Title

Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013 – 2018

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Key Words

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Data sharing statement

The study protocol will be available to investigators at the time of article publication. Individual participant data that underlie the results reported in this article will be available (beginning 9months and ending 36months following article publication) to investigators after de-identification for the purpose of individual participant data meta-analysis, and whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose.

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Author contributions

HJP, CS, and WSL were responsible for study conception and design. HJP, PD, CR, TB, DA, HL, VB, RCE-P, CS, and SE were responsible for data acquisition. HJP, TMM, and CT were responsible for the statistical analysis. HJP and WSL drafted the initial versions of the Article. All authors contributed to data interpretation and read, commented on, and approved the final version of the Article.

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KEY MESSAGES

What is the key question?

Which pneumococcal serotypes are implicated in adult pneumococcal pneumonia and which patient groups are associated with vaccine-serotype disease?

What is the bottom line?

The incidence of pneumococcal CAP is increasing, predominantly due to non-vaccine serotypes and serotype 3. Novel pneumococcal vaccines targeting emerging serotypes are needed.. PCV13-serotype pneumonia (dominated by serotype 3) is more likely in patients in the UK pneumococcal vaccination clinical risk group while PPV23-serotype pneumonia is more likely in patients outside the clinical risk group.

Why read on?

This large prospective cohort study is the first to describe pneumococcal serotype trends and clinical risk groups in adult patients with community-acquired pneumonia in UK using a novel and validated multiplex immunoassay.

ABSTRACT (limit 250 words)

Background. Changes over the last five years (2013–2018) in the serotypes implicated in adult pneumococcal pneumonia and the patient groups associated with vaccine-type disease are largely unknown.

Methods. We conducted a population-based prospective cohort study of adults admitted to two large university hospitals with community-acquired pneumonia (CAP) between September 2013 and August 2018. Pneumococcal serotypes were identified using a novel 24-valent urinary monoclonal antibody assay and from blood cultures. Trends in incidence rates were compared against national invasive pneumococcal disease (IPD) data. Persons at risk of vaccine-type pneumonia (PCV13 and PPV23) were determined from multivariate analyses.

Findings. Of 2934 adults hospitalised with CAP, 1075 (36·6%) had pneumococcal pneumonia. The annual incidence of pneumococcal pneumonia increased from 32·2 to 48·2 per 100,000 population (2013-2018), predominantly due to increases in PCV13non7- and non-vaccine type (NVT)-serotype pneumonia (annual IRR 1·12, 95% CI 1·04-1·21 and 1·19, 95% CI 1·10-1·28 respectively). Incidence trends were broadly similar to IPD data. PCV13non7 (56·9% serotype 3) and PPV23non13 (44·1% serotype 8) serotypes were identified in 349 (32·5%) and 431 (40·1%) patients with pneumococcal pneumonia respectively. PCV13-serotype pneumonia (dominated by serotype 3) was more likely in patients in the UK pneumococcal vaccination clinical risk group (aOR 1·73, 95% CI 1·31-2·28) while PPV23-serotype pneumonia was more likely in patients outside the clinical risk group (aOR 1·54, 95% CI 1·13-2·10).

Interpretation. The incidence of pneumococcal CAP is increasing, predominantly due to NVT serotypes and serotype 3. PPV23-serotype pneumonia is more likely in adults outside currently identified clinical risk groups.

(248 words)

INTRODUCTION

Pneumococcal conjugate vaccines (PCVs) have demonstrated substantial effectiveness in reducing pneumococcal disease due to vaccine serotypes.[1,2] In England and Wales, immunisation of children with a 7-valent pneumococcal conjugate vaccine (PCV7) commenced in 2006 and was replaced in April 2010 with a 13-valent pneumococcal conjugate vaccine (PCV13).[3] Over the same period, individuals aged >2 years with a clinical risk factor for pneumococcal disease and all adults aged ≥65 years have been offered vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV23).[3]

Both PCVs have been associated with rapid and sustained reductions in overall and vaccine-serotype invasive pneumococcal disease (IPD) in young children.[4] PCVs also reduce carriage in vaccinated individuals and hence prevent onward transmission to unvaccinated older children and adults. Thus, reductions in IPD and pneumococcal pneumonia have been observed across all age groups.[4-7]

Since 2013/14, however, overall IPD incidence due to PCV13 serotypes has plateaued in the UK, while IPD due to non-PCV serotypes has increased rapidly, especially in adults and the elderly.[2,4] The USA by contrast, where PCV13 has been recommended as part of the childhood immunisation programme since 2010, has not observed such an increase in non-PCV13-serotype IPD despite large declines in PCV13-serotype disease.[8]

In adults, IPD accounts for less than 10% of pneumococcal pneumonia cases. There are therefore limited contemporary data on the range of serotypes causing pneumococcal pneumonia in adults in the UK.[7] In particular, the contribution of PCV13 and PPV23 serotypes to pneumococcal pneumonia is important to inform national pneumococcal vaccine policy, especially in adults and the elderly.[9,10]

Since 2008, we have conducted a prospective population-based adult pneumococcal pneumonia study to determine changes in clinical disease and the responsible pneumococcal serotypes.[7,11] Recently, a novel, validated 24-valent multiplex urinary immunoassay was developed to detect PCV and PPV serotypes in patients with non-invasive disease.[12] We report the use of this assay in a previously unreported cohort of patients to describe a) serotype trends in adult pneumococcal pneumonia since PCV13 replaced PCV7, and b) the clinical risk groups associated with vaccine-type disease.

