Findings: There were 5158 IPD episodes reported in 5033 children over 12 years and 2.2% (105/4814) of those surviving their first IPD had at least one recurrence. Recurrence risk decreased with increasing age and over time. During 2015/16–2017/18, five years after PCV13 replaced PCV7, IPD recurrence rate was 229.0 (95% CI 154.8–339.0) per 100,000 person-years, with all recurrent cases caused by non-PCV13 serotypes. Where serotype information was available, recurrence was due to the same serotype in 25 cases, with a shorter median (IQR) interval of 88 (57–177) days between recurrent episodes, and in 60 cases due to different serotypes, with a median (IQR) interval of 223 (125–574) days (p=0.001). Compared to healthy children (103.0; 95%CI 63.1–168.1), recurrence rate per 100,000 person-years was 10 times higher in children with any comorbidity (1061.0; 95% CI 827.2–1360.9; 62/78 [79.5%] with available information had comorbidities), and almost 30 times higher in immunosuppressed children (2788.5; 95%CI 2029.0–3832.2; 38/78 [48.7%] were immunosuppressed). The 30-day case-fatality rate after recurrent IPD was 2.9% (3/105) compared to 4.4% (219/4928; p=0.63) after single-episode IPD.
Interpretation: Recurrent IPD is rare in children and occurs mainly in children with comorbidities, especially immunosuppression. Higher-valent PCVs have the potential to further reduce the risk of recurrent IPD in children.

Introduction

Streptococcus pneumoniae is the leading infectious cause of morbidity and mortality worldwide, with the highest incidence at the extremes of age.[1,2] At least 100 different pneumococcal serotypes have been identified based on their unique capsular polysaccharide.[3] Pneumococcal Conjugate Vaccines (PCVs) have had a major impact in reducing the incidence of invasive pneumococcal disease (IPD) through direct protection in vaccinated children and indirect protection across all age groups because the vaccines also prevent carriage of vaccine serotypes in immunised children and, therefore, interrupt onward transmission to others.[4]

In the UK, the 7-valent PCV (PCV7) was implemented in September 2006 as a 2+1 schedule (2, 4 and 12–13 months) and replaced with a 13-valent vaccine (PCV13) in April 2010. Both vaccines were associated with large declines in IPD due to the respective vaccine serotypes, although there was some replacement in IPD caused by non-vaccine serotypes across all age groups.[4]

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Particularly since 2013/14, the UK experienced rapid increases in IPD due to some non-vaccine serotypes, especially serotypes 8, 9N and 12F.[4] Additionally, in January 2020, the UK became the first country to implement a reduced 1+1 PCV13 schedule (12 weeks and 12 months) for infants.[5]

Whilst the vast majority of children with IPD experience a single episode, a small proportion may develop recurrent IPD, although the risk is now substantially lower with routine PCV use.[6] We have reported a very low risk of recurrent IPD in children after implementation of both PCV7 and PCV13, mainly in those with underlying comorbidities, particularly immunosuppression.[7–9] Our experience is consistent with reports from other countries with established national PCV programmes.[6,10–15] With the maturation of the PCV13 programme resulting in a very low incidence of PCV13-type IPD, the emergence of non-PCV13 serotypes causing IPD and the different propensities of the emerging serotypes causing IPD in healthy and vulnerable children,[16,17] we performed a more detailed analysis of recurrent IPD cases since PCV7 implementation in England. Using national surveillance data, we aimed to estimate the incidence and describe trends over time, clinical features, underlying co-morbidities, serotypes responsible and outcomes of recurrent IPD in children over a 12-year period.[8]

Methods

In England, the UK Health Security Agency (UKHSA, formerly Public Health England) has been conducting enhanced national IPD surveillance for more than three decades.[4] Briefly, National Health Service (NHS) laboratories in England electronically report *S. pneumoniae* infections to UKHSA and routinely submit all invasive pneumococcal isolates to the UKHSA Respiratory Vaccine-Preventable Bacteria Reference Unit (RVPBRU) for confirmation and serotyping.[4] Reported cases without isolate submission are actively followed up with the reporting laboratory by the pneumococcal surveillance team. Case ascertainment has remained consistently high and, since 2006, 85%–95% of invasive isolates have been routinely serotyped at the RVPBRU. Additionally, for this analysis, pneumococcal isolates with the same serotype in children with recurrent IPD (39 isolates from 19 patients) were subjected to whole-genome sequencing, as described previously,[18] to determine whether the episodes were caused by the same strain (Supplement p2).

Following PCV7 introduction in 2006, IPD surveillance in England was enhanced using postal questionnaires completed by general practitioners of all confirmed IPD cases to collect data on vaccination status, underlying comorbidities, clinical presentation and outcomes. Surveillance initially included confirmed IPD cases in children aged < 5 years and was later extended to include all children from 2010 (in keeping with the age of children vaccinated in infancy since the start of the PCV7 programme). Unreturned or incomplete questionnaires were followed up with regular reminder letters and phone calls by the national surveillance team.

Definitions

For this analysis, all IPD episodes in children aged < 15 years during the 2006/07 to 2017/18 epidemiological years (01 July to 30 June) were included. This period was selected given the start of the COVID-19 pandemic in 2020, during which there were large reductions in IPD, alongside the implementation of a 1+1 vaccination schedule in England in 2020, which may also have an impact on IPD infections and reinfections.[18,19]

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/polymerase chain reaction) in the cerebrospinal fluid (CSF) or *S. pneumoniae* cultured from blood with radiological and/or clinical features of meningitis. Pneumonia was defined as *S. pneumoniae* identified in pleural/empyema fluid or in blood with a radiological and/or clinical diagnosis of pneumonia. Bacteraemia was defined as *S. pneumoniae* cultured in blood with no clear focus of infection. Patients with multiple clinical presentations were recorded hierarchically in order of meningitis, pneumonia, other (focus of infection) and bacteraemia.

