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Characteristics of Invasive Pneumococcal Disease Caused by Emerging Serotypes After the Introduction of the 13-Valent Pneumococcal Conjugate Vaccine in England: A Prospective Observational Cohort Study, 2014–2018

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Background. England is experiencing a rapid increase in invasive pneumococcal disease (IPD) caused by serotypes 8, 12F, and 9N; their clinical characteristics and outcomes have not been described.

Methods. Public Health England conducts national IPD surveillance. Cases due to emerging serotypes were compared with those included in the 13-valent pneumococcal conjugate vaccine (PCV13) and the remaining non-PCV13 serotypes.

Results. There were 21 592 IPD cases during 2014–15 to 2017–18, including 20 108 (93.1%) with serotyped isolates and 17 450 (86.8%) with completed questionnaires. PCV13 serotypes were responsible for 20.1% (n = 4033), while serotype 8 (3881/20 108 [19.3%]), 12F (2365/20 108 [11.8%]), and 9N (1 296/20 108 [6.4%]) were together responsible for 37.5% of cases. Invasive pneumonia was the most common presentation (11 424/16 346 [69.9%]) and, overall, 67.0% (n = 11 033) had an underlying comorbidity. The median age (interquartile range) at IPD due to serotypes 8 (59 [45–72] years) and 12F (56 [41–70] years) was lower than serotype 9N (67 [53–80] years), PCV13 serotypes (68 [52–81] years), and remaining non-PCV13 serotypes (70 [53–82] years). Serotype 9N IPD cases also had higher comorbidity prevalence (748/1087 [68.8%]) compared to serotype 8 (1901/3228 [58.9%]) or 12F (1042/1994 [52.3%]), and higher case fatality (212/1128 [18.8%]) compared to 8.6% (291/3365) or 10.0% (209/2086), respectively.

Conclusions. Serotypes 8 and 12F were more likely to cause IPD in younger, healthier individuals and less likely to be fatal, while serotype 9N affected older adults with comorbidities and had higher case fatality.

Keywords. serotype replacement; emerging serotypes; conjugate vaccines; immunization; outcome.

Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing invasive pneumococcal disease (IPD) caused by the respective vaccine serotypes [1, 2]. Countries with established childhood PCV programs have observed large declines in IPD caused by the vaccine serotypes across all age groups because of the direct and large indirect (herd) protection afforded by national immunization programs [3–9]. In the United Kingdom (UK), the 7-valent PCV (PCV7) was introduced into the national childhood immunization program at a 2 + 1 schedule in 2006 and replaced with a 13-valent PCV (PCV13) without any catch-up in 2010. Both vaccines were associated with large and sustained declines in overall and vaccine-type IPD, although some increase in IPD due to nonvaccine serotypes was observed following the introduction of each vaccine.

After reaching the lowest IPD incidence of 7.12 cases per 100 000 in 2013–2014, England and Wales experienced a sudden and unexpected increase in IPD due to some non-PCV13 serotypes, with an approximate doubling in incidence of non-PCV13 IPD from 4.20 per 100 000 during 2008–2010 to 7.97 per 100 000 by 2016–2017 [3]. This increase was observed across all age groups, but especially in adults and older adults, with 3 serotypes—8, 12F, and 9N—being responsible for approximately 40% of all laboratory-confirmed IPD cases in England [3]. At the same time, IPD incidence due to some of the PCV13 serotypes plateaued instead of continuing to decline [3].

Little is known about the characteristics of IPD caused by the emerging serotypes. Here, we describe the age distribution, clinical presentation, underlying comorbidities, and outcomes of patients with IPD caused by the persisting PCV13 serotypes, the 3 emerging serotypes, and the remaining non-PCV13 serotypes during the 4 most recent epidemiological years in England.

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METHODS

IPD Surveillance

Public Health England (PHE) has been conducting national surveillance of IPD for > 3 decades. Hospital laboratories across England routinely refer invasive pneumococcal isolates to the PHE Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) for confirmation and serotyping. The laboratories also routinely report all significant infections to PHE electronically through the Second-Generation Surveillance System. Reported IPD cases without submitted isolates to the PHE RVPBRU are actively followed up with the respective hospital laboratory, thus ensuring both high case ascertainment and serotyping rates nationally.

Following the introduction of PCV7 into the childhood immunization program in September 2006, laboratory-confirmed IPD cases in vaccine-eligible children were followed up with their general practitioner (GP) using a postal questionnaire requesting information on vaccination history, clinical presentation, comorbidity status, complications, and outcomes at hospital discharge. Since 2014, IPD cases across all ages are followed up with the GP using standard postal questionnaires. Questionnaires that are not returned or are incomplete are actively followed up by reminder letters and telephone calls. Death status for IPD cases are confirmed through the Personal Demographics Service, an electronic national database of National Health Service patient details, and those deaths occurring within 30 days of sample date are considered to be attributable to IPD.

