Pneumococcal pneumonia trends in adults hospitalised with community-acquired pneumonia over 10 years (2013-2023), and the role of serotype 3

Louise Lansbury[1,2], Tricia M McKeever[1,2], Hannah Lawrence[1,2], Harry Pick[1,3], Vadsala Baskaran[1,2], Rochelle C Edwards-Pritchard[1,2], Laura Matthews[2], Helen Bailey[2], Deborah Ashton[2], Lesley Bendall[2], Chamira Rodrigo[3], Priya Daniel[4], David Litt[5,6], Seyi Eletu[5], Hanshi Parmar[5], Carmen L. Sheppard[5], Shamez Ladhani[6], Caroline Trotter[7], Wei Shen Lim[2,3]

[1]Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK

[2]National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, UK

[3]Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

[4]Respiratory Medicine, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

[5]Respiratory and Vaccine Preventable Bacteria Reference Unit, UK Health Security Agency, Colindale, UK

[6]Immunisation and Vaccine Preventable Diseases, UK Health Security Agency, Colindale, UK

[7]Disease Dynamics Unit, Department of Veterinary Medicine, University of Cambridge, Cambridge, UK

Corresponding author:

Dr Louise Lansbury

School of Medicine

University of Nottingham

Room B104, Clinical Sciences Building

City Hospital Campus

Nottingham, NG5 1PB

UK

+44 (0) 115 8231251

Louise.Lansbury@nottingham.ac.uk

ABSTRACT

Background With higher valency pneumococcal vaccines on the horizon and new adult immunisation strategies under discussion, we aimed to evaluate the contribution of individual pneumococcal serotypes to the burden of pneumococcal community-acquire pneumonia (CAP). Over ten years, trends in pneumococcal pneumonia epidemiology in adults hospitalised with community-acquired pneumonia (CAP) were assessed. The risks factors and severity associated with serotype 3 was examined.

Methods We conducted a prospective cohort study of adults hospitalised with CAP between September 2013-May 2023. Pneumococcal serotypes were identified using a serotype-specific 24-valent urinary-antigen assay. Trends in the proportion of CAP due to pneumococcus and causative serotypes were compared pre and post pandemic. Risk factors and severity of serotype 3 pneumonia were compared to other serotypes using logistic regression.

Results Of 5186 patients with CAP, 2193 (42.2%) had pneumococcal pneumonia. The proportion of CAP due to pneumococcus increased across all ages between 2013-2023 (36.4% to 66.9%, p<0.001). The proportion due to serotype 3 increased significantly from 13.4% (2013) to 48.8% (2023). Serotype 3 pneumonia in adults was associated with older age (p-value<0.001), male sex (adjusted odds ratio (aOR) 2.22, 95% CI 1.64-3.01) and chronic renal disease (aOR 1.81, 95% CI 1.09-3.02). Serotype

3 pneumonia was not observed to be associated with severity, critical-care requirement, mortality or readmission.

Interpretation Serotype 3 is the predominant serotype in adult pneumococcal CAP and has been increasing despite a mature infant pneumococcal immunization programme, consistent with a lack of herd protection for this serotype.

KEY MESSAGES

What is already known on this topic

Following the introduction of pneumococcal conjugate vaccines (PCV) to the infant immunisation programme in 2006, vaccine-serotype invasive pneumococcal disease (IPD) declined across all ages due to direct and indirect protection but more recently the incidence of IPD in children due to serotype 3 has been increasing. It has been reported that compared to other serotypes, serotype 3 may be linked to increased mortality in the elderly, and to respiratory failure and septic shock.

What this study adds

Over a ten-year period, including years before, during and after the COVID-19 pandemic, the proportion of adult CAP due to pneumococcus increased, driven predominantly by serotype 3. This is consistent with a lack of adequate herd protection against adult serotype 3 disease from the infant pneumococcal vaccination programme.

- Serotype 3 pneumococcal CAP was associated with increased age, male sex and chronic renal disease, but not with increased severity or poorer outcomes compared to other serotypes.

How this study might affect research, practice or policy

- A 21-valent PCV is imminent and other higher-valency PCVs are currently under development. The results from this study add to the evidence on changing pneumococcal epidemiology and will contribute to vaccine policy-making decisions, including indirect versus direct adult immunisation strategies and cost-effectiveness analyses .

INTRODUCTION

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide,[1] with *Streptococcus pneumoniae* being the most commonly implicated bacterial pathogen.[2,3]

Pneumococcal vaccines targeting the polysaccharide capsule have made pneumococcal disease at least partially vaccine-preventable, depending upon which pneumococcal serotypes are included in the different vaccines, and how effective they are against specific serotypes. In the United Kingdom, a seven-valent pneumococcal conjugate vaccine (PCV7) was introduced to the childhood immunisation schedule in 2006 and replaced in 2010 by 13-valent vaccine (PCV13). For adults aged ≥65 years and those aged ≥2 years in a clinical risk group for pneumococcal disease, a single dose of pneumococcal polysaccharide vaccine (PPV23) has been recommended since 2003,[4]although its effectiveness in preventing non-invasive pneumonia is likely to be modest.[5]

PCV implementation has been associated with large declines in vaccine-serotype IPD across all age groups due to direct and indirect protection, but with an increase in disease caused by non-PCV serotypes (serotype replacement).[6,7]However, several studies from different countries have indicated that direct and indirect protection against serotype 3 is lower than for other serotypes,[8-10] and the incidence of serotype 3 IPD in children has been increasing despite the use of PCV13 in the infant

immunisation programme.[11] Moreover, there have been reports that compared to other serotypes, serotype 3 may be linked to higher mortality in the elderly,[12]septic shock,[13]and respiratory failure.[14]

With more than 100 pneumococcal serotypes, new pneumococcal vaccines targeting an increasing number of serotypes are on the horizon, including PCV21,[15]PCV24 and PCV30+.[16] PCV immunisation is currently only available for children and the initial herd protection effects on adult CAP are now more limited due to changes to the prevailing serotypes. New adult immunization strategies have been suggested as a means to overcome current limitations in the control of adult pneumococcal disease. An understanding of the contribution of individual pneumococcal serotypes to the burden of pneumococcal CAP is therefore important for the development of updated pneumococcal vaccination policy.

In this study, we employed a 24-valent serotype-specific urinary antigen detection (ssUAD) assay to a) determine trends in hospitalised pneumococcal pneumonia and the epidemiology of pneumococcal serotypes over a ten-year period, which included the pre- and post COVID-19 pandemic period, and b) examine the role of serotype 3 over this period, including risk factors and severity of serotype 3 CAP compared to other serotypes in a cohort of adults with predominantly non-invasive pneumonia. By including data from 2020 until the end of this long-running cohort study we build upon our previously published

findings,[17,18] and aim to summarise the changing epidemiology of pneumococcal CAP that has occurred during the last ten years, including data from the COVID-19 pandemic period which we have not previously reported.

METHODS

Study design

The methods for this prospective cohort study have been previously described[18](See supplement.) For this analysis, data were collected for adults ≥16 years old hospitalised with CAP in two teaching hospitals in Nottingham between September 2013 and May 2023. Recruitment was paused for a period during the pandemic (13 March 2020-2 August 2020). From August 2020 onwards, patients testing positive for SARS-CoV2 were included if they had radiographic evidence of pneumonia.

Microbiology

Urine samples were obtained within 48 hours of admission for pneumococcal-specific urinary antigen detection (UAD) using the Binax-NOW® (Alere, Stockport, UK) assay for pneumococcal C-polysaccharide urinary antigen, and for pneumococcal serotype-specific urinary antigen testing using a validated multiplex immunoassay (Bioplex-24)[19] (detailed in supplement). 'Non-ssUAD' pneumococci were defined as those for which cell-wall polysaccharide was detected but the Bioplex-24 assay was not able to generate a serotype-specific result. Vaccine types were classified according to the serotypes included in their formulation

(supplement). Blood cultures were taken at the discretion of the treating clinician.

Patients were considered to have pneumococcal CAP if they met ≥1criteria: a) positive pneumococcal UAD or b) blood culture positive for *S. pneumoniae* or c) detection of a pneumococcal serotype or cell wall polysaccharide by the Bioplex24 assay.