METHODS

Study design

We conducted a prospective observational cohort study of consecutive adult patients admitted to two large university hospitals with CAP between September 2013 and August 2018. Together, these two hospitals cover the catchment for emergency admissions in the Greater Nottingham area. All patients admitted to acute admission areas were screened for study eligibility every weekday. Patients aged ≥16 years presenting with one or more symptom suggestive of lower respiratory tract infection (LRTI; defined as cough, increasing dyspnoea, sputum production, and fever), with evidence of acute infiltrates consistent with respiratory infection on admission radiography, and treated for a diagnosis of CAP were eligible. Exclusion criteria included hospitalisation within 10 days of index admission, a diagnosis of tuberculosis, or post-obstructive pneumonia. Informed consent was obtained from all study participants; if patients lacked capacity, proxy consent was sought from patient personal consultees. Demographic and clinical characteristic data were collected using a standardised proforma. Study procedures were approved by the Nottingham Research Ethics Committee (REC reference 08/H0403/80).

Microbiology

Baseline microbiological investigations were performed at the discretion of the clinical team. In addition, urine samples for pneumococcal specific microbiological analyses were obtained within 72 hours of admission; Binax-NOW® (Alere, Stockport, UK) assay for pneumococcal C-polysaccharide urinary antigen detection (UAD) was performed in the local microbiological laboratory,[13] with the remaining volume of urine frozen at -80°C and batch transported to Public Health England (PHE)'s Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) in Colindale, London for pneumococcal serotyping using a validated multiplex immunoassay (Bio-plex24.) The Bio-plex24 assay targets the detection of pneumococcal serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F, and the pneumococcal cell-wall polysaccharide.[12] Samples from September 2014 to August 2015 were tested using the original protocol as published by Eletu et al, with a clinical sensitivity of 96·2%, specificity 89·9%.[12] The assay was then updated to include minor protocol modifications and alternative monoclonal clones for serotypes 7F, 18C, 19F, 20, and 22F; this updated assay (validated using 2037 urine samples from patients with CAP or suspected pneumococcal disease, with a calculated clinical sensitivity of 94·3% and specificity of 93·6% - manuscript in preparation) was used for the remainder of the study period. Sixteen of the human monoclonal antibodies within the Bio-plex24 assay exhibit some cross-reactivity with specific non-targeted pneumococcal serotypes. A 'checkerboard' system for interpretation of results allows

serotype identification for 5 of these serotypes. In the remaining 11, based on probabilistic grounds, the designated serotype for analysis was determined according to the predominant serotype observed in national IPD data for the corresponding time period (Appendix 2).[4]

During sample testing between September 2014 and August 2015 (first batch tested), the monoclonal antibodies targeting serotypes 7F, 20, and 22F were found to cross-react with an unknown substance in some urine samples. Therefore, in reporting results for samples from that study year, we excluded all results for serotype 7F and applied a higher diagnostic threshold for serotypes 20 and 22F, with results excluded if these criteria were not satisified.[12] Samples from the four other study years were tested with an improved Bio-plex24 assay, outlined above, eliminating the non-specific cross-reactivity.

Up to September 2017, bacteraemic isolates of *Streptococcus pneumoniae* were identified by standard phenotypic methods and serotyped by slide agglutination tests with latex antisera (ImmuLex™ Pneumotest kit) or standard factor sera (SSI Diagnostica, Denmark). From October 2017, confirmation of pneumococcal isolate identification and serotype prediction was performed by bio-informatical methods following DNA extraction and whole genome sequencing,[14] with the exception of serotypes within serogroup 24 which were identified by conventional methods using antisera.[15]

Patients were considered to have pneumococcal CAP if any of the following criteria were met: a) positive pneumococcal UAD or b) a positive blood culture for *S pneumoniae* or c) pneumococcal serotype or cell wall polysaccharide detection by the Bio-plex24 assay.

Statistical analysis

Serotypes were classified according to the serotype content of vaccines: PCV7 serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), PCV13non7 serotypes (serotypes 1, 3, 5, 6A/C, 7F/A, 19A), PPV23non13 serotypes (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F), and non-vaccine-type (NVT) serotypes (comprising a) any non-PCV13, non-PPV23 serotype and b) 'untyped' pneumococcal disease; Binax UAD positive without subsequent serotype identification, or Bio-plex24 positive for cell wall polysaccharide only.)

Annual incidence rates were derived from mid-year estimates from the Office for National Statistics for the Greater Nottingham area, including local population data stratified by age group (16-49, 50-64, 65-74, 75-84, ≥85 years.) Trends between 2013 and 2018 comparing overall incidence of CAP, pneumococcal CAP, and CAP according to serotype categories were examined. Additionally, serotype trends were compared with corresponding national IPD surveillance data.[4] Poisson regression

models together with 95% confidence intervals were used to assess year to year variation and linear trends in serotype distribution.

Clinical risk factors for pneumococcal disease were defined in accordance with PHE's 'Immunisation against Infectious Diseases' (The Green Book).[3] For analyses of groups at-risk of pneumococcal disease, patients with multiple serotypes that crossed vaccine groups were excluded (e.g. one or more positive serotype in both PCV-13 and PPV23-serotype disease groups). Baseline characteristics and co-morbid risk factors for PCV13- and PPV23-serotype disease were compared using Pearson's chi-square or Fisher's exact tests for categorical variables, and the Mann-Whitney U test for non-parametric continuous variables. Likelihood ratio tests were used to determine the best model fit for continuous variables. Multivariate logistical regression was used to compare the independent association between co-morbid disease and a) PCV13- and b) PPV23-serotype disease. Purposeful selection of variables for inclusion in the multivariate analysis was conducted based on clinical risk factors outlined in PHE's 'Immunisation against Infectious Diseases' (The Green Book),[3] in conjunction with evidence from previous studies of risk factors for pneumococcal and/or vaccine serotype disease, and considering biological plausibility, and were specified *a priori*.[16] Secondary analyses were conducted examining the risk of PCV13- and PPV23-serotype disease in:

(a) the pneumococcal clinical risk group (defined as adults 16-64 years with ≥1 clinical risk factor for pneumococcal disease or age ≥65 years),

(b) specific clinical risk groups: (1) aged 16-64 years without clinical risk factors, (2) aged 16-64 years with ≥1 clinical risk factor, (3) aged ≥65 years without clinical risk factors, and (4) aged ≥65 years with ≥1 clinical risk factor, and

(c) individuals with increasing numbers of clinical risk factors.