Definitions

IPD was defined as isolation of *Streptococcus pneumoniae* from a normally sterile site, or detection of pneumococcal DNA by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) or pleural fluid. Meningitis was defined as identification of *S. pneumoniae* (by culture/PCR) in the CSF or isolation of *S. pneumoniae* from the blood in a patient with clinical features of meningitis. Invasive pneumonia was defined as identification of *S. pneumoniae* (by culture/PCR) in pleural fluid or isolation of *S. pneumoniae* in the blood in a patient with clinical features of pneumonia. Septicemia was defined as isolation of *S. pneumoniae* from the blood without any discernible focus of infection. Patients with multiple clinical presentations were analyzed hierarchically as meningitis > pneumonia > other presentation > septicemia (without a focus of infection).

Comorbidity groups were based on clinical risk groups stated in the *Immunisation Against Infectious Disease* book popularly known as the "Green Book" [10] and included asplenia, chronic respiratory disease, chronic heart disease, chronic kidney disease, diabetes, immunosuppression, cochlear implants, and CSF leaks. Comorbidity status was assessed by its presence or absence, the number of comorbidities for each patient, and whether the comorbidity was immunocompromising or nonimmunocompromising.

Data Management and Analyses

Laboratory and clinical data were regularly imported, matched, cleaned, and de-duplicated in Microsoft Access (Microsoft Corporation, Redmond, Washington) as part of national surveillance. A final dataset containing confirmed IPD cases during the 4 most recent epidemiological (July to June) years (2014–2015 to 2017–2018) was imported into Stata software version 15.1 (StataCorp LP, College Station, Texas) for analysis. Age was grouped into < 15, 15–44, 45–64, 65–79, and ≥ 80 years. The serotype groups were 8, 12F, 9N, PCV13 (subgrouped into serotype 3, serotype 19A, and the remaining PCV13 serotypes for some of the analyses), and the remaining non-PCV13/nonemerging (remaining) serotypes.

Data that did not follow a normal distribution are presented as median with interquartile range and compared using the Mann-Whitney *U* test; proportions were compared using the χ^2 or Fisher exact test, as appropriate. Multinomial logistic regression was used to assess independent risk factors associated with IPD clinical presentation after adjusting for surveillance year, and including age group, serotype group (PCV13 serotypes, serotypes 8, 9N, and 12F and remaining non-PCV13 serotypes), and comorbidity status. Multivariable logistic regression was used to identify any association between comorbidity status and serotype group after adjusting for surveillance year and age group. Independent risk factors for death were also assessed using a logistic regression model after adjusting for surveillance year, with comorbidity status, age group, and serotype group as in dependent variables.

RESULTS

There were 21 592 laboratory-confirmed IPD cases over the 4-year surveillance period (2014–2015 to 2017–2018), including 20 108 (93.1%) with serotyped isolates and 17 450 (86.8%) with completed questionnaires; the characteristics of patients with returned questionnaires were similar to those with unreturned questionnaires, apart from a higher questionnaire completion rate for childhood cases (Table 1). IPD cases in all the serotype groups increased over the 4 surveillance years (Figure 1). PCV13 serotypes were responsible for 4033 of 20 108 (20.1%) IPD cases with available serotype information, mainly due to serotypes 3 (1852/4033 [45.9%]), 19A (1110/4033 [27.5%]), and 7F (433/4033 [10.7%]) which made up > 80% of PCV13-serotype IPD cases. Three emerging serotypes were responsible for 37.5% (7542/20 108) of IPD cases: 8 (3881/20 108 [19.3%]), 12F (2365/20 108 [11.8%]), and 9N (1296/20 108 [6.4%]). Fifty-five other serotypes were responsible for the remaining IPD cases (8533/20 108 [42.4%]), with a median of 39 annual cases for each serotype. The characteristics of patients with IPD are summarized by age group and serotype group in Supplementary Tables 1*A*–*E*.

Table 1. Characteristics of Patients With Confirmed Invasive Pneumococcal Disease in England Over a 4-Year Period (2014–2015 to 2017–2018) With Questionnaires Completed by Their General Practitioners and Those With No Questionnaire Returned

Characteristic	Questionnaire Returned	
	Yes	No
Age, y, median (IQR)	66 (49–67)	67 (53–80)
Age group, y, no. (%)		
<15	1247 (7.2)	21 (0.8)
15–44	2377 (13.6)	382 (14.4)
45–64	4728 (27.1)	773 (29.1)
65–79	4869 (27.9)	810 (30.5)
≥80	4229 (24.2)	672 (25.3)
Sex, no. (%)		
Male	8777 (50.3)	1397 (52.6)
Female	8673 (49.7)	1261 (47.4)
Serotype groups, no. (%)		
8	3365 (19.3)	516 (19.4)
12F	2086 (12.0)	279 (10.5)
9N	1128 (6.5)	168 (6.3)
PCV13 serotypes	3492 (20.0)	541 (20.4)
Remaining non-PCV13 serotypes	7379 (42.3)	1154 (43.4)
30-d case fatality rate, no. (%)		
Yes	2895 (16.6%)	453 (17.0%)
No	14 555 (83.4%)	2205 (83.0%)

Abbreviations: IQR, interquartile range; PCV13, 13-valent pneumococcal conjugate vaccine.