Recurrent IPD was defined as ≥2 episodes in the same individual caused by different serotypes at any time or caused by the same serotype with an interval of ≥30 days between episodes. Patients with recurrent IPD were identified in the national surveillance database using their unique NHS identifier (NHS number) or by linking with name, sex, date of birth and postcode/region. Characteristics of recurrent cases, such as co-morbidities, age, epidemiological year, presentation and vaccination status, were categorised according to their first IPD episode.

Epidemiological years were grouped into three periods: 2006/07–2009/10 (PCV7-period), 2010/11–2014/15 (early PCV13-period) and 2015/16–2017/18 (late PCV13-period). Age-groups were categorised as: < 2, 2–4, 5–9, and 10–14-year-olds. Cases were considered to have a comorbidity if they belonged to any of the IPD clinical risk groups, as defined in the "Green Book on Immunisation against Infectious Diseases."[20] Comorbidities were further classified as immunocompromising (including malignancy and medically-induced immunosuppression) or not immunocompromising. Case-fatality rate (CFR) was defined as any death occurring within 30 days of the specimen date.

Cases were defined as fully-vaccinated, partially-vaccinated or unvaccinated based on the number of doses they received at least 14 days prior to their first IPD episode and the recommended doses at that age: 1 dose by 3 months of age, 2 doses up to their first birthday and three doses after their first birthday for children born on or after 01/09/2006. Children born between 01/09/2004 and 31/08/2006 had been eligible for a limited 12-month catch-up at the start of the PCV7 programme and were considered fully vaccinated if they received ≥1 PCV7 dose at least 14 days before their IPD episode. Children born before 01/09/2004 or aged < 6 weeks were considered ineligible for vaccination. Cases were classified according to vaccine-serotype group as PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F), additional PCV13 (1, 3, 5, 6A, 7F, 19A), additional PPV23 (8, 10A, 11A, 12F, 15B, 22F, 33F, 2, 9N, 17F, 20) and non-vaccine types.

Analysis

Laboratory and clinical questionnaire data are routinely imported into Microsoft Access (Microsoft Corporation, Redmond, Washington), linked and de-duplicated regularly. The final dataset was imported into Stata 17.0 (StataCorp LP, College Station, Texas) for analysis. We compared demographics and clinical characteristics reported during the first episode in children with recurrent IPD with those who developed a single IPD episode.

For recurrent IPD cases, we also assessed the interval between episodes, as well as the serotypes responsible and any differences in clinical presentation between episodes in children infected with the same serotype and those infected with different serotypes.

Continuous variables such as age and time-interval between episodes were analysed using a comparison of medians (Mann-Whitney U test). For categorical variables, we assessed univariate associations using chi-square test, or Fisher's exact test if small numbers (any cell < 10). We used multivariable cox regression to identify risk factors for recurrent IPD (only the first recurrent episode was included) with time scale as time since first episode. Recurrence was included in the model as a binary outcome, with comorbidity status (healthy/immunosuppressed/other comorbidity), vaccine-serotype group, clinical presentation, vaccination (≥1 dose/none) included as co-variates, with age and year as time-varying co-

variates. We tested the proportional-hazards assumption using Schoenfeld residuals' test and plotted Kaplan-Meier curves for recurrence and stratified by comorbidity status. We replicated the model with comorbidity status as a binary variable to estimate the increased risk of recurrent IPD in children with and without comorbidities. For these models, failure was defined as the date of the first recurrence (i.e. the second IPD episode). Follow-up began on 01 July 2006 and individuals entered the study on this date or on their birth date when born after this date. Follow-up ended on the earliest date between death, first recurrence (second IPD episode), turning 15-years-old or 30 June 2018. In cases where a patient died on the same day as the sample date, exit was established as specimen date +0.5 days to ensure they remained in the model. Using the same parameters, we also calculated the recurrence incidence rate per 100,000 person-years overall and by time-period, age-group, sex, comorbidity status and clinical presentation at first episode.

Results

There were 5158 IPD episodes in 5033 children aged < 15 years during 2006/07–2017/2018 (12 epidemiological years). Of the 4814 children who survived the first episode, 2.2% (105/4814) had ≥1 recurrent IPD episode, with 84.8% (89/105) children experiencing two episodes and 15.2% (16/105) experiencing ≥3 episodes. Annual IPD episodes declined from 689 in 2006/07 to 334 in 2017/18 and the proportion of recurrent episodes remained low throughout (range, 3.0% in 2008/09 to 6.9% in 2012/13) and without any temporal trend (Fig. 1). The proportion of invasive isolates serotyped remained high overall (4656/5158, 90.3%; range 85.3–93.6%), with no differences according to recurrence. Completed questionnaires were returned for 3895/5158 (75.5%) IPD episodes and the questionnaire return rate increased year-on-year (Supplement Table 1), remaining > 90% since 2014/15. As enhanced surveillance was initially limited to children aged < 5 years until 2010, the proportion of returned questionnaires was higher in younger children than older children (91.7% [3551/3872] in < 5-year-olds compared to 26.7% [344/1286] in 5–14-year-olds).

Of the 105 children with recurrent IPD, 61.9% (n=65) were male, which was similar to children with a single IPD episode (58.2% males; p=0.45) but their median (IQR) age at first episode was higher (3 [1–5] vs 1 [0–4] years, p < 0.001) (Table 1). The number of IPD cases reduced with increasing age for both single-episode and recurrent cases, with few cases after six years of age (Fig. 1, Table 1).