Sensitivity analyses were conducted to investigate the impact of a) the method used for serotype designation and b) serotype 3 disease. Statistical analyses were conducted using Stata/IC 15 (©StataCorp. 2017).

RESULTS

Study population

During the five-year study period, of 3595 eligible patients, 158 (4·4%) patients had an alternative diagnosis and study consent was not obtained for 503 (14·6%). Patients without consent were older (median age 82·2 years, interquartile range (IQR) 70·2-88·9 years versus 71·3 years, IQR 55·8-81·2 years, p<0·001), more often resident in care home facilities (35·0% versus 4·0%, p<0·001), more likely to have chronic kidney disease (12·8% versus 8·3%, p=0·001), cerebrovascular disease (21·2% versus 7·7%, p<0·001), and cognitive impairment (33·6% versus 3·7%, p<0·001), and less likely to have chronic respiratory disease (19·5% versus 27·9%, p<0·001) compared to the study cohort patients.

Baseline characteristics

The study cohort consisted of 2934 adults hospitalised with CAP between 2013 and 2018 (Table 1); median age 71·3 years (IQR 55·8-81·2 years), 1515 (51·7%) male, and pneumonia severity low, moderate, and high in 1377 (46·9%), 880 (30·0%), and 677 (23·1%) patients respectively. Admission to intensive care occurred in 225 (7·7%) cases and overall 30-day case mortality rate was 7·5% (n= 219).

In 538 of 2934 patients, a urine sample was not available for pneumococcal testing. *Streptococcus pneumoniae* was identified in 1075 (36.6%) patients; Binax-NOW® test was positive in 505 (47·0%) of 1075, Bio-plex24 in 973 (90·5%) and blood cultures in 111 (10·3%). One or more serotype was determined in 843 (78·4%) of 1075 patients with pneumococcal CAP; 2 serotypes were identified in 102 patients and ≥3 serotypes in 15 patients.

Trends in pneumococcal CAP

The overall annual incidence of CAP over the study period was 120·4 (95% confidence interval (CI) 116·4-124·5) per 100,000 population. Annual incidence rates are presented in Table 2. Incidence increased significantly over the five-year period (annual IRR 1·12, 95% CI 1·09-1·14, p<0·001) (Table 3). Adults aged ≥85 years demonstrated the greatest relative increase (115%) between 2013 and 2018 (annual IRR 1·24, 95% CI 1·17-1·31, p<0·001).

The overall annual incidence of pneumococcal CAP was 37·7 (95% CI 35·3-39·8) per 100,000 population. Pneumococcal CAP incidence rates increased over five years particularly in older age groups; for adults aged 65-74 years, 75-84 years, and ≥85years, annual IRR was 1·12 (95% CI 1·02-

1·22, p=0·014), 1·20 (95% CI 1·09-1·32, p<0·001), and 1·15 (95% CI 1·03-1·28, p=0·014), respectively (Table 3).

The overall annual incidence for CAP due to PCV7, PCV13non7, PPV23non13 and NVTs was 2·5 (95% CI 1·9-3·1), 12·2 (95% CI 11·0-13·6), 15·1 (95% CI 13·7-16·6), and 11·2 (95% CI 10·0-12·5) per 100,000 population, respectively (Figure 1). The incidence of PCV13non7-serotype CAP (annual IRR 1·12, 95% CI 1·04-1·21, P=0·003) and NVT-serotype CAP (annual IRR 1·19, 95% CI 1·10-1·28, P<0·001) increased significantly over five years.

Pneumococcal serotypes

A total of 32 different serotypes were identified; 21 were definitively identified by Bio-plex24 or serum agglutination of bacteraemic cases while 11 were designated based on the predominant serotype derived from national IPD surveillance data (Figure 2 and Appendix 2). Of the 11 designated serotypes, nine matched the target serotypes, one was a different vaccine serotype (6A to 6C), and one was a NVT (15B to 15A). PCV7 serotypes were identified in 71 (6·6%) of the 1075 patients with pneumococcal CAP; serotype 19F was commonest (n=25, 33·3% of PCV7 serotypes), followed by serotype 14 (n=17, 22·7%) and 23F (n=11, 14·7%). PCV13non7 serotypes were identified in 349 (32·5%) patients, with serotype 3 being responsible for more than half of these cases (n=205, 56·9% of PCV13non7 serotypes).

PPV23non13 serotypes were identified in 431 (40·1%) patients; serotype 8 was commonest (n=197, 44·1% of PPV23non7 serotypes) followed by serotypes 12F (n=60, 13·4%), 11A (n= 38, 8·5%), 22F (n=36, 8·1%) and 9N (n=35, 7·8%).

An NVT-serotype was identified in 321 (29·9%) patients, with serotype 15A identified in more than a quarter (n=80, 26·9% of NVT serotypes) while no serotype ('untyped' pneumococcal disease) was identified in 231 patients.

Compared to national IPD data over the same period,[4] proportions of serotype 3 disease were higher for CAP while PPV23non13-serotype disease was higher in IPD (Figure 3). The observed increase in serotype 3 pneumonia (annual IRR 1·28, 95% CI 1·24-1·32) was of similar magnitude to serotype 3 in IPD (annual IRR 1·23, 95% CI 1·12 – 1·36) (Table 6 and Figure 4).

