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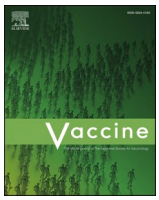

# Assessing the potential impact of the 20-valent (PCV20) and an adult 21-valent (aPCV21) pneumococcal conjugate vaccine on invasive pneumococcal disease in England

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ABSTRACT

*Background:* Several higher-valent pneumococcal conjugate vaccines (PCVs) have been licensed recently, including a 20-valent PCV (PCV20) for children and adults and 21-valent PCV (aPCV21) licensed for adults. We assessed the potential for aPCV21 to further reduce the burden of invasive pneumococcal disease (IPD) in England.

*Methods:* IPD cases are electronically reported to the UKHSA and pneumococcal isolates are routinely submitted to the UKHSA national reference laboratory for confirmation and serotyping. We used national enhanced surveillance data for all IPD cases confirmed in England (July 2023–June 2024) to estimate the number of cases potentially preventable by aPCV21 in addition to the current childhood 13-valent PCV (PCV13) programme and a potential future childhood PCV20 programme.

*Results:* There were 5080 confirmed IPD cases. 4826 cases (95.0%) were serotyped, of which there were 1402 cases (29.1% of serotyped isolates) of PCV13-serotype IPD and 3105 cases (64.3%) of PCV20-serotype IPD, including 1703 cases (35.3%) with additional serotypes compared to PCV13.

aPCV21 contains four shared serotypes with PCV13, seven additional serotypes shared with PCV20 and 10 novel serotypes. This equated to 939 (19.5%), 2642 (54.7%) and 1300 (26.9%) IPD cases with known serotype, respectively.

Across England, 6.9% (271/3942) of aPCV21-serotype IPD cases were in children aged <15 years, 35.8% (1411/3942) in adults aged 15–64 years and 57.3% (2260/3942) in older adults aged ≥65 years. By age group, however, the proportions of IPD cases due to aPCV21 serotypes were similar and there were no significant differences in aPCV21 coverage by clinical presentation or fatal outcomes.

*Conclusions:* aPCV21 has the potential to prevent a large proportion of the remaining IPD burden in adults. Given that the proportion of aPCV21-serotypes within age groups is similar, such a vaccine would have a large impact in the childhood immunisation programme because of the direct and indirect protection offered by the vaccine.

## 1. Introduction

*Streptococcus pneumoniae* (the pneumococcus) is a major cause of infectious morbidity and mortality worldwide. More than 100 different pneumococcal serotypes have been identified, based on their unique polysaccharide capsules. Pneumococcal conjugate vaccines (PCVs) have been highly effective in reducing the incidence of invasive pneumococcal disease (IPD) caused by the respective vaccine serotypes [1,2]. Since conjugate vaccines also prevent carriage acquisition, vaccinating young children, who are the main nasopharyngeal carriers of pneumococci, has also resulted in interruption of transmission of vaccine serotypes to unvaccinated older children and adults, leading to large and sustained declines in vaccine-serotype IPD across all age groups (indirect or herd protection) [3].

In the United Kingdom, a 7-valent PCV (PCV7) was introduced into the national infant immunisation programme in 2006 and replaced with

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a 13-valent vaccine (PCV13) in 2010 [4,5]. A pneumococcal polysaccharide vaccine (PPV23) has been part of the routine offer for individuals from two years of age within a risk group since 1992 and to adults aged 65 years and over since 2003 [6]. While vaccine-type IPD incidence declined rapidly after implementation of both vaccines, cases due to non-vaccine serotypes increased, especially in older adults (serotype replacement disease) [7]. Both immunisation programmes are offered free of charge to eligible groups via the National Health Service (NHS) [6]. Despite a small decline since the COVID-19 pandemic, PCV13 vaccine coverage has remained high at 93.4% for the primary dose coverage at 12 months and 88.6% for the booster dose coverage at 24 months in financial year 2024/2025 [8]. PPV23 uptake accumulates by age following eligibility at 65 years of age but reached 73.6% in individuals aged 65 and over as of March 2025 [9].

By the 2013/14 epidemiological year, the maximum decline in PCV13-type IPD had been achieved and, although overall IPD incidence remained stable in young children thereafter, the incidence in older adults reached pre-PCV13 rates by 2016/17 because of serotype replacement disease [7]. In January 2020, following a period of stable IPD incidence, the UK shifted from a 2 + 1 to a 1 + 1 PCV13 infant immunisation schedule on the premise that the reduced schedule would continue to sustain the indirect (herd) protection afforded across the population [10–12]. Ongoing surveillance shows no significant change in IPD incidence, disease characteristics or outcomes since the shift to the reduced childhood immunisation schedule [13,14].

Given the problems with serotype replacement disease, a novel 21-valent PCV has been developed and licensed for prevention of IPD in adults aged ≥18 years (aPCV21; Capvaxive®), which includes serotypes that commonly cause IPD in adults. A subset of these serotypes are included in both PCV13, used for the childhood immunisation programme, and PCV20, soon to replace PPV23 in the adults and at-risk immunisation programme (Fig. 1). By including serotypes not in the vaccine used in the childhood programme, aPCV21 avoids impacting pneumococcal carriage in children, which is the main driver of serotype replacement disease [15].