Comorbidities

Among children with completed questionnaires, the prevalence of any comorbidity (62/78 [79.5%] vs. 1158/3757 [30.8%]; p < 0.001) and of immunocompromising conditions (38/78 [61.3%] vs 294/3757 [25.4%]; p < 0.001) were both higher among children with recurrent IPD than single-episode cases (Table 1). This higher comorbidity prevalence among recurrent IPD cases was observed both in the < 5-year-olds and the 5 years and older age group, with an overall higher prevalence in the latter (Supplement Table 2). Congenital abnormalities were recorded in a third of cases with comorbidities in both groups. CSF leak (6/62; 9.7%; 95%CI 4.4–19.9% vs 39/1158; 3.4%; 95%CI 2.5%–4.6%; p=0.023) and chronic liver disease (6/62; 9.7%, 95%CI 4.4–19.9% vs 47/1158; 4.1% 95%CI 3.1–5.4; p=0.047) were significantly more prevalent among recurrent compared to single-episode cases. Other conditions such as coeliac disease, renal disease and asplenia were also more prevalent amongst recurrent cases but not significant, likely because of small numbers (Supplement Table 3). Among immunocompromising conditions in children with recurrent IPD, acute lymphoblastic leukaemia (18/38, 47.3%) was the most prevalent, followed by solid organ transplant (4/38, 10.5%).

Clinical presentation

Amongst children with reported clinical presentation (3318/5033; 65.9%), the clinical presentation for single-episode cases and first episode of recurrent cases differed (p=0.008). Bacteraemia was more prevalent among first episodes in recurrent cases (43.5%; 95%CI 32.3–55.3%; 30/69) compared to single-episode cases (26.4% 95%CI 24.9–28.0%; 858/3249), whereas bacteraemic pneumonia was the most frequent presentation for single-episode cases (36.3% 95%CI 34.7–37.9%; 1180/3249) (Table 1). In both groups, the second most common presentation was meningitis, whilst other presentations only occurred among single-episode cases (Table 1).

Vaccination status

Of those with available immunisation information (3473/5033; 69.0%), the proportion of fully-vaccinated children was similar for single-episode and recurrent cases (41.0% and 44.4%, respectively) (Table 1), but the proportion of unvaccinated (including non-eligible) children was higher in recurrent cases than single-episode cases (19/72 [26.4%] vs. 459/3401 [13.5%]; p=0.002), despite a similar proportion of ineligible children in the two groups (4.2% vs 3.4%, respectively) (Table 1).

CFR

CFR after the last IPD episode in children with recurrent IPD was 2.9% (3/105) compared to 4.4% (219/4928; p=0.629) in children with single-episode (Table 1). All three children who died with recurrent IPD had two episodes with different serotypes. The youngest had a severe immune deficiency associated with a cardiac syndrome and developed meningitis in both episodes. The other two were 5–9-year-olds who were both unvaccinated in the first episode and had received one dose prior to the second episode; one with intracranial malignancy developed IPD several years apart and the other had both episodes within six months, but we do not have further details on comorbidities.

Risk factors for recurrence

After adjusting for comorbidities, vaccine-serotype group, clinical presentation and vaccination (≥1 dose), and including age and year as time-varying covariates, children with any comorbidity had 11 times the risk of a second IPD episode than healthy children (aHR 11.6; 95% CI 6.1–22.1). The risk was higher in immunocompromised compared to healthy children (aHR 40.6; 95%CI 2.0–83.4; p < 0.0001) whilst those with other comorbidities had six times the risk compared to healthy children (aHR 6.4; 95%CI 3.1–13.1; p < 0.0001) (Table 2b, Fig. 2). All other variables were not associated with increased hazards for recurrence. The proportional hazards assumption was met.

Recurrence rate

IPD recurrence rate was 364.0 per 100,000 person-years (95%CI, 300.7–440.8), with no differences by sex (Tables 2a). Recurrence rate was highest during the earliest surveillance period and then declined. Recurrence rate also declined with increasing age (Tables 2a). In comparison, the rate of first episodes was 4.1 per 100,000 person-years overall (95%CI 4.0–4.3), and 15.5 (14.6–15.8), 5.0 (4.7–5.2) and 1.5 (1.45–1.6) in < 2-year-olds, 2 to 4-year-olds and 5–14-year-olds, respectively. Compared to healthy children (103.0; 95%CI 63.1–168.1), recurrence rate was 10 times higher in children with comorbidities (1061.0; 95% CI 827.2–1360.9) and almost 30 times higher in immunosuppressed children (2788.5; 95%CI 2029.0–3832.2). Additionally, children presenting with bacteraemia