The contribution of PCV13 serotypes to IPD increased with age from 25.7% (321/1247) in children aged <15 years to 40.2% (1702/4229) in ≥80 year-olds (Table 2); however, only 5.5% (191/3492) of the PCV13-type IPD cases were in children. Of the emerging serotypes, the median age (interquartile range) at IPD due to serotype 8 (59 [45–72] years) and serotype 12F (56 [41–70] years) was lower than serotype 9N (67 [53–80] years), PCV13 serotypes (68 [52–81] years) or the remaining serotypes (70 [53–82] years); consequently, a higher proportion of serotype 9N IPD cases (n = 294/1128 [26.1%]) were in ≥80 year-olds compared to cases due to serotypes 8 (n = 424/3365 [12.6%]) or 12F (n = 270/2086 [12.9%]). On the other hand, the contribution of the remaining non-PCV13 serotypes to total IPD cases was higher in both children (740/1247 [59.3%]) and ≥80 year-olds (2297/4229 [54.3%]) compared to an overall contribution of 42.3% (7379/17 450) across all age groups (Table 2). The main serotypes contributing to the remaining non-PCV13 serotypes were 22F (1218/7379 [16.5%]), 15A (758/7379 [10.3%]), and 33F (632/7379 [8.6%]) (Supplementary Table 2).

Underlying Comorbidities

Overall, 11 033 of 16 726 (67.0%) cases with available information had an underlying comorbidity, which increased with age from 30.1% (355/1180) in children to 82.9% (3392/4092) in ≥80 year-olds, as did the number of underlying comorbidities, with 2.5% (30/1180) of children up to 22.9% (938/4092) of ≥80 year-olds having ≥3 comorbidities. The most prevalent comorbidity was chronic lung disease which increased with age, followed by chronic heart disease (3848/16 237 [23.7%]) and immunosuppression/malignancy (3900/16 726 [23.3]) (Table 2).

Among the PCV13-serotype IPD cases, 65.5% (2188/3342) had an underlying comorbidity, including 68.2% (1067/1564) with serotype 3, 67.5% (615/911) with serotype 19A and 58.4% (506/867) with the remaining PCV13 serotypes. Among the emerging serotypes, those with serotype 9N IPD had a higher comorbidity prevalence (748/1087 [68.8%]) compared to both serotype 8 (1901/3228 [58.9%]) and serotype 12F (1042/1994 [52.3%]) (Table 3). Cases due to the remaining non-PCV13 serotypes had the highest comorbidity prevalence (5154/7075 [72.9%]).

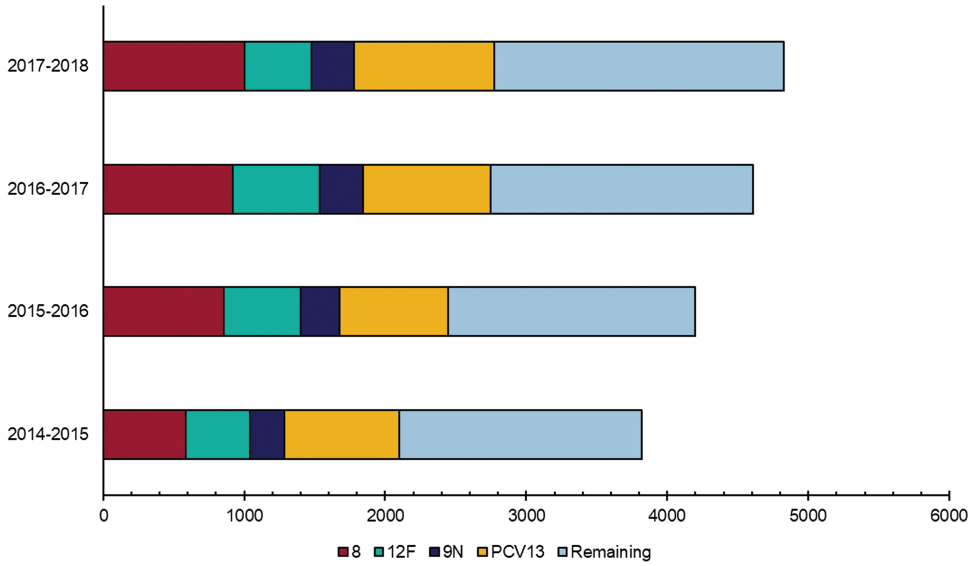

Figure 1. Number of invasive pneumococcal disease cases, by epidemiological year and serotype group. Abbreviation: PCV13, 13-valent pneumococcal conjugate vaccine.

Table 2. Characteristics of Patients With Invasive Disease in England and Information About the Infecting Serotype, by Age Group