Statistical Analysis

Categorical variables for baseline demographics, disease severity and clinical outcomes (critical care admission, 30-day mortality and readmission within 30 days) were expressed as frequencies and as percentages and compared using Pearson's $\chi 2$ or Fisher's exact tests. Continuous variables were summarised as medians with interquartile range and compared using the Mann-Whitney U-test. To account for inter-year variability, a restricted cubic spline model with five knots based on Harrell's recommended percentiles[20] was used to describe trends in patient characteristics, risk factors and outcomes over time. We defined 'pre-pandemic' as September 2013-12th March 2020, the 'pandemic period' as 13th March 2020-31st August 2021, and 'post-restriction period' as 1st September 2021-31st May 2022. Patients admitted during the 'pandemic period' were excluded from the tests for trend of patient characteristics and severity as patients admitted at the height of the pandemic may have been sicker and therefore selectively tested and included.

We used univariable and multivariable logistic regression models to compare associations between pneumonia and the characteristics and outcomes of i) patients with pneumococcal pneumonia versus non-pneumococcal pneumococcal pneumonia and ii) patients with single-serotype 3 disease versus patients with a different single serotype identified. We presented the results as odds ratios (ORs) with 95% confidence intervals (CIs) and the corresponding p-value. As there were no *a priori* restrictions on participants being enrolled more than once over the course of the study and it was not possible to link individuals to their separate admissions, the unit of analysis was each admission rather than individual participant. Variables for inclusion in the multivariable analysis were purposefully selected based on clinical risk factors outlined in the UK Health Security Agency's "Immunisation against Infectious Disease" (The Green Book)[4] and previous studies,[21] and were included in the final model if the p-value was <0.2 on univariate analysis of demographic characteristics. Outcome analyses were adjusted for variables which altered the crude odds ratio by >10%. To minimise bias in those who were excluded from whole case analysis due to incomplete records, we used multiple imputation with five imputations including all analysis variables under the assumption that data are missing at random (see supplement for details of missing observations and the multiple imputation model).

Statistical analyses were conducted using Stata/SE V.18.0 (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

RESULTS

Baseline Characteristics

7078 patients with radiographically-confirmed all-cause pneumonia were admitted between September 2013 and May 2023, with 5186 (73.3%) giving their consent to take part in the study. Urine for pneumococcal testing was available for 5020 (96.8%) consented patients, of which 4933 (98.3%) were tested using Bioplex-24, and 87 (1.7%) were tested only using BinaxNOW.

Based on blood culture, and Bioplex-24/BinaxNOW UAD results pneumococcal pneumonia was diagnosed in 2193 included patients (42.3%).Diagnosis was based solely on the detection of a serotype in urine by Bioplex-24 in 1191 patients (54.3%), and by BinaxNow only in 139 (6.3%). Both Bioplex-24 and BinaxNOW were positive in 794 patients (36.2%). A serotype was detected in blood but not by Bioplex-24 in 24 patients (22 Bioplex not performed, 2 Bioplex negative)(Supplementary figure 1). Serotype 8 accounted for 36.8% of blood culture serotypes, followed by serotypes 3 (9.6%), 19A (8.1%) and 12F (6.7%)(Supplementary figure 2).

The median age of the study cohort was 71.1 years (IQR 56.5–80.9), 2762 (53.4%) were male, and pneumonia severity was low, moderate

and high in 2531 (49.0%), 1522 (29.5%), and 1107 (21.4%) respectively based on the CURB-65 score. Critical care admission was required in 410 (7.9%) patients, and 433 (8.3%) patients died within 30 days of admission. (Table 1)

On multivariable analysis, current smoking, COPD and immunocompromise were independently associated with the risk of pneumococcal pneumonia (aOR 1.36, 95% CI 1.16-1.60; aOR 1.18, 95% CI 1.02-1.36; and aOR 1.32, 95% CI 1.01-1.72 respectively)(Supplementary table 1). Compared to non-pneumococcal CAP, patients with pneumococcal CAP were more likely to be admitted to critical care (aOR 1.36, 95% CI 1.10-1.66), and have higher CURB-65 scores (aOR 1.16, 95% CI 1.08-1.26), although the odds of death within 30-days were lower (aOR 0.64, 95% CI 0.52-0.79).(Table 1 and Supplementary table 2)

Table 1 Baseline characteristics, disease severity and outcomes in community-acquired pneumonia (CAP) and pneumococcal pneumonia

Patient characteristics	**Whole cohort (n=5186)**	**Pneumococcal cohort (n=2193)**	**Non-pneumococcal CAP (n=2993)**	**p-value**
DEMOGRAPHICS				
Age, median; years (IQR)	71.1 (56.5 – 80.9)	70.4 (56.9 – 80.4)	71.6 (56.2 – 81.3)	0.26
Male (%)	2762 (53.4)	1190/2188 (54.4)	1572/2980 (52.8)	0.24
COMORBID DISEASE				
Smoking status*				
Never smoked	1557 (30.9)	623 (29.0)	934 (32.3)	**<0.001**
Ex-smoker	2353 (46.8)	977 (45.5)	1376 (47.6)	
Current smoker	1124 (22.4)	545 (25.4)	579 (20.0)	
COPD	1264 (24.4)	579 (26.4)	685 (22.9)	**0.004**
Diabetes mellitus	870 (16.8)	361 (16.5)	509 (17.0)	0.60
Cerebrovascular disease	408 (7.9)	173 (7.9)	235 (7.9)	0.96
Congestive cardiac failure	351 (6.8)	144 (6.6)	207 (6.9)	0.62
Ischaemic heart disease	632 (12.2)	249 (11.4)	383 (12.8)	0.12
Asthma	601 (11.6)	260 (11.8)	341 (11.4)	0.61
Cognitive impairment	177 (3.4)	65 (3.0)	112 (3.7)	0.13
Liver disease	92 (1.8)	38 (1.7)	54 (1.8)	0.85
Kidney disease	533 (10.3)	234 (10.7)	299 (10.0)	0.43
Immunocompromised	231 (4.4)	223 (5.1)	119 (4.0)	0.05
PPV23 receipt*	1853 (37.3)	812 (38.4)	1041 (36.5)	0.19

SEVERITY				
CURB65 0-1 (low) CURB65 2 (moderate) CURB65 3-5 (high)	2531/5160 (49.0) 1522 (29.5) 1107 (21.4)	1026/2183 (47.0) 642 (29.4) 515 (23.6)	1505/2977 (50.6) 880 (29.6) 592 (19.9)	**0.003**
OUTCOME				
30-day mortality	433 (8.3)	147 (6.7)	286 (9.6)	**<0.001**
30-day re-admission	592/4753 (12.4)	235/2046 (11.5	357/2707 (13.2)	0.08
ICU/HDU admission	410 (7.9)	205 (9.3)	205 (6.8)	**0.001**

Data are presented as n(%) or median (IQR).

CURB-65: confusion, urea >7mmol/L, respiratory rate >30/min, blood pressure <90 mmHg systolic), <60mm Hg (diastolic), age ≥65 years.

*Data regarding smoking status available for 2145 and 2889 patients, and for PPV23 receipt in 2117 and 2849 patients in the pneumococcal and non-pneumococcal cohort respectively.

Trends between 2013 and 2023: pre vs post pandemic

Proportion of CAP due to *S. pneumoniae*

The proportion of CAP attributable to pneumococcus increased significantly over the ten years for all ages, from 36.4% in 2013-14 to 66.9% in 2022-23 (p<0.001). This upward trend was observed pre-pandemic (p-value for trend <0.001)(Table 2) but was particularly marked in all age groups from 2020 when COVID-19 pandemic restrictions were introduced in the UK (Figure 1). In the final winter season (2022-23), the proportion of CAP attributed to pneumococcus remained higher than pre-pandemic, particularly in patients ≥75 years

although the upward trend was less marked or reversing in younger age groups (Figure 1). The proportion of patients with pneumococcal pneumonia who were bacteraemic fell after the onset of the pandemic and was lowest during 2021-22 (4.6%), but had increased to 11.3% in 2022-23 and was similar to pre-pandemic proportions (Figure 2).