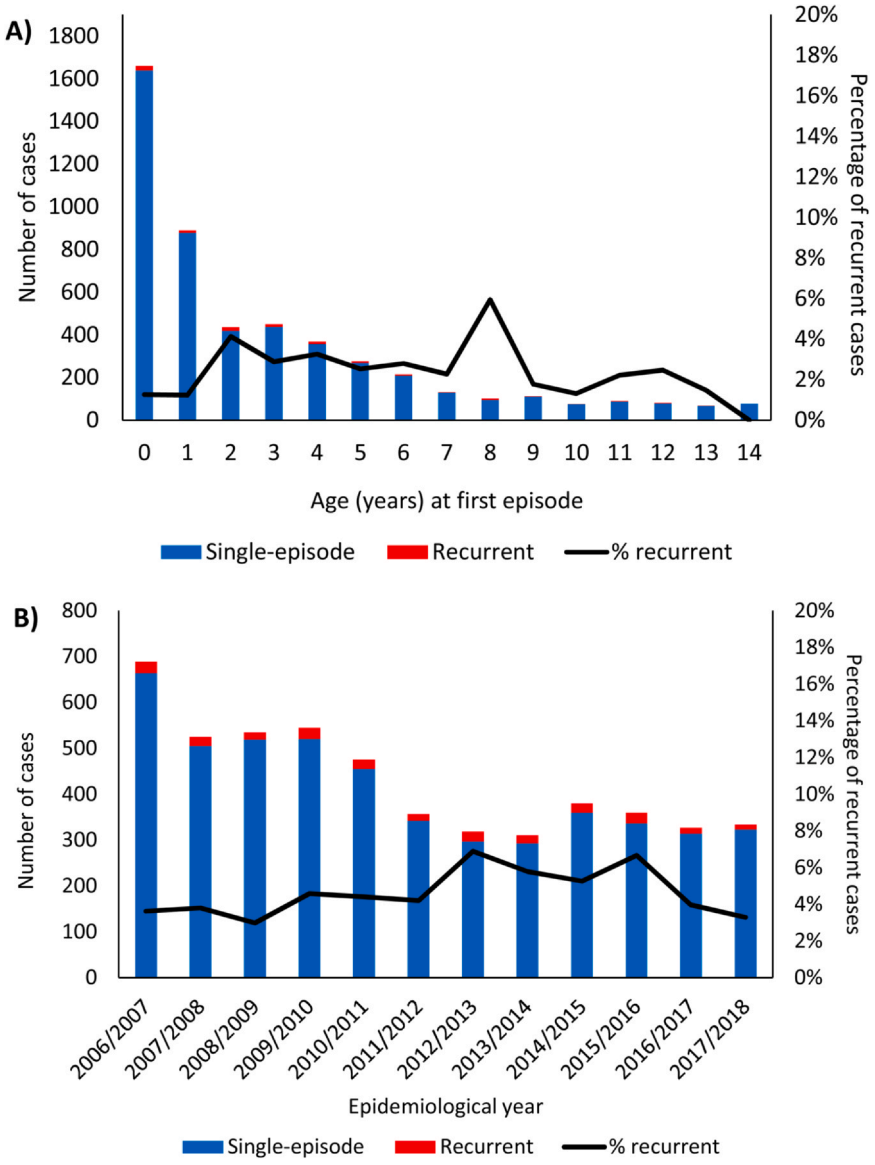

Fig. 1. Number of IPD episodes at first episode by recurrence group in children < 15-years-old (bars) and percentage of recurrence (line) by age (A) and by epidemiological year (B), England, 2006/07–2017/18.

during their first episode had a higher recurrence rate than those with meningitis or bacteraemic pneumonia (Tables 2a,2b). The median interval between episodes was around six months [199 days; IQR 90–548 days] (Table 3), with 25.7% (27/105) having their second episode within three months of their first episode. Only one apparently healthy two-year-old had a recurrence with two different serotypes (12 F and 15 A) and presented with bacteraemia within 30 days. Five other children had recurrence within 45 days (4.8%), 10 within 45–60 days and 11 within 61–90 days of their first episode. Where the infecting serotype was identified, the median interval between episodes was shorter in the 25 (25/85, 29.4%) children infected with the same serotype compared to the 60 children infected with a different serotype (88 days (IQR 57–177) vs. 223 days (IQR 125–574); p=0.001) (Table 3).

Serotypes responsible

The serotypes responsible for IPD varied according to the surveillance period, with the contribution of PCV7 and the additional six PCV13 serotypes declining with time (Table 1, Fig. 3). During the PCV7-period, 25.5% (516/2024) of all IPD cases and 43.9% (18/41) of first IPD episodes in recurrent cases were due to PCV7 serotypes. These proportions reduced to 3.6% (47/1298) and 3.3% (1/30), respectively, during the early PCV13 period. Since 2015/16, most single episodes (1011/1203; 84.0%) and all first infections in recurrent episodes (24/24, 100%) were due to non-PCV13 serotypes (Table 1, Fig. 3).

Among recurrent cases with the same serotype (n=25), the serotypes isolated (and proportion of recurrent episodes compared to total episodes for the individual serotypes) in order of overall prevalence were: serotype 1 (8/567; 1.4%), 7 F (12/446;2.7%), 3 (3/235,1.3%), 22 F (16/221;7.2%), 8 (10/206;4.9%), 10 A (7/166;4.2%), 23B (13/163;8.0%), 19 F (9/131,6.9%), 24 F (10/121;8.3,%), 15 A (16/110, 14.5%), 6B (7/94;7.4%), 38 (6/68,8.8%), 4 (2/29;6.9%) and 17 F (5/21;23.8/%) (Supplement Fig. 1).

WGS results were available for 19/25 (76%) children with recurrence due to the same serotype. In 17/19 (89.5%) children, the same strain was isolated in both episodes, with intervals ranging between 5 weeks to 15 months. The two cases due to different strains of the same serotype were due to serotype 3 and serotype 15B/C and with

Table 1
Characteristics of single episode and recurrent IPD cases at first episode.