Persons with PCV13-serotype pneumonia

Of 983 patients eligible for analysis (single serotype, or multiple serotypes not crossing vaccine serogroup classes), 325 had PCV13-serotype and 658 had non-PCV13-serotype disease (supplementary table 1). Increasing age (per year increase, adjusted Odds Ratio (aOR) 1·02, 95% CI

1·01-1·03, p<0·001) and chronic kidney disease (aOR 1·71, 95% CI 1·02-2·86, p=0·019 respectively) were significantly associated with higher odds of PCV13-serotype disease compared to non-PCV13-serotype disease. Conversely, those living in residential care (aOR 0·28, 95% CI 0·10-0·75, p=0·012) or with active malignancy (aOR 0·52, 95% CI 0·31-0·90, p=0·019) had significantly lower odds of PCV13-serotype disease. On multivariate analysis, patients in the pneumococcal clinical risk group (aOR 1·73, 95% CI 1·31-2·28, p<0·001) and patients aged ≥65years with ≥1 risk factor (aOR 1·69, 95% CI 1·24-2·30, p=0·001) had significantly higher odds of PCV13-serotype whilst patients aged 16-64 years without risk factors had significantly lower odds of PCV13-serotype disease (aOR 0·59, 95% CI 0·43-0·81, P=0·001)(Table 4).

Sensitivity analysis excluding all cases with designated serotypes (n=157) did not significantly alter findings. Patients >65years with 1 or more clinical risk factor were no longer at increased risk of PCV-13 serotype disease when cases of serotype 3 were excluded and the associations between PCV-13 serotype disease and other risk groups were less pronounced but remained significant (Supplementary data).

Persons with PPV23 serotype pneumonia

Of 1048 patients eligible for analysis (single serotype, or multiple serotypes not crossing vaccine serogroup classes), 732 had PPV23-serotype and 316 had non-PPV23-serotype disease (supplementary table 2). There were no significant associations between risk of PPV23 serotype disease and individual co-morbidities identified in the multivariate analysis. On multivariate analysis of clinical risk and PPV23 serotype disease, both the pneumococcal clinical risk group (aOR 0·65, 95% CI 0·48-0·88, p=0·006) and patients 16-64 years with ≥1 risk factor (aOR 0·51, 95% CI 0·35-0·73, p<0·001) had significantly lower odds of PPV23-serotype disease (Table 5). Patients 16-64 years without risk factors had significantly higher odds of PPV23-serotype disease (aOR 1·54. 95% CI 1·13-2·10, p=0·006).

Sensitivity analyses excluding 1) all cases with designated serotypes (n=183) and 2) all cases of serotype 3, from the model did not significantly alter findings.

An exploratory analysis to identify persons at risk of PPV23non13-serotype disease found that patients aged 16-64 years without risk factors had significantly higher odds of PPV23non13-serotype disease (aOR 1·94, 95% CI 1·42-2·65, p<0·001), whilst patients aged ≥65 years with ≥1 risk factor (aOR 0·69, 95% CI 0·51-0·94, p=0·017) and pneumococcal clinical risk group (aOR 0·52, 95% CI 0·38-0·70, p<0·001) had significantly lower odds of PPV23non13-serotype disease compared to non-PPV23non13-serotype disease.

DISCUSSION

The key study findings are 1) the annual incidence of adult pneumococcal CAP has increased from 32·2 per 100,000 population in 2013 to 48·2 per 100,000 population in 2018, concurrent with increases in the incidence of overall CAP, 2) this increase is predominantly due to increases in PCV13non7- and NVT-serotype pneumonia, 3) serotype 3 accounts for more than half of PCV13non7-serotype pneumonia, 4) PCV13-serotype pneumonia is 73% more likely in patients in pneumococcal clinical risk group, while 5) PPV23-serotype pneumonia is 54% more likely in younger patients who are not in the pneumococcal clinical risk group.

The epidemiology of adult pneumococcal pneumonia in Europe appears to be diverging from that seen in the US. We found evidence of pneumococcal infection in more than a third of adults hospitalised with CAP, consistent with other recent reports from Europe.[17,18] In contrast, in the US, *Streptotoccus pneumoniae* has been recently implicated in only 8 - 12% of hospitalised cases of CAP.[19,20] During 2008-2013, we had observed early indications of a decline in CAP due to PCV13 serotypes in adults following PCV7 substitution with PCV13 in the childhood immunisation programme. However, our latest findings in a previously untested and unreported cohort of patients from Nottingham indicate that PCV13 serotypes continue to account for a large proportion (40·6%) of adult CAP, with serotype 3 alone comprising 47·1% of PCV13 serotype cases. Pneumococcal carriage studies[21,22] and national surveillance of IPD[5] have also observed a limited direct and indirect effect of PCV13 vaccination on serotype 3. These results are consistent with data indicating the serotype 3 antigen within PCV13 may provide suboptimal direct and indirect protection.[23] Notwithstanding serotype 3, there appears to be a persistence of PCV13 serotypes causing CAP. Serotypes 3, 5 and 6A were relatively more common in CAP compared to IPD , possibly indicating a predilection for pneumonia (rather than IPD) with these serotypes, as also observed by others.[24,25]

We identified multiple serotypes in 10.9% of patients with pneumococcal pneumonia. This is higher than the proportion with multiple serotypes identified in IPD cohorts. The relevance and implications of this finding warrants further investigation.