Table 2 Trend in proportion of all-cause CAP attributable to pneumococcus between 2013 and 2023

Study year	**Pneumococcal CAP (N)**	**All-Cause CAP (N)**	**% CAP due to pneumococcus**
1/9/2013 – 31/8/2014	180	495	36.4
1/9/2014 – 31/8/2015	202	583	34.7
1/9/2015 – 31/8/2016	165	516	32.0
1/9/2016 – 31/8/2017	248	644	38.5
1/9/2017 – 31/8/2018	283	697	40.6
1/9/2018 – 31/8/2019	321	734	43.7
1/9/2019 – 31/8/2020*†	238	570	41.8
1/9/2020 – 31/8/2021*	125	285	43.8
1/9/2021 – 31/8/2022	219	345	63.5
1/9/2022 – 31/5/2023	212	317	66.9
Total	**2193**	**5186**	**42.3**

P-value for trend for entire study period, **excluding** patients admitted between 13 March 2020 and 31 August 2021 <0.001

P-value for trend from 2013 to 13 March 2020 only =<0.001

*Lockdown measures for SARS-CoV2 pandemic in force

†The study was paused to recruitment between 13 March 2020 and 2 August 2020 due to the COVID-19 pandemic

Trends in demographics and severity

Patient characteristics for the pre-pandemic period and over the entire study period are described in table 3 and supplementary table 3. The proportion of patients who had ever received PPV23 vaccine increased

from 36.2% in 2013 to 50.5% in 2023, but after adjusting for age, sex and COPD and excluding patients admitted between March 2020-August 2021, there was an overall decreased trend in the proportion of patients of vaccinated over the study period (p-value for trend=0.02).

The proportion of patients with pneumococcal CAP dying within 30 days varied from year to year, although the overall trend was towards increasing mortality (p-value=0.02). Mortality was highest between September 2020-August 2021 (Table 3). From the start of the pandemic until the end of the study, 90/923 (9.8%) of patients with all-cause CAP tested positive for SARS-CoV2 on admission. Mortality was significantly higher in those who were SARS-CoV2 positive (15/90, 16.7%) compared to those who were negative (69/833, 7.2%)(p-value=0.009), but did not differ significantly between SARS-CoV2 positive pneumococcal CAP (7/50, 14.0%) and SARS-CoV2 positive non-pneumococcal CAP (8/40, 20.0%)(p-value=0.45).

Readmission rates and critical care admissions did not change significantly over the study period.

Table 3 Trends in characteristics of pneumococcal CAP patients between 2013 and 2023 by study year

	Study year (number of patients)										
	2013-14 (n=180)	**2014-2015 (n=202)**	**2015-2016 (n=165)**	**2016-2017 (n=248)**	**2017-2018 (n=283)**	**2018-2019 (n=321)**	**2019-2020 (n=238)**	**2020-2021 (n=125)**	**2021-2022 (n=219)**	**2022-23 (n=212)**	p-value for trend
Median Age (IQR)	67.4 (49.9-80.1)	68.0 (51.5-77.4)	66.9 (50.9-78.7)	70.1 (53.9-81.1)	71.8 (59.2-81.7)	71.9 (58.4-81.5)	72.8 (60.2-81.3)	71.6 (58.5-80.3)	69.5 (60.0-78.6)	70.8 (60.1-80.0)	0.14†[a] 0.10‡[a]
Sex, male (%)	91 (50.6)	96 (47.5)	86 (52.1)	110 (44.4)	132 (46.6)	169 (52.2)	136 (56.7)	99 (79.2)	136 (62.1)	135 (63.7)	0.22†[a] 0.06‡[a]
PPV23 receipt (%)	59/163 (36.2)	80/189 (52.3)	46/153 (29.9)	79/234 (33.8)	96/262 (36.6)	100/321 (31.2)	81/238 (34.0)	55/125 (44.0)	109/219 (49.8)	107/212 (50.5)	**0.02†**[a] **0.03‡**[a]
SEVERITY											
30-day mortality (%)	8 (4.4)	11 (5.4)	4 (2.4)	19 (7.7)	12 (4.2)	30 (9.3)	20 (8.4)	14 (11.2)	20 (9.1)	9 (9.1)	**0.02†**[b] **0.01‡**[b]
Readmitted (%)	20/172 (11.6)	19/191 (9.9)	12/161 (7.4)	20/223 (9.0)	25/271 (9.2)	46/291 (15.8)	34/218 (15.6)	12/111 (10.8)	30/199 (19.6)	20/203 (9.8)	0.63†[c] 0.20‡[c]
Critical care admission (%)	18 (10.0)	22 (10.9)	19 (11.5)	28 (11.3)	22 (7.8)	29 (9.0)	27 (11.3)	12 (9.6)	15 (6.8)	13 (6.1)	0.52†[d] 0.50‡[d]

Trends in characteristics and outcomes in patients hospitalised with pneumococcal CAP between 2013 and 2023 by study year. Absolute numbers and the corresponding percentages are presented for each variable for each year. Estimated p-values for trends were obtained by restricted cubic spline regression with five knots at admission dates of 6 April 2014, 24 June 2016, 5 February 2018, 2 September 2019 and 25 December 2022 for the entire

study period, and at 12 March 2014, 5 January 2016, 9 August 2017, 12 November 2018 and 29 December 2019 for the pre-pandemic period only, based on Harrell's recommended percentiles.

†p-value for trend across the ten-year study period excludes patients admitted between 13 March 2020 and 31 August 2021

‡p-value for pre-pandemic trend between 2013-14 and 2019-2020 only

[a]Adjusted for sex, PPV23 receipt and COPD

[b]Adjusted for age, smoking status and CURB65

[c]Adjusted for age, PPV23 receipt and COPD

[d]Adjusted for age, PPV23 receipt and CURB65

Serotype distribution

The most prevalent serotypes over the study period were serotypes 3 (29.3%), 8 (21.4%), non-ssUAD (7.8%), 15A (4.9%) and 9N (4.1%). Trends in the distribution of individual serotypes over the study period are shown in Figure 3 and supplementary table 4. Over the ten years there was a marked steady increase in serotype 3, accounting for 13.4% of pneumococcal CAP in 2013 to 48.8% in 2023. Serotype 8, the second most prevalent serotype, accounted for between 17.0% to 19.7% of pneumococcal CAP pre-pandemic, but peaked at 37.4% between September 2020 and August 2021. By mid-2023 the proportion of CAP in which serotype 8 was implicated had decreased back to 19.9%, similar to that seen pre-pandemic. Over the study, there was a decrease in proportion of CAP caused by non-ssUAD pneumococci from 12.4% in 2013-2014 to 2.6% in 2022-23. Other serotypes in which there was a decline in proportions were serotypes 7F (PCV13), 12F (PCV20), 15A and16F (PCV21). (Supplementary table 4)

Between 2013 and 2023, there was an increase in the proportion of multiple serotypes detected in the Bioplex-24 assay, from 9.1% to 36.6% (p-value for trend <0.001). In 2021-2022, 52.4% of detections were multiple serotypes. Serotype 3 was the most prevalent serotype detected with one or more other serotype in 313 of 466 (67.2%) patients with multiple serotype detections. The combination of serotypes 3 plus 8 accounted for 183 (39.3%) of multiple detections followed by serotype 5 plus serogroup 15 (5.4%)(Supplementary Figure 3).

Figure 4 shows the trend by pneumococcal vaccine type over the study period. The proportion of pneumococcal CAP caused by PCV13 serotypes increased significantly between 2013 and 2023 (p-value for trend =0.0005), ranging from 22.6% in 2014-2015 to 64.4% in 2022-23. The increasing trend was occurring pre-pandemic (p-value for trend=0.01). When serotype 3 was excluded, the trend for the remaining PCV13 serotypes was statistically non-significant (p-value =0.29).The proportion of PCV20-nonPCV13 serotypes peaked at 37.9% in 2020-2021 but decreased in 2021-2022 (13.0%) and again in 2022-23 (11.4%), corresponding to the pattern observed with serotype 8. Non-vaccine serotypes decreased over the study (p-value =0.006) from a peak of 28.7% in 2014-15 to 6.9% in 2020-21. Over the study period, 44.2% of serotypes were covered by PCV13, 49.6% by PCV15 and 78.3% by PCV20. The PCV21 would have covered 80.8% of all serotypes.(Supplementary Table 5)

Serotype 3 pneumonia

Older patients were more likely to have CAP due to serotype 3 compared to people aged 16-49 years (p-value for trend by increasing age category <0.001, aOR for 75-84 years 2.25, 95% CI 1.50-3.41, and ≥85 years aOR 2.52, 95% CI 1.40-4.52). Male sex, chronic renal disease and asthma were also associated with the risk of serotype 3 CAP compared to

other serotypes (aOR 2.22, 95% CI 1.64-3.01; aOR 1.81, 95% CI 1.09-3.02; and aOR 1.60, 95% CI 1.08-2.38 respectively)(Table 4).

Patients with serotype 3 CAP were less likely to have bacteraemia compared to patients with other serotypes (aOR 0.43, 95% CI 0.27-0.68). After adjusting for age we did not observe any significant differences in severity (as measured by CURB-65), critical care admission, 30-day mortality, or 30-day readmission (Table 5).