	Age Group							
Characteristic	<2 y	2–4 y	5–14 y	15–44 y	45–64 y	65–79 y	≥80 y	All Ages
Serotype group	n = 682	n = 312	n = 253	n = 2377	n = 4728	n = 4869	n = 4229	n = 17450
8	61 (8.9)	15 (4.8)	27 (10.7)	720 (30.3)	1214 (25.7)	904 (18.6)	424 (10.0)	3365 (19.3)
12F	84 (12.3)	54 (17.3)	30 (11.9)	460 (19.4)	730 (15.4)	458 (9.4)	270 (6.4)	2086 (12.0)
9N	30 (4.4)	8 (2.6)	7 (2.8)	135 (5.7)	330 (7.0)	324 (6.7)	294 (7.0)	1128 (6.5)
PCV13 including 3, 19A	87 (12.8)	46 (14.7)	58 (22.9)	424 (17.8)	888 (18.8)	1045 (21.5)	944 (22.3)	3492 (20.0)
3	49 (7.2)	13 (4.2)	12 (4.7)	124 (5.2)	373 (7.9)	541 (11.1)	513 (12.1)	1625 (9.3)
19A	20 (2.9)	22 (7.1)	14 (5.5)	119 (5.0)	250 (5.3)	276 (5.7)	245 (5.8)	946 (5.4)
Remaining non-PCV13 serotypes	420 (61.6)	189 (60.6)	131 (51.8)	638 (26.8)	1566 (33.1)	2138 (43.9)	2297 (54.3)	7379 (42.3)
Clinical presentation	n = 672	n = 295	n = 235	n = 2165	n = 4373	n = 4573	n = 4033	n = 16346
Meningitis	191 (28.4)	116 (39.3)	90 (38.3)	220 (10.2)	435 (10.0)	215 (4.7)	62 (1.5)	1329 (8.1)
Pneumonia	210 (31.3)	108 (36.6)	75 (31.9)	1510 (69.8)	2957 (67.6)	3369 (73.7)	3195 (79.2)	11424 (69.9)
Other presentations[a]	42 (6.3)	27 (9.2)	31 (13.2)	213 (9.8)	523 (12.0)	510 (11.2)	389 (9.6)	1735 (10.6)
Bacteremia/sepsis	229 (34.1)	44 (14.9)	39 (16.6)	222 (10.3)	458 (10.5)	479 (10.5)	387 (9.6)	1858 (11.4)
At least 1 comorbidity	n = 641	n = 301	n = 238	n = 2316	n = 4664	n = 4810	n = 4182	n = 17211
Yes	96 (15.0)	133 (44.2)	126 (52.9)	792 (34.2)	2697 (57.8)	3797 (78.9)	3392 (81.1)	11033 (66.0)
No	545 (85.0)	168 (55.8)	112 (47.1)	1524 (65.8)	1967 (42.2)	1013 (21.1)	790 (18.9)	5693 (34.0)
Comorbidities[b]	n = 123	n = 176	n = 171	n = 1026	n = 4139	n = 7251	n = 6643	n = 19529
Chronic lung disease	27 (4.3)	23 (7.9)	43 (18.7)	342 (15.9)	1185 (27.0)	1904 (41.3)	1344 (33.8)	4868 (29.9)
Chronic heart disease	35 (5.6)	22 (7.5)	9 (3.9)	42 (2.0)	460 (10.6)	1371 (29.9)	1909 (47.8)	3848 (23.7)
Chronic renal disease	10 (1.6)	16 (5.4)	9 (3.9)	50 (2.3)	239 (5.1)	809 (17.7)	1383 (34.7)	2516 (15.5)
Chronic liver disease	10 (1.6)	9 (3.1)	6 (2.6)	138 (6.4)	402 (9.3)	260 (5.8)	59 (1.5)	884 (5.5)
CNS disease	5 (0.8)	6 (2.1)	10 (4.4)	47 (2.0)	113 (2.4)	138 (3.0)	141 (3.6)	460 (2.9)
Immunosuppression/malignancy	15 (2.3)	74 (24.6)	72 (30.3)	259 (11.7)	955 (21.2)	1560 (33.3)	965 (23.6)	3900 (23.3)
Asplenia/splenic dysfunction	11 (1.8)	8 (2.8)	7 (3.1)	18 (0.9)	38 (0.9)	29 (0.6)	12 (0.3)	123 (0.8)
Sickle-cell disease	7 (1.2)	7 (2.5)	11 (4.9)	15 (0.7)	13 (0.3)	5 (0.1)	5 (0.1)	63 (0.4)
Diabetes mellitus	2 (0.3)	3 (1.0)	0 (0.0)	109 (5.1)	712 (16.3)	1136 (24.8)	810 (20.5)	2772 (17.1)
Cochlear implants	0 (0.0)	6 (2.1)	2 (0.9)	2 (0.1)	4 (0.1)	10 (0.2)	6 (0.2)	30 (0.2)
Celiac disease	1 (0.2)	2 (0.7)	2 (0.9)	4 (0.2)	18 (0.4)	29 (0.6)	9 (0.2)	65 (0.4)
30-d case fatality rate	n = 682	n = 312	n = 253	n = 2377	n = 4728	n = 4869	n = 4229	n = 17450
	29 (4.3)	15 (4.8)	10 (4.0)	93 (3.9)	494 (10.5)	799 (16.4)	1455 (34.4)	2895 (16.6)

The total number of cases with available information is indicated by "n ="; data are presented as no. of cases (% of total cases with available information).

Abbreviations: CNS, central nervous system; PCV13, 13-valent pneumococcal conjugate vaccine.

[a]In children, the main other clinical presentations were septic arthritis, cellulitis, and mastoiditis; in adults, septic arthritis, cellulitis, and epiglottitis; and in older adults, biliary sepsis, urosepsis, and septic arthritis.

[b]Invasive pneumococcal disease cases may have multiple comorbidities.