Based on data from 2008 – 2013, we previously reported that PCV13-serotype CAP was *less* common in adults in the pneumococcal clinical risk group compared to adults aged 16 – 64 years without clinical risk factors.[26] Those data reflected the situation within the first few years after introduction of the childhood PCV13 immunisation programme. Since then, the burden of PCV13-serotype CAP has shifted and adults in pneumococcal clinical risk group are at increased risk of infection. This association is dominated by serotype 3 which may reflect the invasiveness potential of this serotype, its penchant for pneumonia (compared to IPD) and its persistent carriage amongst children and

adults. The influence of the recently emerged Clade II lineage (of serotype 3) in relation to clinical disease presentation is unclear.[27,28]

A large proportion of pneumococcal CAP was due to PPV23non13-serotype pneumonia (40·2%) with no significant change in incidence during 2013-2018. Serotype 8 was commonest, similar to national IPD trends.[4] Although carriage of serotype 8 in children is rare, colonisation in young adults has been observed and may represent the reservoir from which adult pneumococcal infections arise.[29] In England and Wales, uptake of PPV23 vaccination in older adults and pneumococcal clinical risk groups has remained stable (~70%) over the study period.[30] The lack of significant change in the incidence of PPV23non13-serotype pneumonia suggests the replacing serotypes in pneumococcal pneumonia are predominantly NVT serotypes not covered by either PCV13 nor PPV23 vaccines. This is consistent with the observed increase in incidence of NVT-serotype pneumococcal pneumonia both in this study, and in other cohorts.[4,8]

We found the odds of PPV23-serotype CAP was *higher* in patients *outside* the pneumococcal clinical risk group, specifically in patients aged 16-64 years without risk factors (aOR 1·54), but lower in patients in the pneumococcal clinical risk group (aOR 0·61). These associations were amplified when the analyses were restricted to patients with PPV23non13-serotype pneumonia (aOR 2·39 and aOR 0·42) and could reflect individual direct protection offered by PPV in 'at-risk' adults.[31]

Strengths and limitations

This large prospective population-based cohort study describes trends in pneumococcal serotypes implicated in adult pneumococcal pneumonia over the last five years, during which PCV13 replaced PCV7 in the national childhood immunisation programme. Unlike laboratory-based studies, our study population is not over-represented by patients with chronic lung disease or those requiring invasive respiratory procedures.[25] Use of the novel Bio-plex24 assay enabled identification of PCV13 and PPV23 serotypes in patients presenting with non-invasive disease, which is the vast majority of adults with CAP, compared with previous studies which have been unable to identify PPV23-non13-serotype disease from non-invasive samples and have classified these cases as non-vaccine-type infection only.

We observed an increased incidence in all-cause CAP and pneumococcal CAP over a 5 year period which we have interpreted as representing a true increase in disease burden. We cannot exclude the possibility that some of this increase may have been due to healthcare system changes resulting in a shift from primary to secondary care management for CAP. However, the lack of any substantial

change over time in the distribution of low versus high severity pneumonia on admission suggests this is unlikely to be a major factor.

One limitation of this study relates to cross-reactivity of the Bio-plex24 assay. Non-specific cross-reactivity for serotypes 7F, 18C, 20 and 22F was noted during testing of samples from September 2014 to August 2015. We chose to report results conservatively, accepting some under-representation of serotypes 7F, 18C, 19F, 20, and 22F for that year. Following modifications to the assay, this non-specific cross-reactivity did not affect results for the other 4 years. For 11 serotypes displaying cross-reactivity with other serotypes not targeted by the Bio-plex24 assay we designated cases to a single serotype based on the predominant serotype derived from national IPD data. A consequence of this methodology is the potential under-representation of less frequent serotypes. In sensitivity analyses investigating the influence of the method of serotype designation on results, no major differences were detected (supplementary data available on request). Any overall under-representation of NVT serotypes arising from serotype designation would mean that our reported finding of an increased incidence of NVT-serotype CAP is conservative.

Secondly, all untyped pneumococcal isolates were considered NVT serotypes, potentially leading to an over-representation of NVT-serotype CAP. The impact of this on the overall findings is likely to be small given the high sensitivities of the serotyping methods used.

Additionally, as this study was performed in one geographical area, the serotype trends observed may have been due to local/regional epidemiological changes and our findings may not be applicable to other populations. Nevertheless, the main findings are consistent with trends observed from national IPD data.

Implications

We report an increase in pneumococcal CAP, predominantly due to increases in NVT serotypes and serotype 3. Pneumococcal vaccines targeting emerging serotypes are needed.

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TABLE 1: Baseline characteristics, disease severity, and outcomes of community-acquired pneumonia (CAP) cohort and pneumococcal CAP cohort

	CAP cohort	Pneumococcal CAP cohort
Patients	2934	1075
Demographics		
Age, years (IQR)	71·3 (55·8-81·2)	69·3 (53·9-80·1)
16-49 years	522 (17·8)	214 (20·0)
50-64 years	590 (20·1)	228 (21·2)
65-74 years	610 (20·8)	246 (22·9)
75-84 years	757 (25·8)	226 (21·0)
≥85 years	455 (15·5)	161 (14·9)
Male	1515 (51·7)	513 (47·8)
Care Home Resident	116 (4·0)	35 (3·3)
Comorbid disease		
Smoking status#		
Never smoker	836 (29·5)	292 (28·0)
Ex-smoker	1311 (46·3)	438 (42·0)
Current smoker	685 (24·1)	314 (30·1)
Alcohol excess	80 (2·7)	42 (3·9)
Malignancy	269 (9·2)	91 (8·5)
Liver disease	48 (1·6)	24 (2·2)
Kidney disease	244 (8·3)	83 (7·7)
Chronic heart disease	460 (15·7)	145 (13·5)
Congestive cardiac failure	185 (6·3)	64 (6·0)
Ischaemic heart disease	321 (10·9)	101 (9·4)
Chronic lung disease (excluding asthma)	819 (27·9)	292 (27·2)
COPD	723 (24·6)	261 (24·3)
Asthma	312 (10·6)	122 (11·4)
Diabetes Mellitus	469 (16·0)	163 (15·2)
Cerebrovascular disease	225 (7·7)	82 (7·6)
Cognitive impairment	107 (3·7)	36 (3·4)
Immunocompromise	109 (3·7)	47 (4·4)
Disease Severity		
CURB-65 0-1	1377 (46·9)	483 (44·9)
CURB-65 2	880 (30·0)	320 (29·8)
CURB-65 ≥3	677 (23·1)	272 (25·3)
Outcomes		
Critical Care admission	225 (7·7)	108 (10·1)
30-day mortality	219 (7·5)	54 (5·0)