Characteristic	Single-episode cases n (%) N=4928	Recurrent cases n (%) N=105	Total (n %) N=5033	P-value‡
Questionnaire returned	3740 (75.9%)	71 (67.6%)	3811 (75.8%)	0.0504
Sex	4926	105	5031	
Female	2057 (41.8%)	40 (38.1%)	2097 (41.7%)	0.451
Male	2869 (58.2%)	65 (61.9%)	2934 (58.3%)	
Age	4928	105	5033	
Median years (IQR)	1(0–4)	3 (1–5)		< 0.001†
< 2 y	2517 (51.1%)	32 (30.5%)	2549 (50.6%)	
2–4 y	1212 (24.6%)	43 (41%)	1255 (24.9%)	< 0.001*
5–9 y	813 (16.5%)	24 (22.9%)	837 (16.6%)	
10–14 y	386 (7.8%)	6 (5.7%)	392 (7.8%)	
Comorbidity status	3757	78	3835	
Healthy	2599 (69.2%)	16 (20.5%)	2615 (68.2%)	< 0.001
Any comorbidity:	1158 (30.8%)	62 (79.5%)	1220 (31.8%)	
Immunosuppression	294 (25.4%)	38 (61.3%)	332 (27.2%)	< 0.001
Other comorbidities	864 (74.6%)	24 (38.7%)	888 (72.8%)	
Epidemiological years	4928	105	5033	
2006/07–2009/10	2208 (44.8%)	47 (44.8%)	2255 (44.8%)	0.673
2010/11–2014/15	1387 (28.1%)	33 (31.4%)	1420 (28.2%)	
2015/16–2017/18	1333 (27%)	25 (23.8%)	1358 (27%)	
Serotype group (n=4549/4928)	4454	95	4549	
PCV7	570 (12.8%)	19 (20%)	589 (12.9%)	< 0.001
PCV13	1679 (37.7%)	15 (15.8%)	1694 (37.2%)	
PPV23	1416 (31.8%)	34 (35.8%)	1450 (31.9%)	
NVT	789 (17.7%)	27 (28.4%)	816 (17.9%)	
2006/07–2009/10 (n=2024/2255)	1983	41	2024	
PCV7	498 (25.1%)	18 (43.9%)	516 (25.5%)	0.004*
PCV13	1004 (50.6%)	10 (24.4%)	1014 (50.1%)	
PPV23	336 (16.9%)	9 (22%)	345 (17%)	
NVT	145 (7.3%)	4 (9.8%)	149 (7.4%)	
2010/11–2014/15 (n=1298/1420)	1268	30	1298	
PCV7	46 (3.6%)	1 (3.3%)	47 (3.6%)	0.039*
PCV13	509 (40.1%)	5 (16.7%)	514 (39.6%)	
PPV23	410 (32.3%)	13 (43.3%)	423 (32.6%)	
NVT	303 (23.9%)	11 (36.7%)	314 (24.2%)	
2015/16–2017/18 (n= 1227/1358)	1203	24	1227	
PCV7	26 (2.2%)	0 (0%)	26 (2.1%)	0.049*
PCV13	166 (13.8%)	0 (0%)	166 (13.5%)	
PPV23	670 (55.7%)	12 (50.0%)	682 (55.6%)	
NVT	341 (28.3%)	12 (50.0%)	353 (28.8%)	
Clinical presentation	3249	69	3318 (65.9%)	
Meningitis	1065 (32.8%)	20 (29%)	1085 (32.7%)	0.008*
Pneumonia	1180 (36.3%)	19 (27.5%)	1199 (36.1%)	
Other	146 (4.5%)	0 (0%)	146 (4.4%)	
Bacteraemia	858 (26.4%)	30 (43.5%)	888 (26.8%)	
Vaccination status (n=3473)	3401	72	3473 (69%)	
Fully vaccinated	1394 (41%)	32 (44.4%)	1426 (41.1%)	0.002*
Partially vaccinated	1548 (45.5%)	21 (29.2%)	1569 (45.2%)	
Not vaccinated (incl. not eligible)	459 (13.5%)	19 (26.4%)	478 (13.8%)	
Not eligible	115 (3.4%)	3 (4.2%)	118 (3.4%)	
30-day case fatality¥	4928	105	5033	
Died < 30d	219 (4.4%)	3 (2.9%)	222 (4.4%)	0.629*

‡ P-value obtained from chi-square (no symbol) or fisher exact test (*) or Mann-Whitney test (†). ¥ Death after 30-days for recurrent cases is included for any episode after the first episode.

an interval of 10 weeks and 40 months between episodes, respectively.

Children presenting with meningitis as their first episode were significantly more likely to re-present with meningitis (16/17 94.1%) compared to pneumonia (8/15; 53.3%) or bacteraemia (9/18; 50.0%) (p=0.007), although these were rare occurrences (Supplement Table 4). Only 16/965 (1.7%) children with first presentation of meningitis who survived had a recurrence with meningitis and 8 of the 16 recurrent meningitis cases had known comorbidities compared to 136/865 (15.7%) of single-episode cases (p=0.002).

Discussion

Recurrent IPD in children was rare, occurring in 2.2% of cases who survived their initial episode. Most children with recurrent IPD had significant comorbidities, especially immunosuppression, and the serotypes responsible varied over time, because of the different PCVs implemented. After 4 years of PCV13 use, all recurrent IPD cases were due to non-PCV13 serotypes. A higher proportion of recurrent cases were undervaccinated, but reassuringly, CFR remained very low in children with recurrent IPD despite the high comorbidity prevalence.

There are few studies on recurrent IPD in countries with established PCV13 programmes for comparison. Previous estimates of IPD recurrence include 1.4% (65/4513) in US children (0–17 y) during 1995–1998,[13] 2.2% (90/4067) in US children (< 18 y) during the pre-PCV13 period (1993–2006),[10] 2.1% in Spanish patients of all ages during 2007–11,[21] 2.4% (59/2418) in Danish children (0–15 y) during 1980–2013,[11] and 1.1% (87/7836) in Australian children (< 18 y) during 1991–2016.[6] Consistent with the published studies, we also observed a declining risk of recurrent IPD following the implementation of successively higher-valent PCVs. Additionally, as

Table 2a
Univariate rate of recurrence (per 100,000) among children aged 15 years and under who experienced at least one IPD episode by different characteristics (at first episode).