Clinical Presentation

Pneumonia

Invasive pneumonia was the most common presentation, responsible for 69.9% (11 424/16 346) of cases with available clinical information. The proportion presenting with invasive pneumonia increased with age, from 32.7% (393/1202) in children <15 years to 79.2% (3195/4033) in ≥80 year-olds (Table 2). The responsible serotypes were 8 (n = 2516 [22.0%]), 12F (n = 1330 [11.6%]), 3 (n = 1138 [10.0%]), 22F (n = 830 [7.3%]), and 9N (788 [6.9%]) (Supplementary Table 2). In children, serotypes 12F (48 [12.2%]), 23B (39/393 [9.9%]), and 15B/C (32 [8.1%]) were the 3 most prevalent serotypes. Among PCV13-serotype IPD cases, presentation with invasive pneumonia increased with age, reaching 83.0% (742/894) of cases in ≥80 year-olds, while presentation with meningitis and septicemia declined with age (Supplementary Tables 1*A*–*E*). Among cases due to the remaining non-PCV13 serotypes, invasive pneumonia was less prevalent and other clinical presentations more prevalent than PCV13 serotype IPD cases (Table 3); in children, however, invasive pneumonia (250/715 [35.0%]) was the most common clinical presentation among the remaining non-PCV13 serotype IPD cases (Supplementary Table 2). In the multinomial logistic regression model, independent of surveillance year, age group, serotype group, and comorbidity prevalence, the relative risk of presenting with pneumonia compared to septicemia (the reference group) was higher with increasing age and lower for the remaining non-PCV13 serotypes (adjusted relative risk ratio [aRRR], 0.57 [95% confidence interval {CI}, .49–.66]) compared to PCV13 serotypes (Table 4).

Meningitis

Meningitis was the least prevalent clinical presentation (1329/16 346 [8.1%]) and more common in the younger age groups, with children accounting for 33.0% (397/1202) and

Table 3. Characteristics of Invasive Pneumococcal Disease Cases in England, by Serotype Group in All Ages

Serotype Group	Serotype 8	Serotype 12F	Serotype 9N	PCV13	Remaining	All
Clinical presentation	n = 3176	n = 1966	n = 1061	n = 3244	n = 6899	n = 16346
Meningitis	170 (5.4)	186 (9.5)	73 (6.9)	220 (6.8)	680 (9.9)	1329 (8.1)
Pneumonia	2516 (79.2)	1330 (67.7)	788 (74.3)	2464 (76.0)	4326 (62.7)	11424 (69.9)
Other presentations	202 (6.4)	235 (12.0)	97 (9.1)	255 (7.9)	946 (13.7)	1735 (10.6)
Bacteremia/sepsis	288 (9.1)	215 (10.9)	103 (9.7)	305 (9.4)	947 (13.7)	1858 (11.4)
Any comorbidity	n = 3228	n = 1994	n = 1087	n = 3342	n = 7075	n = 16726
Yes	1901 (58.9)	1042 (52.3)	748 (68.8)	2188 (65.5)	5154 (72.8)	11033 (66.0)
No	1327 (41.1)	952 (47.7)	339 (31.2)	1154 (34.5)	1921 (27.2)	5693 (34.0)
Comorbidities[a]	n = 3240	n = 1740	n = 1453	n = 4011	n = 9935	n = 20379
Chronic lung disease	1076 (34.1)	520 (26.6)	345 (32.5)	942 (29.0)	1985 (29.0)	4868 (29.9)
Chronic heart disease	549 (17.5)	316 (16.3)	254 (24.0)	813 (25.0)	1916 (27.9)	3848 (23.7)
Chronic renal disease	339 (10.9)	187 (9.6)	169 (16.0)	526 (16.2)	1295 (19.0)	2516 (15.5)
Chronic liver disease	118 (3.8)	90 (4.6)	63 (6.0)	177 (5.5)	436 (6.4)	884 (5.5)
CNS disease	66 (2.1)	39 (2.0)	40 (3.8)	87 (2.7)	228 (3.4)	460 (2.9)
Asplenia/splenic dysfunction	6 (0.2)	10 (0.5)	5 (0.5)	9 (0.3)	93 (1.4)	123 (0.8)
Immunosuppression/malignancy	458 (14.2)	278 (13.9)	291 (26.8)	746 (22.3)	2127 (30.0)	3900 (23.3)
Sickle-cell disease	8 (0.3)	6 (0.3)	3 (0.3)	11 (0.3)	35 (0.5)	63 (0.4)
Malignancy	327 (10.5)	201 (10.3)	240 (22.7)	556 (17.2)	1760 (25.7)	3084 (19.0)
Diabetes	532 (17.0)	237 (12.2)	199 (18.9)	548 (16.9)	1256 (18.4)	2772 (17.1)
Cochlear implants	6 (0.2)	1 (0.1)	0 (0.0)	4 (0.1)	19 (0.3)	30 (0.2)
Celiac disease	12 (0.4)	7 (0.4)	6 (0.6)	10 (0.3)	30 (0.4)	65 (0.4)
30-d case fatality rate	n = 3365	n = 2086	n = 1128	n = 3492	n = 7379	n = 17450
	291 (8.6)	209 (10.0)	212 (18.8)	737 (21.1)	1446 (19.6)	2895 (16.6)

n = denotes total number of cases with available information; data are presented as no. of cases (% of total cases with available information).

Abbreviations: CNS, central nervous system; PCV13, 13-valent pneumococcal conjugate vaccine.