Data are presented as n (%) or median (interquartile range). COPD: chronic obstructive pulmonary disease; CURB-65: confusion, urea >7 $mmol.L^{-1}$, respiratory rate >30 $breaths.min^{-1}$, blood pressure <90mmHg [systolic] <60mmHg [diastolic], age ≥65years. #: Data regarding smoking status available for 2832 and 1040 participants in the CAP cohort and Pneumococcal CAP cohort respectively.

TABLE 2: Incidence rates of community-acquired pneumonia (CAP), pneumococcal CAP, and CAP due to vaccine and non-vaccine groups by study year

	Patient age, years	Year 6, 2013-2014			Year 7, 2014-2015 *			Year 8, 2015-2016			Year 9, 2016-2017			Year 10, 2017-2018		
		n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI
All CAP		538	96·3	88·4-104·8	688	120·9	112·1-130·3	548	95·8	88·0-104·2	744	129·3	120·2-139·0	919	158·4	148·4-169·0
	16-49	91	27·3	22·0-33·5	117	34·8	28·8-41·7	114	33·7	27·8-40·5	112	33.0	27·1-39·7	102	29·9	24·4-36·3
	50-64	93	80·2	64·7-98·2	127	107·6	89·7-128·1	114	94·9	78·3-114·0	145	119·7	101·0-140·8	180	146·9	126·3-170·0
	65-74	105	181·3	148·3-219·5	148	248·7	210·3-292·2	101	164·2	133·7-199·5	131	210·4	175·9-249·6	194	310·4	268·3-357·3
	75-84	145	400·6	338·0-471·3	181	495·9	426·3-573·6	142	386·9	325·9-456·0	199	541·3	468·7-622·0	207	559·5	845·8-641·1
	≥85	104	707·5	578·1-857·2	115	766·7	633·0-920·3	77	505·4	398·9-631·7	157	1024·1	870·2-1197·5	236	1522·6	1334·5-1729·7
Pneumococcal CAP		180	32·2	27·7-37·3	200	35·2	30·5-40·4	166	29.0	24·8-33·8	247	42·9	37·7-48·6	282	48·6	43·1-54·6
	16-49	45	13·5	9·8-18·0	46	13·7	10·0-18·3	36	10·6	7·5-14·7	46	13·5	9·9-18·1	41	12.0	8·6-16·3
	50-64	36	31.0	21·7-43·0	40	33·9	24·2-46·2	37	30·8	21·7-42·5	55	45·4	34·2-59·1	60	49.0	37·4-63·0
	65-74	38	65·6	46·4-90·1	48	80·7	59·5-107·0	41	66·6	47·8-90·4	50	80·3	59·6-105·9	69	110·4	85·9-139·7
	75-84	28	77·3	51·4-111·8	45	123·3	89·9-165·0	34	92·6	64·2-129·5	59	160·5	122·2-207·0	63	170·3	130·8-217·8
	≥85	33	224·5	154·5-315·3	21	140.0	86·7-214·0	21	137·8	85·3-210·7	37	241·4	170·0-332·7	49	316·1	233·9-417·9
PCV7-serotype CAP		10	1·8	0·9-3·3	14	2·5	1·3-4·1	12	2·1	1·1-3·7	17	3.0	1·7-4·7	18	3·1	1·8-4·9
	16-49	1	0·3	0·0-1·7	2	0·6	0·1-2·2	3	0·9	0·2-2·6	2	0·6	0·1-2·1	1	0·3	0·0-1·6
	50-64	1	0·9	0·0-4·8	1	0·8	0·0-4·7	2	1·7	0·2-6·0	1	0·8	0·0-4·6	2	1·6	0·2-5·9
	65-74	3	5·2	1·1-15·1	3	5.0	1·0-14·7	3	4·9	1·0-14·2	6	9·6	3·5-21·0	5	8.0	2·6-18·7
	75-84	1	2·8	0·1-15·4	6	16·4	6·0-35·8	2	5·4	0·7-19·7	3	8·2	1·7-23·9	6	16·2	6·0-35·3
	≥85	4	27·2	7·4-69·7	2	13·3	1·6-48·2	2	13·1	1·6-47·1	5	32·6	10·6-76·1	4	25·8	7·0-66·1
PCV13non7-serotype CAP		64	11·5	8·8-14·6	56	9·8	7·4-12·8	51	8·9	6·6-11·7	88	15·3	12·3-18·8	90	15·5	12·5-19·1
	16-49	15	4·5	2·5-7·4	4	1·2	0·3-3·0	7	2·1	0·8-4·3	11	3·2	1·6-5·8	5	1·1	0·5-3·4
	50-64	15	12·9	7·2-21·3	8	6·8	2·9-13·4	11	9·2	4·6-16·4	14	11·6	6·3-19·4	23	18·8	11·9-28·2
	65-74	14	24·2	13·2-40·6	21	35·3	21·8-54·0	14	22·8	12·4-38·2	21	33·7	20·9-51·6	23	36·8	23·3-55·2
	75-84	12	33·1	17·1-57·9	13	35·6	19·0-60·9	8	21·8	9·4-43·0	29	78·9	52·8-113·3	22	59·5	37·3-90·0
	≥85	8	54·4	23·5-107·2	10	66·7	32·0-122·6	11	72·2	36·0-129·1	13	84·8	45·2-145·0	17	109·7	63·9-175·6
PPV23non13-serotype CAP		71	12·7	9·9-16·0	93	16·3	13·2-20·0	73	12·8	10·0-16·0	99	17·2	14·0-21·0	95	16·4	13·3-20·0
	16-49	19	5·7	3·4-8·9	27	8.0	5·3-11·7	20	5·9	3·6-9·1	23	6·8	4·3-10·2	21	6·1	3·8-9·4
	50-64	16	13·8	7·9-22·4	19	16·1	9·7-25·1	19	15·8	9·5-24·7	21	17·3	10·7-26·5	20	16·3	10·0-25·2
	65-74	13	22·5	12·0-38·4	17	28·6	16·6-45·7	16	26.0	14·9-42·2	20	32·1	19·6-49·6	22	35·2	22·1-53·3
	75-84	13	35·9	19·1-61·4	21	57·5	35·6-87·9	12	32·7	16·9-57·1	21	57·1	35·4-87·3	19	51·4	30·9-80·2
	≥85	10	68.0	32·6-125·1	9	60.0	27·4-113·9	6	39·4	14·4-85·7	14	91·3	49·9-153·2	13	83·9	44·7-143·4
Non-vaccine-		50	9.0	6·6-11·8	55	9·7	7·3-12·6	47	8·2	6·0-10·9	70	12·2	9·5-15·4	99	17·1	13·9-20·8