Table 4 Risk factors for serotype 3 CAP compared to other pneumococcal serotypes

	Serotype 3 CAP N=441 (%)	**Non-ST3 CAP N=1133 (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Baseline characteristics						
Median age (IQR)	73.3 (62.7-82.1)	67.5 (53.0-78.5)		**<0.001**		
Age category						
16-49 years	41 (9.3)	247 (21.8)	Ref	**<0.001‡**	Ref [a]	**0.006‡**
50-64 years	95 (21.5)	255 (22.5)	1.71 91.19-2.470		1.63 (1.12-2.37)	
65-74 years	105 (23.8)	270 (23.8)	2.09 (1.33-3.27)		1.78 (1.11-2.87)	
75-84 years	122 (27.6)	229 (20.2)	2.69 (1.86-3.89)		2.25 (1.50-3.41)	
≥85 years	78 (17.7)	132 (11.6)	3.06 (1.86-5.04)		2.52 (1.40-4.52)	
Sex, male	297 (67.3)	549 (48.4)	2.17 (1.57-3.00)	**0.001**	2.22 (1.64-3.01)[a]	**<0.001**
PPV23 vaccine receipt	182/434 (41.9)	357/1081 (33.0)	1.49 (1.21-1.84)	**0.001**	1.22 (1.01-1.48)[a]	**0.04**
Smoking						
Never	131/436 (30.0)	310/1103 (28.1)	Ref	0.42‡	Ref[a]	0.70‡
Ex	209 (47.9)	480 (43.5)	1.10 (0.75-1.61)		0.92 (0.60-1.40)	
Current	96 (22.0)	313 (28.4)	0.79 (0.47-1.33)		0.94 (0.61-1.46)	
Liver disease	6 (1.4)	23 (2.0)	0.57 (0.26-1.22)	0.14	0.54 (0.25-1.17)[a]	0.11

Chronic kidney disease	71 (16.1)	84 (7.4)	2.20 (1.38-3.51)	**0.005**	1.81 (1.09-3.02)[a]	**0.03**
Chronic cardiac failure	37 (8.4)	65 (5.7)	1.39 (0.66-2.92)	0.32	0.90 (0.36-2.21)[a]	0.77
Ischaemic heart disease	61 (13.8)	109 (9.6)	1.50 (0.97-2.32)	0.06	1.07 (0.64-1.81)[a]	0.75
Chronic lung disease	41 (9.3)	72 (6.3)	1.25 (0.90-1.73)	0.17	1.15 (0.81-1.64)[a]	0.41
COPD	114 (25.8)	297 (26.2)	1.05 (0.50-1.38)	0.68	0.91 (0.68-1.23)[a]	0.51
Asthma	57 (12.9)	129 (11.4)	1.20 (0.85-1.70)	0.26	1.60 (1.08-2.38)[a]	**0.02**
Diabetes	78 (17.7)	171 (15.1)	1.19 (0.72-1.97)	0.43	1.00 (0.59-1.69)[a]	0.99
Cerebrovascular disease	41 (9.3)	75 (6.6.)	1.37 (0.73-2.60)	0.27	1.00 (0.52-1.95)[a]	0.97
Cognitive impairment	13 (2.9)	30 (2.6)	0.81 (0.40-1.64)	0.52	0.60 (0.27-1.30)[a]	0.17
Immunosuppression	28 (6.3)	48 (4.2)	1.33 (0.88-2.01)	0.17	1.26 (0.81-1.96)[a]	0.28

Number of clinical risk factors			Ref	**0.04‡**	Ref [b]	0.22‡
0	148 (33.6)	440 (38.8)	1.28 (0.99-1.65)		1.10 (0.86-1.40)	
1	160 (36.3)	442 (39.0)	1.50 (1.01-2.22)		1.16 (0.78-1.74)	
2	77 (17.5)	179 (15.8)	2.08 (1.106-3.94)		1.53 (0.80-2.94)	
≥3	56 (12.7)	72 (6.4)				

‡ P-value for trend

[a] Adjusted for age, sex, PPV23 receipt, chronic lung disease, ischaemic heart disease, chronic renal disease, liver disease and immunocompromise

[b] Adjusted for age

Table 5 Association between severity of disease in single serotype 3 CAP patients compared to other single serotypes pneumococcal CAP

	Serotype 3 CAP N=441 (%)	**Non-ST3 CAP N=1133 (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
CURB-65 score						
0–1 (low)	177/439 (40.3)	569/1127 (50.5)	Ref	**0.02‡**	Ref [a]	0.75‡
2 (moderate)	140 (31.9)	321 (28.5)	1.47(1.02-2.10)		1.02 (0.70-1.45)	
≥3 (high)	122 (27.8)	237 (21.0)	1.65 (1.15-2.38)		1.05 (0.76-1.44)	
Critical care admission	39 (8.8)	113 (10.0)	0.83 (0.52-1.33)	0.40	0.90 (0.52-1.57) [b]	0.67
30–day mortality	37 (8.4)	65 (5.7)	1.72 (1.20-2.47)	**0.01**	1.32 (0.93-1.89) [c]	0.11
30-day readmission	43/404 (10.6)	110/1066(10.3)	1.07 (1.20-2.47)	0.78	0.92 (0.53-1.58) [d]	0.72
Bacteraemic disease	12 (2.7)	149 (13.2)	0.39 (0.25-0.63)	**<0.001**	0.43 (0.27-0.68)[e]	**0.001**

‡p-value for trend

[a] Adjusted for age and chronic renal disease
[b] Adjusted for age and sex
[c] Adjusted for age and CURB65
[d] Adjusted for age, sex and chronic renal disease
[e] Adjusted for age and PPV23 receipt

DISCUSSION

Over the course of ten years up to mid-2023 the proportion of hospitalised all-cause pneumonia caused by *S. pneumoniae* has been increasing. Although the absolute number of all-cause pneumonia cases declined during 2020-21, coinciding with the COVID-19 pandemic, the upward trend in the proportion due to pneumococcus continued to increase, and rose markedly in all age groups in 2021-22. In the UK, COVID-19 restrictions were lifted in July 2021. The societal and behavioural changes during the pandemic resulted in less exposure to pathogens spread by the respiratory route and led to observed alterations to patterns of community-circulation of respiratory viral pathogens in many countries.[22] This likely affected the contribution to all-cause pneumonia from other respiratory pathogens and may explain the higher relative contribution from pneumococcus during this period. Thresholds for hospital admission changed during this period and patients with milder illness due to non-pneumococcal pneumonia may have been less likely to be hospitalized, so to a certain extent the marked increase in proportion of CAP due to pneumococcus observed after 2020 may reflect a change in the hospitalised population. In the final year the proportion of CAP attributable to pneumococcus was declining, or at least stabilising in younger age groups, but remained very high in people aged 75 years and above. Ongoing observation is required to assess whether the proportion of pneumococcal pneumonia in older people will return to pre-pandemic

levels; potentially influenced by SARS-CoV2 as an endemic pathogen, changes in pneumococcal vaccine coverage and new or altered immunization programmes against respiratory pathogens.

Most cases of pneumococcal pneumonia are not invasive and prior to the pandemic between 10% and 15% of our patients had pneumococcal bacteraemia. This declined sharply when COVID-19 restrictions were in place and remained low in 2021-2022 after restrictions had been eased. This observation is in accordance with a national surveillance study of invasive pneumococcal disease (IPD) in England,[23] although we noted that in 2022-23 the proportions of invasive disease had returned to >10%, similar to proportions expected before the pandemic. Co-colonisation with other respiratory pathogens has been linked to high pneumococcal nasopharyngeal carriage density,[24]which in turn has been identified as a risk factor for invasive pneumococcal disease.[25] The decreased circulation of other respiratory pathogens between 2020 and 2022 may therefore help to explain our observation. Despite the observation that the pandemic was associated with reductions in IPD, we observed an increase proportionately in pneumococcal pneumonia. Post-2020, remote primary-care consultations increased and this has been associated with a 23% increase in antibiotic prescribing in adults with acute respiratory infections.[26,27] Pre-admission antibiotics would have a much greater influence on blood culture positivity than on Bioplex positivity, and this may partly explain the difference in IPD and non-culture based detection of pneumococcal infection.