[a]Invasive pneumococcal disease cases may have multiple comorbidities.

15- to 44-year-olds accounting for 10.2% (220/1202) of pneumococcal meningitis cases. The main serotypes responsible were 12F (186 [14.0%]), 8 (170 [12.8%]), and 3 (120 [9.0%]), with 43 other serotypes responsible for the remaining cases. Serotypes 9N (n = 73) and 19A (n = 42) were less common causes of pneumococcal meningitis, while serotype 7F, which used to be the most common cause of pneumococcal meningitis prior to PCV13 introduction, contributed to 16 cases only (Supplementary Table 2). In the multinomial logistic regression model, the relative risk of presenting with meningitis compared to septicemia (the reference group) was lower for ≥65-year-olds, those with underlying comorbidity, and infection with serotype 8 (Table 4).

Other Presentations

Other clinical presentations included septic/osteoarthritis, cellulitis, endocarditis, and urosepsis, which contributed to 10.6% (1735) of IPD cases across all ages (Table 2). Septicemia without a focus represented 11.4% (1858) of cases and was more prevalent in children (312/1202 [26.0%]) compared to the other age groups. For other clinical presentations, the risk in adult age groups remained at around 4–5 times higher than in children; those with remaining non-PCV13 serotypes had 1.22-fold (95% CI, 1.00–1.49) higher risk of other presentations relative to PCV13 serotypes (Table 4).

Case Fatality Rates

There were 2895 deaths within 30 days of IPD (case fatality rate [CFR], 16.6% [95% CI, 16.0%–17.2%]). CFR increased with age from 4.3% (54/1247) in children to 34.4% (1455/4229) among ≥80-year-olds (Table 2). The main serotypes contributing to death were 3 (434 [26.7%] of deaths), 8 (291 [10.1%]), 9N (212 [7.3%]), 12F (209 [7.2%]), and 22F (193 [6.7%]) (Supplementary Table 2). Among the emerging serotypes, IPD cases due to serotype 9N was associated with a higher CFR (212/1128 [18.8%]) compared to serotype 8 (291/3365 [8.7%]) or serotype 12F (209/2086 [10.0%]) in the univariate analysis (Table 3). In the logistic regression model, death was independently associated with increasing age, PCV13-serotype IPD, and clinical presentation with meningitis or septicemia (relative to invasive pneumonia) (Table 5). Underlying comorbidity was also independently associated with a higher CFR (adjusted odds ratio [aOR], 1.37 [95% CI, 1.22–1.53]). When comorbidity status was replaced with number of comorbidities in the model, the risk of death increased in a stepwise manner with an aOR of 1.25 (95% CI, 1.10–1.41; $P = .001$) for 1 comorbidity, 1.43 (95% CI, 1.25–1.63; $P < .001$) for 2 comorbidities, and 1.54 (95% CI, 1.34–1.77; $P < .001$) for ≥3 comorbidities compared to those with no comorbidity. Among IPD cases with an underlying comorbidity, the odds of death were not increased for immunocompromising conditions vs nonimmunocompromising conditions (aOR, 0.99 [95% CI, .89–1.09]).

Table 4. Multinomial Logistic Regression Model With Clinical Presentation as Outcome and Reference Category as Septicemia for Cases of Invasive Pneumococcal Disease in England; Independent Variables in the Model Included the Surveillance Year, Age Group, Serotype Group, and Comorbidity Status

Clinical Presentation	No. (%)	aRRR (95% CI)	*P* Value
Septicemia			
Age group, y			
<15	312 (16.8)	Ref	
15–44	222 (12.0)	Ref	
45–64	458 (24.7)	Ref	
65–79	479 (25.8)		
≥80	387 (20.8)	Ref	
Comorbidity status			
Comorbidity present	1062 (62.8)	Ref	
Healthy	630 (37.2)	Ref	
Serotype group			
8	288 (15.5)	Ref	
12F	215 (11.6)	Ref	
9N	103 (5.5)	Ref	
PCV13	305 (16.4)	Ref	
Remaining	947 (51.0)	Ref	
Meningitis[a]			
Age group, y			
<15	397 (29.9)	1.00 (base)	
15–44	220 (16.6)	0.97 (.75–1.25)	.82
45–64	435 (32.7)	1.01 (.81–1.25)	.95
65–79	215 (16.2)	0.50 (.39–.64)	<.001
≥80	62 (4.7)	0.18 (.13–.24)	<.001
Comorbidity status			
Comorbidity present	533 (42.1)	0.59 (.5–.7)	<.001
Healthy	734 (57.9)	1.00 (base)	
Serotype group			
8	170 (12.8)	0.70 (.53–.91)	.008
12F	186 (14.0)	0.89 (.68–1.18)	.42
9N	73 (5.5)	1.03 (.72–1.48)	.89
PCV13 serotypes	220 (16.6)	1.00 (base)	
Remaining serotypes	680 (5.2)	1.03 (.84–1.28)	.76
Pneumonia			
Age group, y			
<15	393 (3.44)	1.00 (base)	
15–44	1510 (13.2)	5.25 (4.21–6.54)	<.001
45–64	2957 (25.9)	4.75 (3.93–5.75)	<.001
65–79	3369 (29.5)	5.23 (4.31–6.34)	<.001
≥80	3195 (28.0)	6.76 (5.54–8.25)	<.001
Comorbidity status			
Comorbidity present	7721 (69.2)	1.11 (.99–1.25)	.08
Healthy	3440 (30.8)	1.00 (base)	
Serotype group			
8	2516 (22.0)	1.10 (.92–1.32)	.31
12F	1330 (11.6)	0.83 (.68–1.01)	.06
9N	788 (6.9)	0.92 (.72–1.19)	.54
PCV13 serotypes	2464 (21.6)	1.00 (base)	
Remaining serotypes	4326 (37.9)	0.57 (.49–.66)	<.001
Other presentations			
Age group, y			
<15	100 (5.8)	1.00 (base)	
15–44	213 (12.3)	4.19 (3.06–5.75)	<.001
45–64	523 (30.1)	4.9 (3.71–6.48)	<.001
65–79	510 (29.4)	4.38 (3.30–5.81)	<.001
≥80	389 (22.4)	4.24 (3.17–5.68)	<.001