serotype CAP	16-49	12	3·6	1·9-6·3	15	4·5	2·5-7·4	10	3.0	1·4-5·4	13	3·8	2·0-6·5	13	3·8	2·0-6·5
	50-64	9	7·8	3·5-14·7	13	11.0	5·9-18·8	7	5·8	2·3-12·0	21	17·3	10·7-26·5	19	15·5	9·3-24·2
	65-74	12	20·7	10·7-36·2	13	21·8	11·6-37·4	11	17·9	8·9-32·0	12	19·3	10·0-33·7	25	40.0	25·9-59·0
	75-84	4	11.0	3·0-28·3	11	30·1	15·0-53·9	11	30.0	15·0-53·6	16	43·5	24·9-70·7	22	59·5	37·3-90·0
	≥85	13	88·44	47·1-151·2	3	20.0	4·1-58·4	8	52·5	22·7-103·4	8	52·2	22·5-102·8	20	129.0	78·8-199·3

PCV7-serotype CAP: CAP due to serotypes included in PCV7; PCV13non7-serotype CAP: CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13-serotype CAP: CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13; Non-vaccine-serotype CAP: CAP due to a) any non-PCV13- non-PPV23-serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only.. #: per 100,000 population

TABLE 3: Linear trends and variation in CAP due to serotype groups, and non-vaccine serotype CAP

	2013-14	2014-15		2015-16		2016-17		2017-18		Change in IRR per year	95% CI	p value for trend
	IRR	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI			
All CAP	1·0	1·26	1·12-1·41	0·99	0·88-1·12	1·34	1·20-1·50	1·64	1·48-1·83	1·12	1·09-1·14	**<0·001**
Pneumococcal CAP	1·0	1·09	0·89-1·33	0·9	0·73-1·11	1·33	1·10-1·61	1·49	1·23-1·79	1·11	1·06-1·16	**<0·001**
PCV7-serotype CAP	1·0	1·37	0·61-3·09	1·17	0·51-2·71	1·65	0·76-3·60	1·73	0·80-3·75	1·13	0·96-1·34	0·135
PCV13non7-serotype CAP	1·0	0·86	0·60-1·23	0·78	0·54-1·12	1·33	0·97-1·84	1·35	0·98-1·87	1·12	1·04-1·21	**0·003**
PPV23non13-serotype CAP	1·0	1·29	0·94-1·75	1.00	0·72-1·39	1·35	1·0-1·84	1·29	0·95-1·75	1·06	0·99-1·13	0·112
Non-vaccine-serotype CAP	1·0	1·08	0·74-1·58	0·92	0·62-1·37	1·36	0·95-1·95	1·91	1·36-2·68	1·19	1·10-1·28	**<0·001**

Data are presented as incidence rate ratio (IRR) with 95% confidence intervals. PCV7-serotype CAP: CAP due to serotypes included in PCV7; PCV13non7- serotype CAP: CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13 -serotype CAP: CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13; Non-vaccine - serotype CAP: CAP due to a) any non-PCV13-, non-PPV23- serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only.

TABLE 4: Association between clinical risk group and PCV13-serotype disease

	PCV13	Non-PCV13	OR (95% CI)	P value	aOR (95% CI)	P value
16-64 years, no clinical risk factor	72 (22·2)	208 (31·6)	0·62 (0·45-0·84)	**<0·001**	0·59 (0·43-0·81)	**0·001**
16-64 years, ≥1 risk factor	34 (10·4)	99 (15·1)	0·66 (0·44-0·99)	0·049	0·65 (0·43-0·98)	0·04
≥65 years, no clinical risk factor	75 (23·1)	137 (20·8)	1·14 (0·83-1·57)	0·419	1·14 (0·83-1·57)	0·422
≥65 years, ≥1 risk factor	144 (44·3)	214 (32·5)	1·65 (1·26-2·17)	**<0·001**	1·73 (1·31-2·28)	**<0·001**
Pneumococcal clinical risk group*	253 (77·8)	450 (68·4)	1·62 (1·19-2·21)	**0·002**	1·69 (1·24-2·30)	**0·001**
Number of risk factors						
0	147 (45·2)	345 (52·4)	Reference		Reference	
1	114 (35·1)	212 (32·2)	1·26 (0·94-1·70)		1·29 (0·96-1·74)	
2	46 (14·2)	81 (12·3)	1·33 (0·88-2·01)		1·40 (0·93-2·12)	
>3	18 (5·5)	20 (3·0)	2·11 (1·08-4·12)	**0·013#**	2·14 (1·10-4·18)	0·056#