The upward trend in pneumococcal pneumonia appears to have been driven largely by serotype 3, which at the end of our study accounted for almost half of pneumococcal cases. The predominance of serotype 3 has also been seen in patients with IPD in England[23] and in non-invasive pneumococcal CAP elsewhere in Europe.[28-30] In comparison to our findings a recent study in Bristol 2021-2022 found a lower overall proportion of pneumococcal pneumonia in patients with CAP, with serotype 8 most prevalent.[31] A different serotype-specific UAD assay was used in the Bristol study which may have different test characteristics for serotype 3 resulting in the discrepancies in findings; for instance differences in the ability to detect pneumococcal colonisation. Whole genome sequencing has identified that between 2017-18 and 2022-23 most IPD cases of serotype 3 belonged to very similar circulating strains, with most belonging to Global Pneumococcal Sequencing Cluster 12.[23] Although we do not have genomic data to confirm this for our pneumonia cases, it is feasible that we are also observing expansion of a previously circulating strain of serotype 3.

In patients with confirmed IPD, serotype 3 has been associated with a higher incidence of septic shock,[13]empyema and complicated pneumonia,[32] and major adverse cardiac events.[33] However we found no evidence that serotype 3 caused more severe disease, increased mortality, or the requirement for critical care compared to other serotypes. A comparable study in patients with CAP in Germany (CAPNETZ) reported that patients with serotype 3 CAP required oxygen

administration more frequently than patients with CAP due to other serotypes, but similar to our findings, they did not find evidence that serotype 3 was associated with higher ICU admission rates, clinical cure and/or 28-day mortality compared to other serotypes.[28]

The burden of serotype 3 disease in older adults remains substantial despite the introduction of PCV13 immunisation in children in the UK in 2010. We found that age and male sex are independent predictors of serotype 3 CAP, consistent with previously reported associations.[34,35]. With the proportion of the UK population aged ≥65 years rising from 16.4% in 2011 to 18.6% in 2021,[36] an increasingly older population may account for some of the increased burden of serotype 3 observed. Furthermore, despite an overall decline in childhood carriage of PCV13 serotypes since the introduction of childhood immunisation, carriage of serotype 3 has persisted in the UK. The indirect protective effects of childhood PCV13 immunisation against IPD in adults has been observed to be lower for serotype 3;[8,11,37] consistent with the observations with respect to serotype 3 pneumonia in adults. These factors taken together likely explain the on-going relative increase in adult serotype 3 pneumonia despite the current infant PCV13 immunisation programme.[38] In 2020 the UK moved from a 2+1 childhood immunisation schedule to 1+1.[39] A recent surveillance study of IPD three years after the introduction of the revised schedule did not observe significantly different breakthrough and vaccine failures in children who received the reduced schedule compared to those who received the 2+1

PCV13 schedule.[23] Taking into consideration the relatively recent schedule implementation, and the likely disruptive effects of the pandemic on the epidemiology of pneumococcal disease, the impact of the 1+1 change on adult pneumococcal pneumonia cannot be adequately assessed in this study.

Implications of this study

Our findings underline the importance of on-going efforts to prevent and reduce the impacts of pneumococcal pneumonia on adults, particularly older adults. The UK population aged ≥85 years is projected to increase by one million over the next 15 years.[40] Driven largely by the ageing population, the number of people living with chronic kidney disease is also forecast to increase to 7.6 million by 2033.[41] These changes may impel further increases in serotype 3 disease unless other interventions are introduced. In addition to the indirect herd protection from childhood programmes, the further role of direct vaccination of adults needs to be considered. This is especially pertinent now given the increased availability of higher-valent conjugate vaccines, including a PCV21 specifically designed to cover serotypes affecting adults, which may provide better protection than the currently used PPV23.

Our study has several strengths. It is a large prospective cohort study conducted over many years allowing us to accrue data on a large number of hospitalised patients with all-cause CAP and to compare trends in pneumococcal pneumonia as a whole and in the distribution of

pneumococcal serotypes before and after the pandemic. Use of the urinary 24-valent Bioplex-24 assay allowed detection of serotypes implicated in non-invasive pneumococcal pneumonia that would otherwise not be classified by culture-based methods.

There are limitations to this study. The 24-valent ssUAD assay was the main tool for identifying pneumococcal disease so it is likely that we missed some cases of pneumococcal disease in patients who did not have a urine samples tested by the ssUAD assay. Although >80% of serotypes over the ten years were PCV21 serotypes, we likely underestimated PCV21-CAP as not all PCV21 serotypes are detected by the current 24-valent assay. There are recognised cross-reactions in the Bioplex-24 assay with serotypes which are not targeted in the assay, where the serotype was designated based on the predominant serotype using national IPD data. This may have caused under-reporting of less common non-vaccine serotypes and thus underestimation of the prevalence of non-vaccine-type pneumonia.

As there were no *a priori* restrictions on multiple recruitment of participants in different study years and we were not able to link individual participants to their separate admissions, prior CAP is a confounder that could plausibly change the effect for many risks and outcomes modelled and is a limitation which needs to be recognised, although fewer than 5% of participants were enrolled more than once over the course of the study. Also, the study was conducted at a single

centre and may not be representative of pneumococcal and serotype trends elsewhere in the UK. However, the results from two further UK sites over a 2-year period are similar to our findings.[17] Changes in the admission process for patients with pneumonia in Nottingham occurred during the pandemic, with most patients directed to one hospital, and this may also have altered hospitalisation thresholds. In addition, after the recruitment pause was lifted it was only possible to recruit patients from that one hospital due to staff redeployment to urgent COVID-19 studies; therefore we could not be certain that all potentially eligible adults were identified for study inclusion. Given these differences, it was deemed inappropriate to calculate and compare the incidence of pneumococcal pneumonia pre-versus-post pandemic as the potential change in denominator values would tend towards an underestimate of post-restriction period incidence.

In conclusion, a large proportion of CAP continues to be caused by pneumococcal infection, with serotype 3 predominating and continuing to increase proportionately. We have not observed serotype 3 pneumonia to be more severe than other serotypes. Non-serotype 3 PCV13-vaccine type pneumonia does not appear to have increased significantly over the last ten years. It is important for new pneumococcal vaccines to provide good protection against serotype 3 if adult pneumococcal pneumonia is to be reduced in future years, whether via direct or indirect protection.

Acknowledgements

The authors would like to thank Gemma Clarke and colleagues from the Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust for processing urine samples using the BinaxNOW assay; Saima Ashref, Zorba Begum, Jo Butler, Shammah Chikuri, Paige Draper, Mina Fatemi, Wendy Gerrard-Tarpey, Meghan Jones, Hannah Kerr, Teju Limbu, Nicola Neesham, Rebecca Nicol, Katherine Smith , Louise Conner, Sevim Hodge, Cecilia Peters, Lucy Ryan, Claudia Washbrook, Sonya Finucane, Megan McAuley, Amy Clark and the clinicians, nurses and staff of Nottingham University Hospitals NHS Trust who recruited patients, collected samples and collected data; Georgina Bartlett, Evelyn Butkevicius and Depu Parakkal Papu for data entry and study administration; the Nottingham Pneumonia Patients and Public Involvement group for their ongoing input into respiratory infection research, and all participants who gave their consent for the study.

Conflict of Interest

WSL's institution received unrestricted investigator-initiated research funding from Pfizer for the conduct of this study (please see funding statement). WSL reports research funding from NIHR for a multi-centre clinical trial of aspirin in community acquired pneumonia in which WSL is a co-applicant. WSL is Deputy Chair of the Joint Committee of Vaccination and Immunisation (JCVI)(unpaid), and unpaid Chair of the NIHR Respiratory-Translational Research Centre's Acute Respiratory Infection National Strategy Research Group. CT participated in a CMV vaccine advisory board meeting in May 2022, unrelated to the topic of this paper. SE declares participation in a Virtual Advisory Board for a pneumococcal project organised by Sanofi Pasteur SA unrelated to the submitted work. The UK Health Security Agency (UKHSA) received monies from the University of

Nottingham from an unrestricted grant from Pfizer for this work. The Vaccine Preventable Bacteria Section of UKHSA has received grants from GSK and Pfizer for investigator led research unrelated to the current project. The UKHSA provides vaccine manufacturers (GlaxoSmithKline (GSK), MSD, Pfizer) with post marketing surveillance reports on vaccine-preventable disease, including pneumococcal infections for which a cost recovery charge is made and which is unrelated to the submitted work.

No other authors declare competing interests.

Funding

This study is independent research supported by the Nottingham National Institute for Health Research Biomedical Research Centre (NIHR BRC) from an unrestricted investigator-initiated research grant from Pfizer. The study concept was developed and agreed by the authors with no input from the funding bodies; Pfizer had no part in the design or execution of the study, the analysis and interpretation of the results, the writing of this manuscript or the decision to submit for publication. The data are the sole responsibility of the authors and the sponsor for the study was Nottingham University Hospitals NHS Trust.