We used enhanced national IPD surveillance data for the latest available epidemiological year (2023/24) to assess the potential impact of aPCV21 implementation in England.

## 2. Methods

### 2.1. Surveillance

The UK Health Security Agency (UKHSA) conducts enhanced IPD surveillance in England [5]. Briefly, all diagnostic laboratories in England are required to notify any cases of confirmed invasive *Streptococcus pneumoniae* infections to the UKHSA; this is done electronically through the Second-Generation Surveillance System (SGSS), ensuring very high case ascertainment for laboratory-confirmed IPD.

Additionally, the UKHSA Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) provides a national reference service for confirmation and serotyping of invasive pneumococcal isolates referred by hospital laboratories. *S. pneumoniae* was identified by colony morphology, optochin sensitivity and whole-genome sequence analysis, and serotype was determined by genomic prediction supplemented by bacterial slide agglutination, as previously described [16,17].

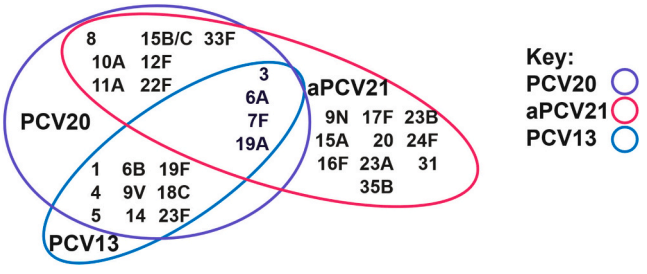



**Fig. 1.** Serotypes included in 13-valent, 20-valent and adult 21-valent pneumococcal conjugate vaccines.

Electronically reported cases without isolate submission to the RVPBRU are actively followed up with the reporting laboratory, thus ensuring very high serotyping rates nationally. The general practitioners of all confirmed IPD cases are then requested to complete a short surveillance questionnaire requesting vaccination history, underlying conditions, clinical presentation and outcomes of infection.

### 2.2. Definitions

Invasive pneumococcal disease was defined as isolation of *S. pneumoniae* from a normally sterile site, or detection of pneumococcal DNA by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) or pleural fluid. Clinical presentation of IPD were defined as: "meningitis" where *S. pneumoniae* was detected by culture or PCR in the cerebrospinal fluid or isolation via culture from blood and clinical features of meningitis; "bacteraemic pneumonia" where there was identification of *S. pneumoniae* by culture or PCR in pleural fluid or isolation of *S. pneumoniae* in blood cultures with clinical features of pneumonia. Isolation of *S. pneumoniae* from other normally sterile sites was defined as "other presentations". In patients without a focus of infection, clinical presentation was classified as "septicaemia".

We analysed IPD cases confirmed during the 2023–2024 epidemiological year (01 July to 30 June).

Cases were categorised into five serotype groups:

- PCV13-only serotypes (serotypes in both PCV13 and PCV20, and not in aPCV21): 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F
- Common PCV serotypes (serotypes in PCV13, PCV20 and aPCV21): 3, 6A, 7F, 19A
- PCV20/aPCV21 serotypes (serotypes not in PCV13 but in PCV20 and in aPCV21): 8, 10A, 11A, 12F, 15B/C, 22F, 33F
- aPCV21-only serotypes (serotypes only in aPCV21): 9N, 15A, 16F, 17F, 20, 23A, 23B, 24F, 31, 35B
- Serotypes not in PCV13, PCV20 or aPCV21

Fatal outcomes and dates of death were identified through linkage of laboratory-confirmed IPD cases with the Personal Demographic Service, a national database of all patients registered with the NHS [18].

### 2.3. Analysis

Ages were grouped into <1 year, 1–4 years, 5–14 years, 15–44 years, 45–54 years, 55–64 years, 65–74 years, 75–84 years and 85+ years, and in broader age categories of 0–14 (children), 15–64 (adults) and 65+ years (older adults). We analysed the distribution of IPD cases, clinical presentation and 7-day case-fatality rates (CFR) by age group and serotype group during the 2023/24 epidemiological year. Age-specific incidence was calculated using Office for National Statistics (ONS) mid-year population estimates. Continuous data that did not follow a normal distribution are described as medians with interquartile ranges and categorical data are presented as percentages. Data were analysed using R Version 4.3.3.

## 3. Results

During 2023/24, there were 5080 confirmed IPD cases in England and, of these, 4826 (95%) were serotyped. Of the 4826 cases with serotyping information, 2523 (52.3%) were male and 2689 (55.7%) occurred in individuals aged 65 years and older. The overall questionnaire completion rate for 2023/24 was 90.2% (4355/4826).