Data are presented as n (%). Adjusted OR are corrected for residential care status. Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

*: age ≥65years or age 16-64years with ≥1 risk factor, #: p value for trend

TABLE 5: Association between clinical risk group and PPV23-serotype disease

	PPV23	Non-PPV23	OR (95% CI)	P value	aOR (95% CI)	P value
16-64 years, no clinical risk factor	223 (30·5)	70 (22·1)	1·54 (1·13-2·10)	**0·006**	1·54 (1·13-2·10)	**0·006**
16-64 years, ≥1 risk factor	79 (10·8)	61 (19·3)	0·51 (0·35-0·73)	**<0·001**	0·51 (0·35-0·73)	**<0·001**
≥65 years, no clinical risk factor	160 (21·9)	70 (22·2)	0·98 (0·72-1·35)	0·916	0·98 (0·72-1·35)	0·706
≥65 years, ≥1 risk factor	270 (36·9)	115 (36·4)	1·02 (0·78-1·34)	0·879	1·02 (0·78-1·34)	0·685
Pneumococcal clinical risk group*	509 (69·5)	246 (77·9)	0·65 (0·48-0·88)	**0·006**	0·65 (0·48-0·88)	**0·006**
Number of risk factors						
0	383 (52·3)	140 (44·3)	Reference		Reference	
1	221 (30·2)	129 (40·8)	0·63 (0·47-0·84)		0·63 (0·47-0·84)	
2	95 (13·0)	41 (13·0)	0·85 (0·56-1·28)		0·85 (0·56-1·28)	
>3	33 (4·5)	6 (1·9)	2·01 (0·82-4·91)	0·617#	2·01 (0·82-4·91)	**0·002#**

Data are presented as n (%). Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

*: age ≥65years or age 16-64years with ≥1 risk factor, #: p value for trend

TABLE 6: Incident rate ratios for pneumococcal pneumonia cohort and IPD cohort between 2013 and 2018.

	2013-14	2014-15	2015-16	2016-17	2017-18	Change in IRR per year (95% CI)	p value for trend
	IRR	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)		
National IPD cohort - serotype 3	1.0	1·42 (1·19-1·70)	1·91 (1·61-2·25)	2·27 (1·93-2·67)	2·87 (2·45-3·36)	1·28 (1·24-1·32)	**<0·001**
CAP cohort - serotype 3	1.0	1·53 (0·93-2·53)	0·94 (0·54-1·64)	2·21 (1·38-3·54)	2·31 (1·45-3·68)	1·23 (1·12-1·36)	**<0·001**
National IPD cohort - PCV7-serotype	1.0	1·12 (0·86-1·48)	1·09 (0·82-1·43)	1·26 (0·96-1·64)	1·35 (1·04-1·75)	1·07 (1·01-1·14)	**0·015**
CAP cohort - PCV7-serotype	1.0	1·37 (0·61-3·09)	1·17 (0·51-2·71)	1·65 (0·76-3·60)	1·73 (0·80-3·75)	1·13 (0·96-1·34)	0·135
National IPD cohort - PCV13non7-serotype	1.0	1·20 (1·08-1·33)	1·16 (1·04-1·29)	1·29 (1·17-1·43)	1·48 (1·34-1·64)	1·09 (1·07-1·11)	**<0·001**
CAP cohort - PCV13non7-serotype	1.0	0·86 (0·60-1·23)	0·78 (0·54-1·12)	1·35 (0·98-1·86)	1·35 (0·98-1·87)	1·12 (1·04-1·21)	**0·003**
National IPD cohort - PPV23non13-serotype	1.0	1·43 (1·34-1·53)	1·80 (1·69-1·91)	1·83 (1·72-1·95)	1·88 (1·77-2·00)	1·15 (1·13-1·16)	**<0·001**
CAP cohort - PPV23non13-serotype	1.0	1·29 (0·94-1·75)	1·00 (0·72-1·39)	1·35 (1·00-1·84)	1·29 (0·95-1·75)	1·06 (0·99-1·13)	0·112
National IPD cohort - Non-vaccine-serotype	1.0	1·12 (1·01-1·22)	1·05 (0·96-1·16)	1·16 (1·06-1·27)	1·32 (1·20-1·44)	1·06 (1·04-1·08)	**<0·001**
CAP cohort - Non-vaccine serotype	1.0	1·04 (0·65-1·65)	0·84 (0·51-1·36)	1·17 (0·74-1·82)	2·06 (1·38-3·08)	1·21 (1·10-1·33)	**<0·001**

Data are presented as incidence rate ratio (IRR) with 95% confidence intervals. IPD: invasive pneumococcal disease; CAP: Community-acquired pneumonia; PCV7-serotype: pneumococcal disease due to serotypes included in PCV7; PCV13non7- serotype: pneumococcal disease due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13 - serotype: pneumococcal disease due to serotypes included in PPV23, excluding serotypes also included in PCV13;

CAP cohort: Non-vaccine-serotype: pneumococcal disease due to a) any non-PCV13-, non-PPV23- serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only ‘

National IPD cohort: Non-vaccine-serotype: pneumococcal disease due to any non-PCV13-, non-PPV23-serotype case