Table 4. Continued

Clinical Presentation	No. (%)	aRRR (95% CI)	*P* Value
Comorbidity status			
Comorbidity present	1123 (66.2)	0.94 (.80–1.1)	.41
Healthy	574 (33.8)	1.00 (base)	
Serotype group			
8	202 (11.6)	0.80 (.62–1.03)	.08
12F	235 (13.5)	1.24 (.95–1.61)	.11
9N	97 (5.6)	1.04 (.74–1.46)	.82
PCV13	255 (14.7)	1.00 (base)	
Remaining	946 (54.5)	1.22 (1.00–1.49)	.05

Abbreviations: aRRR, adjusted relative risk ratio; CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; Ref, reference group.

[a]Example of output interpretation for the aRRR: Meningitis cases were relatively less frequent in the oldest age groups as compared to septicemia cases, after adjusting for the other variables, including serotype group and comorbidity status; similarly, those with comorbidity were less likely to present with pneumococcal meningitis compared to healthy individuals. Additionally, individuals with pneumococcal meningitis were less likely to be infected with serotype 8 compared to the PCV13 serotypes.

Serotype 3 was associated with a higher CFR compared to the remaining PCV13 serotypes (434/1625 [26.7%] vs 303/1867 [16.2%]; $P < .001$). Using PCV13 serotypes without serotype 3 as baseline in the logistic regression model, the odds of death was significantly higher for serotype 3 (aOR, 1.56 [95% CI, 1.30–1.86]) and lower for serotype 8 (aOR, 0.56 [.46–.67]) and 12F (aOR, 0.68 [.55–.83]) as well as the remaining serotypes (aOR, 0.81 [95% CI, .72–.90]), but not for serotype 9N (aOR, 1.08 [95% CI, .88–1.33]).

DISCUSSION

The recently emerging serotypes causing IPD in England each have unique epidemiological and clinical characteristics. Serotypes 8 and 12F share similarities in that they cause IPD in younger individuals who are more likely to be healthy and less likely to die from their infection when compared to PCV13 serotypes. Serotype 9N, on the other hand, behaves more like PCV13 serotypes, and is associated with a higher comorbidity prevalence and CFR compared to the other 2 emerging serotypes. While cases due to PCV13 serotypes have declined significantly, they still accounted for 20% of all IPD cases. Serotype 3 IPD cases, in particular, have been increasing since 2013–2014, with one of the highest CFRs and contributing the most to total IPD deaths. Fifty-five other serotypes were responsible for the remaining 42.5% of IPD cases; these serotypes were more likely to cause IPD in those with underlying comorbidities, and less likely to cause pneumonia or death when compared to PCV13-serotype IPD.

Table 5. Logistic Regression for Death Within 30 Days of an Invasive Pneumococcal Disease Episode

Variable	no./No. (30-d CFR, %)	Adjusted Odds Ratio (95% CI)	*P* Value
Age group, y			
< 15	54/1247 (4.3)	1.00 (base)	
15–44	93/2377 (3.9)	1.05 (.73–1.51)	.801
45–64	494/4728 (10.4)	2.81 (2.07–3.81)	<.001
65–79	799/4869 (16.4)	4.33 (3.2–5.87)	<.001
≥80	1455/4229 (34.4)	10.89 (8.05–14.75)	<.001
Serotype group			
8	291/3365 (8.6)	0.44 (.38–.52)	<.001
12F	209/2086 (10.0)	0.54 (.45–.64)	<.001
9N	212/1128 (18.8)	0.86 (.71–1.03)	.103
PCV13 serotypes	737/3492 (21.1)	1.00 (base)	
Remaining serotypes	1466/7379 (19.6)	0.81 (.72–.90)	<.001
Clinical presentation			
Meningitis	145/1329 (10.9)	1.22 (1.00–1.49)	.054
Pneumonia	1974/11 424 (17.3)	1.00 (base)	
Other presentations	293/1735 (16.9)	1.04 (.90–1.20)	.636
Septicemia	349/1858 (18.8)	1.46 (1.27–1.68)	<.001
Comorbidity status			
Healthy	560/5693 (9.8)	1.00 (base)	
Comorbidity present	2228/11 033 (20.2)	1.37 (1.22–1.53)	<.001

Dependent variables included surveillance year, age group, serotype group, clinical presentation, and comorbidity status.