Contributors

WSL and CS were responsible for study conception and design. HL, HP, VB, RCE-P, LM, HB, DA, LB, PD, TB, CR, DL, SE, HP and SL were responsible for data acquisition and analysis. TM, LL and CT were responsible for the statistical analysis. LL and WSL drafted the initial version of the article. All authors contributed to data interpretation and read, commented on and approved the final version of the article. WSL is the guarantor.

Ethics approval

The work was approved by the Nottingham Research Ethics Committee (REC reference 08/H0403/80).

REFERENCES

[1] Quan TP, Fawcett NJ, Wrightson JM, et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998-2014. Thorax. 2016;71(6):535-42.10.1136/thoraxjnl-2015-207688

[2] Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med. 2015;373(5):415-27.10.1056/NEJMoa1500245

[3] Cillóniz C, Ewig S, Polverino E, et al. Community-acquired pneumonia in outpatients: aetiology and outcomes. Eur Respir J. 2012;40(4):931-8.10.1183/09031936.00168811

[4] UK Health Security Agency. Chapter 25. Pneumococcal. Immunisation against infectious disease. Available from: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book. 2020

[5] Berild JD, Winje BA, Vestrheim DF, et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. Pathogens. 2020;9(4).10.3390/pathogens9040259

[6] Hanquet G, Krizova P, Dalby T, et al. Serotype Replacement after Introduction of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccines in 10 Countries, Europe. Emerg Infect Dis. 2022;28(1):137-8.10.3201/eid2801.210734

[7] Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis. 2018;18(4):441-51.10.1016/s1473-3099(18)30052-5

[8] Dagan R, Patterson S, Juergens C, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. Clin Infect Dis. 2013;57(7):952-62.10.1093/cid/cit428

[9] Horácio AN, Silva-Costa C, Lopes JP, et al. Serotype 3 Remains the Leading Cause of Invasive Pneumococcal Disease in Adults in Portugal (2012-2014) Despite Continued Reductions in Other 13-Valent Conjugate Vaccine Serotypes. Front Microbiol. 2016;7:1616.10.3389/fmicb.2016.01616

[10] van der Linden M, Falkenhorst G, Perniciaro S, et al. Effects of Infant Pneumococcal Conjugate Vaccination on Serotype Distribution in Invasive Pneumococcal Disease among Children and Adults in Germany. PLoS One. 2015;10(7):e0131494.10.1371/journal.pone.0131494

[11] Andrews N, Kent A, Amin-Chowdhury Z, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: The indirect cohort design, 2006-2018. Vaccine. 2019;37(32):4491-8.10.1016/j.vaccine.2019.06.071

[12] Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. Clin Infect Dis. 2010;51(6):692-9.10.1086/655828

[13] Ahl J, Littorin N, Forsgren A, et al. High incidence of septic shock caused by Streptococcus pneumoniae serotype 3--a retrospective epidemiological study. BMC Infect Dis. 2013;13:492.10.1186/1471-2334-13-492

[14] Burgos J, Luján M, Larrosa MN, et al. Risk factors for respiratory failure in pneumococcal pneumonia: the importance of pneumococcal serotypes. Eur Respir J. 2014;43(2):545-53.10.1183/09031936.00050413
[15] Platt H, Omole T, Cardona J, et al. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, US-based trial. Lancet Infect Dis. 2023;23(2):233-46.10.1016/s1473-3099(22)00526-6
[16] Campling J, Vyse A, Liu HH, et al. A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom. Expert Rev Vaccines. 2023;22(1):785-800.10.1080/14760584.2023.2256394
[17] Lansbury L, Lawrence H, McKeever TM, et al. Pneumococcal serotypes and risk factors in adult community-acquired pneumonia 2018-20; a multicentre UK cohort study. Lancet Reg Health Eur. 2024;37:100812.10.1016/j.lanepe.2023.100812
[18] Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-18. Thorax. 2020;75(1):38-49.10.1136/thoraxjnl-2019-213725
[19] Eletu SD, Sheppard CL, Rose S, et al. Re-validation and update of an extended-specificity multiplex assay for detection of Streptococcus pneumoniae capsular serotype/serogroup-specific antigen and cell-wall polysaccharide in urine specimens. Access Microbiol. 2020;2(3):acmi000094.10.1099/acmi.0.000094
[20] Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression and Survival Analysis.: Springer New York, NY; 2001.
[21] Torres A, Blasi F, Dartois N, et al. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015;70(10):984-9.10.1136/thoraxjnl-2015-206780
[22] Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. Nat Rev Microbiol. 2023;21(3):195-210.10.1038/s41579-022-00807-9
[23] Bertran M, D'Aeth JC, Abdullahi F, et al. Invasive pneumococcal disease 3 years after introduction of a reduced 1 + 1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study. Lancet Infect Dis. 2024.10.1016/s1473-3099(23)00706-5
[24] Neal EFG, Chan J, Nguyen CD, et al. Factors associated with pneumococcal nasopharyngeal carriage: A systematic review. PLOS Glob Public Health. 2022;2(4):e0000327.10.1371/journal.pgph.0000327
[25] Wolter N, Tempia S, Cohen C, et al. High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia. J Infect Dis. 2014;210(10):1649-57.10.1093/infdis/jiu326
[26] Yang Z, Bou-Antoun S, Gerver S, et al. Sustained increases in antibiotic prescriptions per primary care consultation for upper respiratory tract infections in England during the COVID-19 pandemic. JAC Antimicrob Resist. 2023;5(1):dlad012.10.1093/jacamr/dlad012
[27] Vestesson E, De Corte K, Chappell P, et al. Antibiotic prescribing in remote versus face-to-face consultations for acute respiratory infections in primary care in England: an observational study using target maximum likelihood estimation. EClinicalMedicine. 2023;64:102245.10.1016/j.eclinm.2023.102245
[28] Forstner C, Kolditz M, Kesselmeier M, et al. Pneumococcal conjugate serotype distribution and predominating role of serotype 3 in German adults with community-acquired pneumonia. Vaccine. 2020;38(5):1129-36.10.1016/j.vaccine.2019.11.026

[29] Torres A, Menéndez R, España PP, et al. The Evolution and Distribution of Pneumococcal Serotypes in Adults Hospitalized With Community-Acquired Pneumonia in Spain Using a Serotype-Specific Urinary Antigen Detection Test: The CAPA Study, 2011-2018. Clin Infect Dis. 2021;73(6):1075-85.10.1093/cid/ciab307
[30] Silva-Costa C, Gomes-Silva J, Santos A, et al. Adult non-invasive pneumococcal pneumonia in Portugal is dominated by serotype 3 and non-PCV13 serotypes 3-years after near universal PCV13 use in children. Front Public Health. 2023;11:1279656.10.3389/fpubh.2023.1279656
[31] Hyams C, Lahuerta M, Theilacker C, et al. Surveillance of pneumococcal serotypes in adults hospitalised with acute lower respiratory tract infection in Bristol, UK. Vaccine. 2024;42(7):1599-607.10.1016/j.vaccine.2024.02.007
[32] Silva-Costa C, Gomes-Silva J, Pinho MD, et al. Continued Vaccine Breakthrough Cases of Serotype 3 Complicated Pneumonia in Vaccinated Children, Portugal (2016-2019). Microbiol Spectr. 2022;10(4):e0107722.10.1128/spectrum.01077-22
[33] Africano HF, Serrano-Mayorga CC, Ramirez-Valbuena PC, et al. Major Adverse Cardiovascular Events During Invasive Pneumococcal Disease Are Serotype Dependent. Clin Infect Dis. 2021;72(11):e711-e9.10.1093/cid/ciaa1427
[34] Gutiérrez F, Masiá M, Mirete C, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect. 2006;53(3):166-74.10.1016/j.jinf.2005.11.006
[35] Wagenvoort GH, Sanders EA, Vlaminckx BJ, et al. Sex differences in invasive pneumococcal disease and the impact of pneumococcal conjugate vaccination in the Netherlands, 2004 to 2015. Euro Surveill. 2017;22(10).10.2807/1560-7917.Es.2017.22.10.30481
[36] Office for National Statistics (ONS). released 3 April 2023, ONS website, article, Profile of the older population living in England and Wales in 2021 and changes since 2011

2023 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/profileoftheolderpopulationlivinginenglandandwalesin2021andchangessince2011/2023-04-03.
[37] Sings HL, De Wals P, Gessner BD, et al. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Invasive Disease Caused by Serotype 3 in Children: A Systematic Review and Meta-analysis of Observational Studies. Clin Infect Dis. 2019;68(12):2135-43.10.1093/cid/ciy920
[38] Tiley KS, Ratcliffe H, Voysey M, et al. Nasopharyngeal Carriage of Pneumococcus in Children in England up to 10 Years After 13-Valent Pneumococcal Conjugate Vaccine Introduction: Persistence of Serotypes 3 and 19A and Emergence of 7C. J Infect Dis. 2023;227(5):610-21.10.1093/infdis/jiac376
[39] Ladhani SN, Andrews N, Ramsay ME. Summary of evidence to reduce the two-dose infant priming schedule to a single dose of the 13-valent pneumococcal conjugate vaccine in the national immunisation programme in the UK. Lancet Infect Dis. 2021;21(4):e93-e102.10.1016/s1473-3099(20)30492-8
[40] Office for National Statistics (ONS). released 30 January 2024, ONS website, statistical bulletin, National population projections: 2021-based interim

[Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2021basedinterim.