	Failures	Person-time	Recurrence rate per 100,000 (95%CI)
Overall	105	0.29	364.0 (95% CI 300.7–440.8)
Sex			
Female	40	0.12	334.2 (95% CI 245.1–455.6)
Male	65	0.17	385.6 (95% CI 302.4–491.8)
Age group			
< 2 years	17	0.03	617.5 (95% CI 383.9–993.3)
2 to 4 years	44	0.07	598.2 (95% CI 445.1–803.8)
5 to 9 years	31	0.13	248.1 (95% CI 174.5–352.8)
10 to 14 years	13	0.06	208.4 (95% CI 121–358.8)
Time period			
2006/07–2010/11	32	0.04	750.3 (95% CI 530.6–1060.9)
2010/11–2014/15	48	0.14	351.3 (95% CI 264.7–466.2)
2015/16–2017/18	25	0.11	229 (95% CI 154.8–339)
Underlying conditions			
Healthy	16	0.16	103.0 (95% CI 63.1–168.1)
Any comorbidity:	62	0.06	1061.0 (95% CI 827.2–1360.9)
Immunosuppression	38	0.01	2788.5 (95% CI 2029–3832.2)
Other comorbidities	24	0.04	535.6 (95% CI 359–799.1)
Clinical presentation			
Meningitis	20	0.06	344.0 (95% CI 221.9–533.2)
Pneumonia	19	0.07	274.0 (95% CI 174.8–429.6)
Other focus	0	0.01	-
Bacteraemia	30	0.03	899.2 (95% CI 628.7–1286)

expected, given the very low PCV-13 type IPD incidence in countries with mature PCV13 programmes, most recurrent IPD episodes are now due to non-PCV13 serotypes. Notably, half the reinfections with known serotypes were due to the additional serotypes included in the PPV23 vaccine, which is recommended for high-risk individuals from 2 years of age in England. Given that most children with recurrent IPD were immunosuppressed, however, the effectiveness of any pneumococcal vaccine in this cohort is uncertain.[22]

Comorbidities, especially immunosuppression, continue to remain an important risk factor for recurrent IPD, with prevalence estimates of 60–92%.[10–14] In the published literature, reported comorbidities varied by geographical region and over time. In countries with a mature PCV13 programme, such as Australia, for example, similar comorbidities were identified, such as immunosuppression (16.7%), congenital abnormalities (13.3%), premature birth (11.7%) and chronic illnesses (11.7%) although, 55% (33/60) had no known comorbidities.[6] This compares with 80% in our cohort, including 61.3% with immunosuppression. In immunocompromised children, not only does the underlying immunodeficiency increase their IPD risk,[16] but they are also likely to have central venous catheters, which are often the focus of infection. This likely explains their higher rates of clinical presentation with bacteraemia – we do not specifically ask about line infections in our surveillance questionnaire.

Recurrent IPD in otherwise healthy children is very rare and invariably requires detailed immunological investigations for primary immunodeficiencies including single-gene mutation and B-cell dysfunction.[11–13,23–26] In contrast, children with PCV failure are unlikely to have an underlying immune deficiency or increased risk of recurrent IPD,[27] which was also observed in the current analysis. Additionally, apparently healthy children with recurrent bacterial meningitis caused by any bacteria should be investigated for both underlying immunodeficiency and anatomical cranial defects associated with CSF leak,[11,12] especially given that most children with recurrent IPD who presented with meningitis in their first episode also developed meningitis in their second episode.

The high serotyping rates in our surveillance allowed us to compare the risk of recurrent IPD with the same or different

Table 2b
Results from cox regression model among children aged 15 years and under who experience at least one IPD episode by different characteristics (at first episode).

	Unadjusted hazards ratio (95% CI; p-value)	Adjusted hazards ratio (95% CI; p-value)[a]
Underlying conditions		
Healthy	Ref	Ref
Any comorbidity:		
Immunosuppression	29.1 (95%CI 16.2–52.3; p < 0.001)	40.6 (95% CI 2.0–83.4; p < 0.001)
Other comorbidities	5.0 (95%CI 2.6–9.4; p < 0.001)	6.4 (95% CI 3.1–13.1; p < 0.001)
Clinical presentation		
Meningitis	0.4 (95%CI 0.20–0.62; p < 0.001)	Ref
Pneumonia	0.3 (95%CI 0.15–0.49; p < 0.001)	1.0 (95% CI 0.5–1.9; p=0.933)
Other	0.0	-
Bacteraemia	Ref	1.2 (95% CI 0.6–2.2; p=0.634)
Vaccine-serotype group		
PCV7	Ref	Ref
PCV13	0.4 (95%CI 0.22–0.86; p=0.017)	0.6 (95% CI 0.2–1.8; p=0.413)
PPV23	2.2 (95%CI 1.2–3.9; p=0.010)	1.4 (95% CI 0.6–3.6; p=0.467)
NVT	3.4 (95%CI 1.8–6.4; p < 0.001)	1.4 (95% CI 0.5–3.8; p=0.509)
Vaccination status		
Unvaccinated	Ref	Ref
At least one dose	1.2 (95%CI 0.8–1.8; p=0.449)	1.0 (95% CI 0.5–1.9; p=0.956)

[a] Results from multivariable analysis, including breakdown for comorbidity status. Model was adjusted for the variables included in the table and age and year as time-varying covariables.