Abbreviations: CFR, case fatality ratio; CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine.

Serotypes 8 and 12F share many features of highly invasive serotypes in that they cause invasive disease but are rarely found in carriage (ie, they have a high case-to-carrier ratio) [11, 12], affect healthy, younger individuals, and have a low CFR compared to the PCV13 serotypes. Serotype 9N, on the other hand, was previously not present in carriage but became the ninth most prevalent serotype in the 2015–2016 UK carriage study, being isolated from < 5-year-olds, 5- to 19-year-olds, and adults [12]. The characteristics of this serotype, therefore, reflects other carried serotypes, especially non-PCV13 serotypes in that it affects older individuals and those with underlying comorbidity, resulting in higher CFRs compared to 8 and 12F. Serotype 9N has persistently been associated with more severe disease and high case fatality [13].

Other European countries offering 10-valent PCV or PCV13 in their childhood immunization program have had differential indirect (herd) impact in adults and older adults after 5 years, in terms of persistence of vaccine-type IPD and replacement disease with nonvaccine serotypes [14]. The emerging serotypes have also varied in different countries, often without predominance of any particular serotype, although some have reported higher IPD incidence due to serotype 12F or 8 after higher-valent PCV implementation [15]. In comparison, the United States—where a 3 + 1 PCV13 schedule has been used for almost a decade—has reported very little replacement disease; although some studies have reported an increase in IPD due to serotypes 8 and 9N, both of these serotypes had only a minor contribution to overall disease burden [16, 17]. There is no clear explanation for this disparity, although differences in sampling, population demographics, risk factors, serotype interactions, and choice of vaccine schedule have been suggested to impact serotype replacement [16].

For the individual pneumococcal serotypes, it is difficult to disentangle the impact of vaccination from natural secular trends, especially the nonvaccine serotypes involved in replacement disease. Even among the vaccine serotypes, while PCV7 serotypes were virtually eliminated in carriage and disease after PCV7 introduction in the UK [18, 19], IPD due to serotypes 3 and 19A declined during the first 4 years after PCV13 implementation [11], but subsequently serotype 19A cases plateaued while serotype 3 IPD cases increased to rates above pre-PCV13 incidence [3], despite significant reductions in carriage of both these serotypes after PCV13 implementation [12]. These 2 serotypes have persisted in other countries with different PCV13 immunization schedules [20] and are, therefore, likely to remain in circulation even in countries with high PCV13 uptake.

In contrast to the highly invasive, less carried serotypes, those that are found in both carriage and disease are usually more predictable in terms of their propensity to cause invasive disease and death [21]. Reassuringly, the replacing serotypes in carriage after PCV13 implementation had a lower case-to-carrier ratio and were, therefore, less likely to cause IPD [12]. Clinical follow-up of cases confirms that the remaining non-PCV13 serotypes, which are commonly carried in children, are predominantly opportunistic, causing IPD mainly in those with underlying comorbidity; moreover, our analysis indicates that while these serotypes in themselves are less likely to be fatal, the underlying comorbidity is independently associated with a significantly higher risk of death. Overall, however, the large contribution of serotypes 8 and 12F to total IPD burden in recent years means that the overall CFR is likely to be lower now compared to the pre-PCV7 or the pre-PCV13 era [22].

The strength of this study is in the long-term national surveillance with high case ascertainment rates and near-complete serotyping of invasive isolates. Extending the enhanced surveillance to cover all age groups since 2014 has been challenging, with more than 5000 cases confirmed annually, but the high questionnaire return rates highlights the continued support provided by the primary care teams for the national immunization program. A limitation of the study is the limited clinical information collected for IPD cases; the postal questionnaire was restricted to a single page to encourage high return rates for national surveillance. Another limitation is that the focus of infection relied on clinical judgement rather than strict definitions, such as radiological confirmation of pneumonia cases. We also restricted our analysis to the 3 major emerging serotypes and compared them to PCV13 serotypes and the remaining non-PCV13 serotypes to demonstrate the unique characteristics of IPD caused by these serotypes.

CONCLUSIONS

In the UK, 3 serotypes have recently emerged as major causes of IPD in England, each with unique clinical and epidemiological characteristics when compared to PCV13 serotypes and the remaining non-PCV13 serotypes. The low CFR associated with serotypes 8 and 12F IPD, which contribute to a significant proportion of IPD cases, is reassuring. The remaining non-PCV13 serotypes mainly caused opportunistic infections in those with underlying comorbidity. Our study highlights the importance of monitoring clinical disease and outcomes of individual serotypes to better understand their contribution to the total IPD burden.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The Immunisation and Countermeasures Division has provided vaccine manufacturers (GlaxoSmithKline [GSK], Pfizer, Sanofi) with postmarketing surveillance reports on pneumococcal and meningococcal infection, which the companies are required to submit to the United Kingdom Licensing authority in compliance with their risk management strategy. A cost recovery charge is made for these reports. S. N. L. performs contract research on behalf of St George's University of London and Public Health England for pharmaceutical companies (GSK, Pfizer, Sanofi, Merck Sharp & Dohme) but receives no personal remuneration. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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