[41] Kidney Research UK. Kidney Disease: a UK Public Health Emergency 2023 [Available from: https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-full-report_accessible.pdf.

Figure Captions and Legends

Figure 1 The absolute proportion of community-acquired pneumonia caused by *Streptococcus pneumoniae* between 2013 and 2023 by study year and according to age group. The numerator is the number of patients with pneumococcal pneumonia per age group and the denominator is the total number of patients admitted with all-cause CAP for that age group.

Covid-19 pandemic restrictions March 2020 to June 2021

Figure 2 The absolute proportion of hospitalised patients with pneumonia due to *Streptococcus pneumoniae* who were bacteraemic during each year of the study from 2013 to 2023.

Covid-19 pandemic restrictions March 2020 to June 2021

Figure 3 Stacked area plot showing the relative proportion of individual pneumococcal serotypes detected by urinary Bioplex-24 assay for each year of the study between 2013 and 2023. The numerator is the number of detections of each individual serotype and the numerator the total number of serotype detections for each year.

Figure 4 Stacked area plot showing the relative proportion of pneumococcal serotypes detected during each year of the study which are

covered by pneumococcal vaccines: PCV7, PCV13-nonPCV7, PCV15-nonPCV13, PCV20- only, PPV23-only serotypes, and non-vaccine types (serotypes not covered by these vaccines or non-Bioplex24 serotypes).

PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F

Additional PCV13 serotypes: 1, 3, 5, 6A, 7F, 19A,

PCV15nonPCV13 serotypes: 22F, 33F

PCV20non13/15 serotypes: 8, 10A, 11A, 12F, 15B

PPV23non20 serotypes: 2, 9N, 17F, 20

NVT= Non-vaccine types

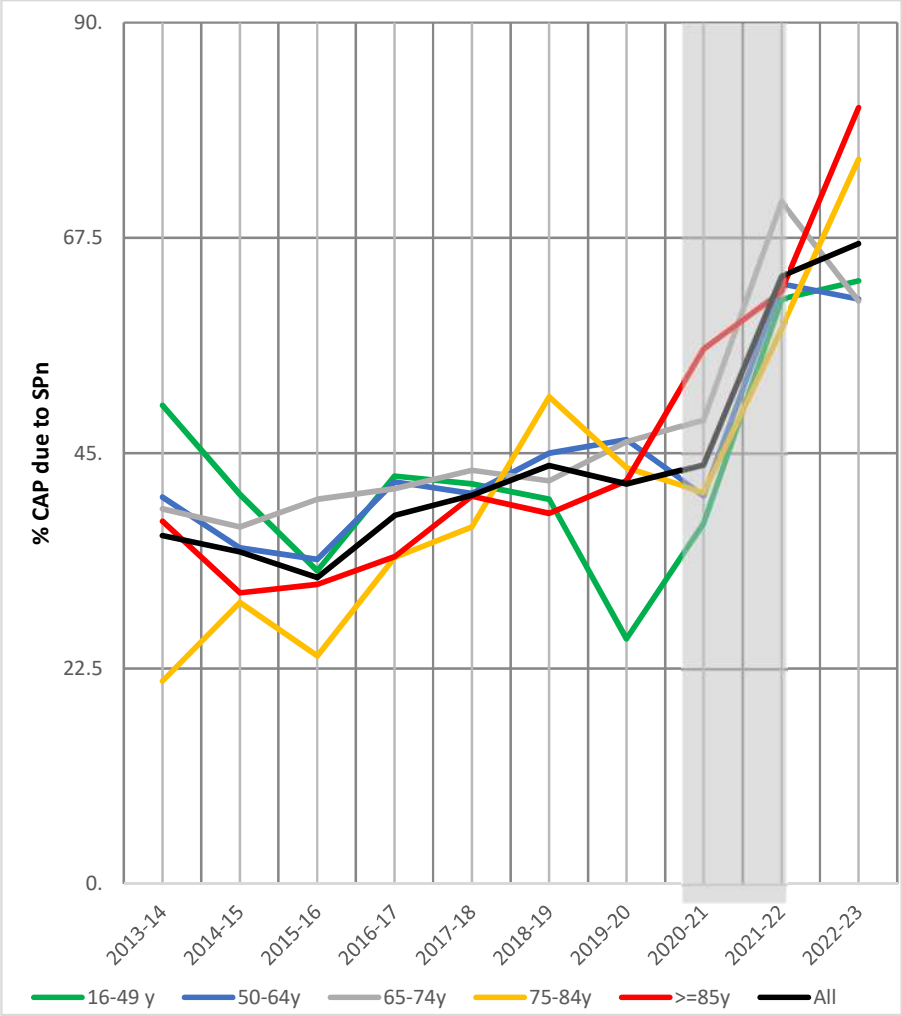

Figure 1 The absolute proportion of community-acquired pneumonia caused by Streptococcus pneumoniae between 2013 and 2023 by study year and according to age group. The numerator is the number of patients with pneumococcal pneumonia per age group and the denominator is the total number of patients admitted with all-cause CAP for that age group.

Covid-19 pandemic restrictions March 2020 to June 2021

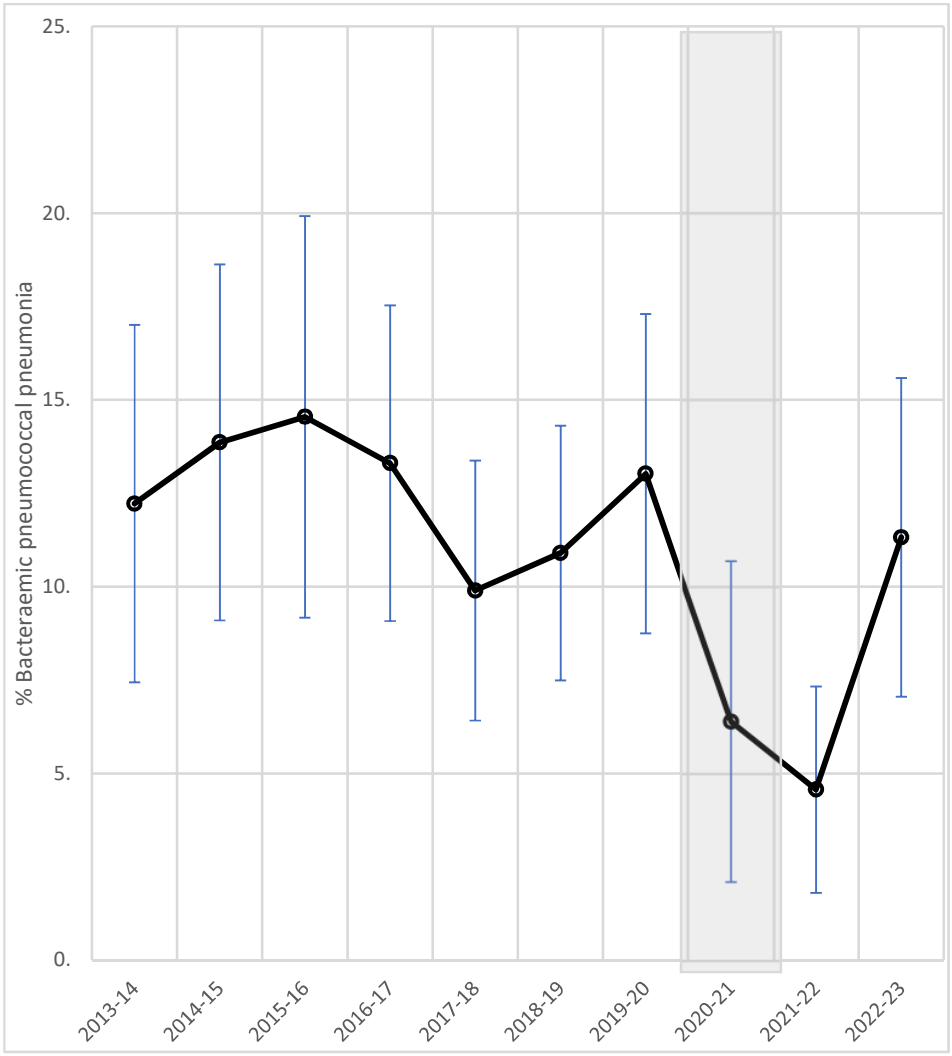

Figure 2 The absolute proportion of hospitalised patients with pneumonia due to Streptococcus pneumoniae who were bacteraemic during each year of the study from 2013 to 2023.