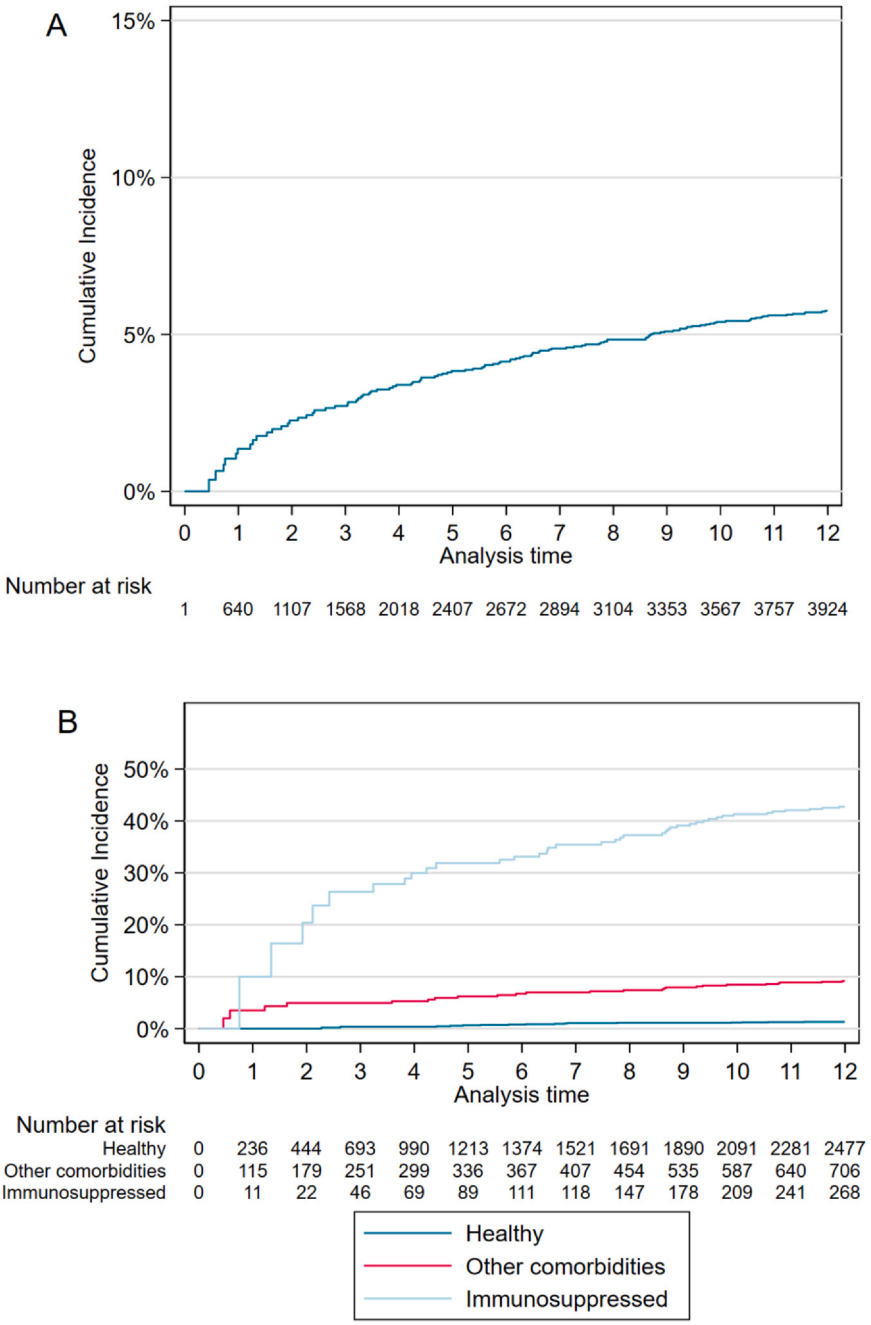

Fig. 2. A) Cumulative probability of first recurrence of invasive disease in England in children under 15-years-old, 01 July 2006 to 30 June 2018. B) Cumulative probability of first recurrence of invasive disease in England in children under 15-years-old, stratified by underlying conditions group, 01 July 2006 to 30 June 2018. Note: Axis in graphs differ.

serotypes. We found that recurrence with the same serotype had a shorter interval between episodes, similar to previous studies,[28] and nearly all (17/19) were caused by the same strain. Given the limited data collected through surveillance questionnaires, we were however unable to differentiate between relapse and re-infection[12,14] – some studies defined relapse as reinfection with the same serotype within a certain time-period, ranging from 7–30 days,[11,13,28] while others have characterised the responsible serotypes to confirm identical genetic sequences.[10,12,28] In our surveillance, we considered reinfection with the same serotype within 30 days to be the same episode and, therefore, only re-infections with a different serotype during this interval were included – there was only one such case. Among recurrent IPD cases with a > 30-day interval, we found little difference in the characteristics of children who developed recurrent IPD due to the same or different serotypes (Table 3).

Finally, CFR was reassuringly low after recurrent IPD, even when compared to children with a single episode, whilst others have reported no deaths among the recurrent IPD cases in children.[11,12,14] This could be because those at highest risk of death would have succumbed after their first episode, or, alternatively, since most children with recurrent IPD had comorbidities, they could have lower thresholds for seeking medical care and clinicians would have lower thresholds for treating such children.

Strengths and limitations

Our enhanced national surveillance covered 12 years, with 90% of isolates serotyped and 76% of completed questionnaires, which allowed us to provide detailed estimates of risk and outcomes. There are some limitations. Firstly, our enhanced surveillance only began

Table 3
Characteristics of recurrent cases grouped by cases infected with the same or different serotypes in the first two episodes.

Characteristic	Different serotypes (n=60)		Same serotype (n=25)		Total (n=105)[a]		p-value
Interval							
Median days (IQR)	223 (IQR 125–574)		88 (IQR 57–177)		199 (IQR 90–548)		0.001
0–29 days	1	1.7%	0	0.0%	1	1.0%	0.018[b]
30–44 days	2	3.3%	3	12.0%	5	4.8%	
45–60 days	2	3.3%	6	24.0%	10	9.5%	
61–90 days	5	8.3%	4	16.0%	11	10.5%	
91 days to <6 months	11	18.3%	5	20.0%	18	17.1%	
6 months to 1 year	16	26.7%	4	16.0%	23	21.9%	
1–2 years	13	21.7%	2	8.0%	20	19.0%	
≥2 years	10	16.7%	1	4.0%	17	16.2%	
Clinical presentation	39		19		58		
Meningitis	11	28.2%	7	36.8%	18	31.0%	0.21[b]
Pneumonia	13	33.3%	2	10.5%	15	25.9%	
Other	0	0.0%	0	0.0%	0	0.0%	
Bacteremia	15	38.5%	10	52.6%	25	43.1%	
Same presentation	18/30	60.0%	11/15	73.3%	29/45	64.4%	0.514[b]
Comorbidities	44		20		64		
Healthy	6	13.6%	7	35.0%	13	20.3%	0.098[b]
Any comorbidity	38	86.4%	13	65.0%	51	79.7%	
Immunocompromising	26	68.4%	7	53.8%	33	64.7%	
Non-immunocompromising	12	31.6%	6	46.2%	18	35.3%	
Age at first episode	60		25		85		0.342[b]
<2 y	13	21.7%	10	34.8%	23	34.8%	
2–4 y	29	48.3%	9	39.1%	38	39.1%	
5–9 y	16	26.7%	5	21.7%	21	21.7%	
10–14 y	2	3.3%	1	4.3%	3	4.3%	
Serotype group	60		25		85		
PCV7	14	23.3%	4	16.0%	18	21.2%	0.846[b]
PCV13	9	15.0%	5	20.0%	14	16.5%	
PPV23	20	33.3%	9	36.0%	29	34.1%	
NVT	17	28.3%	7	28.0%	24	28.2%	
WGS[c]	NA[c]		19		NA[c]		
Same strain	NA[c]		17	89.5%	NA[c]		
Different strain	NA[c]		2	10.5%	NA[c]		
30 day case-fatality	3	0.05	0	0.0%			0.552[b]

[a] The total column includes all recurrent cases for the time interval, but only those with serotype information for all other characteristics.
[b] Fisher-exact test.
[c] Analysis only included for recurrent cases due to the same serotype in the first and second episodes.

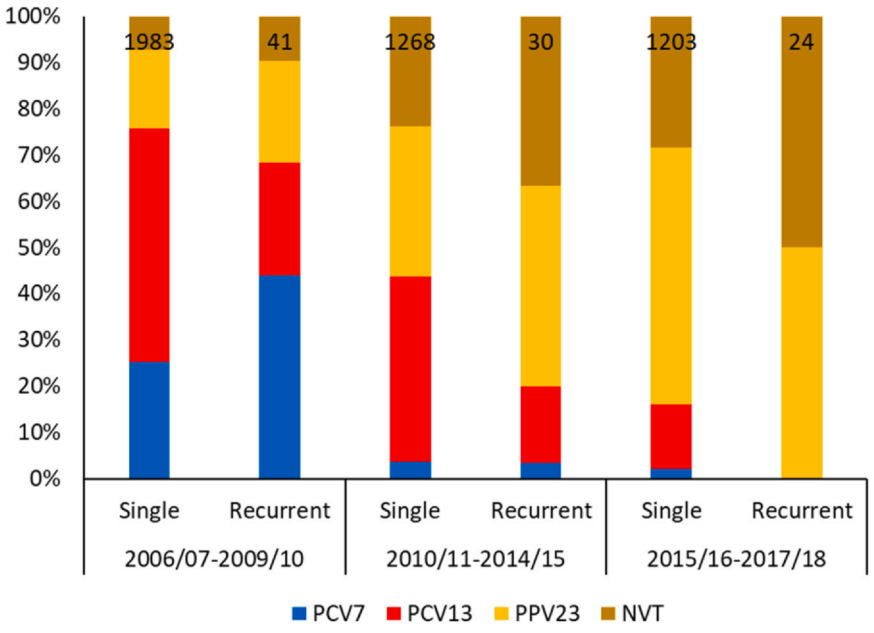

Fig. 3. Percentage of cases according to vaccine serotype group and time period in children with single-episode and recurrent IPD. [PCV7: 7 valent pneumococcal conjugate vaccine; PCV13: additional serotypes in 13 valent pneumococcal conjugate vaccine; PPV23: additional serotypes in 23 valent polysaccharide vaccine; NVT: non-vaccine type; Number in bar indicates total number of IPD episodes].

after PCV7 was implemented and was initially restricted to < 5-year-olds before extending to all age groups. Serotyping and questionnaire completion rates were also lower at the start of the programme but have improved significantly over time.[29] We also collected limited clinical data and, therefore, cannot comment on specific risk factors (e.g. presence of central venous catheter), disease severity, investigations performed, treatment or complications among survivors.

Conclusions

Recurrent IPD is rare in children and occurs mainly in children with comorbidities, especially immunosuppression. Recurrent infections are currently due to non-PCV13 serotypes. Reassuringly, CFR remains low after recurrent IPD. Higher-valent PCVs have the potential to provide direct and indirect protection against many of the serotypes currently responsible for recurrent IPD.

Contributors

SNL, GO, MER, DL and NJA were responsible for the conceptualisation of the study. ZA, MB and FA were involved in data curation. MB and FA conducted the epidemiological analysis and JCD, SE and DL conducted the genomic analysis and its interpretation. ZA, MB and FA accessed and verified the data. MB wrote the first draft of the manuscript, which was edited and reviewed by all authors. All authors have seen and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability

Applications for relevant anonymised data should be submitted to the UK Health Security Agency office for Data Release: https://www.gov.uk/government/publications/accessing-ukhsa-protected-data.

Declaration of Competing Interest

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *Journal of Infection* and was not involved in the editorial review or the decision to publish this article. - SNL.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The Immunisation Department provides vaccine manufacturers with post-marketing surveillance reports about pneumococcal and meningococcal disease 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. (SL, MB, FA, MR, NJA, DL, ZA). The Vaccine Preventable Bacteria Section of the Respiratory and Vaccine Preventable Bacteria Reference Unit, UKHSA, has received payments for investigator-led research on pneumococcal carriage in humans from Glaxo SmithKline and Pfizer. (DL, JCD, SE). SE participated in a Virtual Advisory Board for a pneumococcal project on acute otitis media and pneumonia indication organised by Sanofi Pasteur SA. SNL performs contract research on behalf of St. George's University of London and the UK Health Security Agency for pharmaceutical agencies, including vaccine manufacturers, but receives no personal remuneration.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106490.

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