Covid-19 pandemic restrictions March 2020 to June 2021

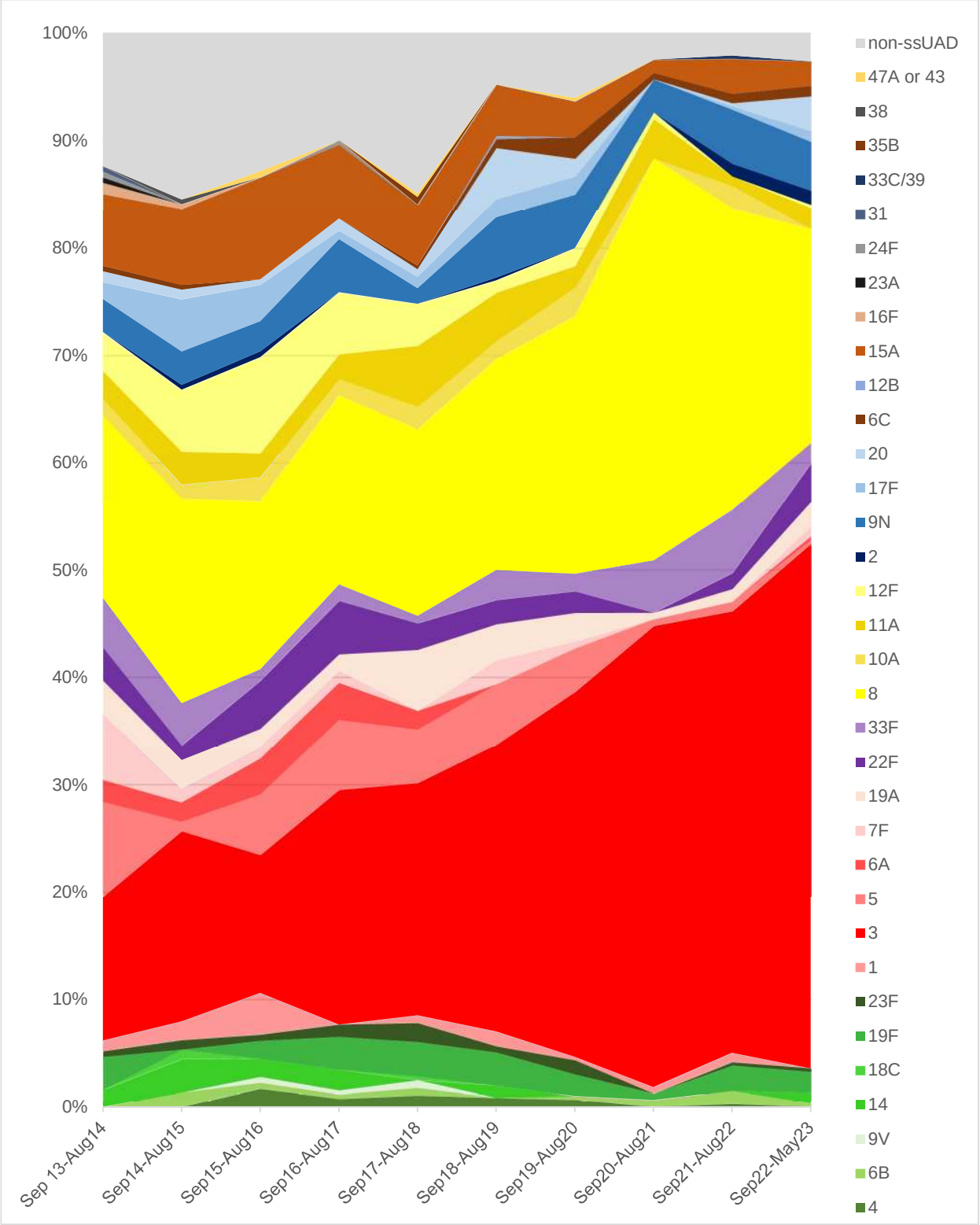

Figure 3 Stacked area plot showing the relative proportion of individual pneumococcal serotypes detected by urinary Bioplex-24 assay for each year of the study between 2013 and 2023. The numerator is the number of detections of each individual serotype and the numerator the total number of serotype detections for each year.

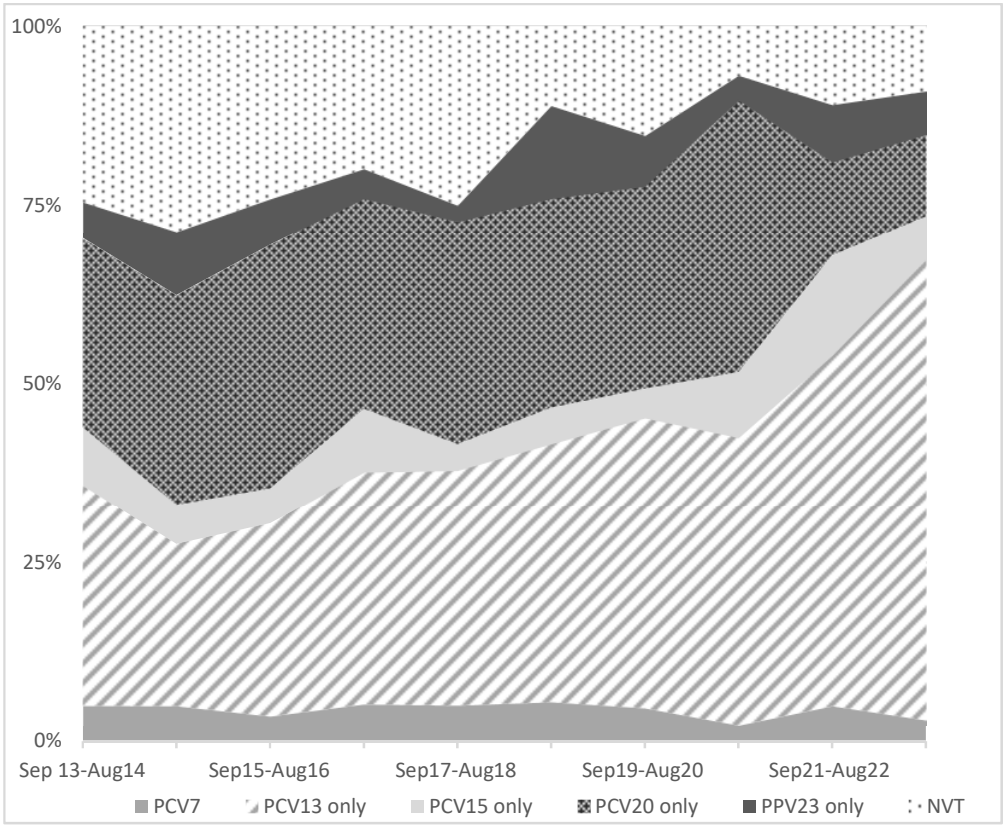

Figure 4 Stacked area plot showing the relative proportion of pneumococcal serotypes detected during each year of the study which are covered by pneumococcal vaccines: PCV7, PCV13-nonPCV7, PCV15-nonPCV13, PCV20- only, PPV23-only serotypes, and non-vaccine types (serotypes not covered by these vaccines or non-Bioplex24 serotypes).

PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F

Additional PCV13 serotypes: 1, 3, 5, 6A, 7F, 19A,

PCV15nonPCV13 serotypes: 22F, 33F

PCV20non13/15 serotypes: 8, 10A, 11A, 12F, 15B

PPV23non20 serotypes: 2, 9N, 17F, 20

NVT= Non-vaccine types