### 3.1. PCV13-type IPD

Of the 4826 cases with serotyped isolates, 1402 (29.1%) had PCV13-serotype IPD (Table 1). Serotypes 3 ($n = 698$; 49.8% of PCV13 isolates), 4 (326; 23.3% of PCV13 isolates) and 19A (229; 16.3% of PCV13 isolates) were the main serotypes responsible (Table 2). Serotype predominance among PCV13-serotype IPD differed across age groups (Fig. 2). Among children (aged <15 years), there were 59 PCV13-serotype IPD cases, due to serotype 19A (26/59, 44.1%) followed by serotypes 3 (16/59, 27.1%) and 19F (14/59, 23.7%). Among adults (15–64 year-olds), there were 611 PCV13-serotype IPD cases, which were predominantly serotype 4 (244/611, 39.9%). Among 732 PCV13-serotype IPD cases aged above 65 years-old, serotype 3 IPD predominated (463/732, 63.3%). Notably, too, the proportion of PCV13-serotype IPD cases due to serotype 4 decreased with increasing age, from 39.9% of isolates in cases aged 15–64 years to 4.4% of isolates in cases aged ≥85 years.

### 3.2. PCV20-type IPD

There were 3105 cases of (64.3% of serotyped isolates) PCV20-serotype IPD, equating to an additional 1703 (35.0% of serotyped isolates) compared with PCV13, given the overlap in serotypes covered between the two vaccines (Table 2). The most common serotypes covered by PCV20 were serotypes 3 (698; 22.5% of PCV20 isolates), 8 (680; 21.9%) and 22F (446; 14.4%).

Cases covered by PCV20 also varied by age (Fig. 2). In children, there were 190 cases covered by PCV20, of which serotype 10A (31/190, 16.3% of PCV20-type IPD cases) was the most prevalent, followed by serotypes 19A (13.7%, 26/190) and 8 (13.7%, 26/190). Of 1311 PCV20-serotype IPD cases among 15–64 year-olds, most isolates were serotypes 8 (28.4%; 373/1311) and 4 (18.6%; 244/1311). From 65 years of age, the contribution of these two serotypes to IPD declined, with serotype 3 being more common, accounting for 28.9% (463/1604) of isolates from cases within this age group.

### 3.3. aPCV21 vs PCV13

In total, there were 3942 (81.7% of cases with serotyped isolates) aPCV21-serotype cases, of which 939 (19.5%) were cases with serotypes shared with PCV13 (serotypes 3, 19A, 6A and 7F). The remaining 3003 cases had isolates with serotypes exclusive to aPCV21. This corresponds to an additional 62.2% of serotyped isolates covered by aPCV21 compared to serotyped isolates covered by PCV13 (1402; 29.1% of serotyped isolates).

**Table 2**
Count and percentage of vaccine-serotype cases by serotype and vaccine serotype groups (PCV13, PCV20 and aPCV21), July 2023 – June 2024.

| Serotype | Vaccine serotype group | n | Percentage |
|---|---|---|---|
| 4 | PCV13/PCV20 | 326 | 7.4 |
| 19F | PCV13/PCV20 | 86 | 2.0 |
| 9V | PCV13/PCV20 | 17 | 0.4 |
| 6B | PCV13/PCV20 | 10 | 0.2 |
| 14 | PCV13/PCV20 | 9 | 0.2 |
| 23F | PCV13/PCV20 | 7 | 0.2 |
| 18C | PCV13/PCV20 | 4 | 0.1 |
| 5 | PCV13/PCV20 | 2 | <0.1 |
| 1 | PCV13/PCV20 | 2 | <0.1 |
| 3 | PCV13/PCV20 and aPCV21 | 698 | 15.8 |
| 19A | PCV13/PCV20 and aPCV21 | 229 | 5.2 |
| 6A | PCV13/PCV20 and aPCV21 | 6 | 0.1 |
| 7F | PCV13/PCV20 and aPCV21 | 6 | 0.1 |
| 8 | PCV20 and aPCV21 | 680 | 15.4 |
| 22F | PCV20 and aPCV21 | 446 | 10.1 |
| 10A | PCV20 and aPCV21 | 157 | 3.6 |
| 33F | PCV20 and aPCV21 | 151 | 3.4 |
| 11A | PCV20 and aPCV21 | 108 | 2.5 |
| 12F | PCV20 and aPCV21 | 88 | 2.0 |
| 15B/C | PCV20 and aPCV21 | 73 | 1.7 |
| 9N | aPCV21 only | 407 | 9.2 |
| 23B | aPCV21 only | 181 | 4.1 |
| 15A | aPCV21 only | 175 | 4.0 |
| 23A | aPCV21 only | 153 | 3.5 |
| 24F | aPCV21 only | 107 | 2.4 |
| 31 | aPCV21 only | 87 | 2.0 |
| 35B | aPCV21 only | 63 | 1.4 |
| 17F | aPCV21 only | 49 | 1.1 |
| 16F | aPCV21 only | 48 | 1.1 |
| 20 | aPCV21 only | 30 | 0.7 |
| **Total** | | **4405** | **100** |

### 3.4. aPCV21 vs PCV20

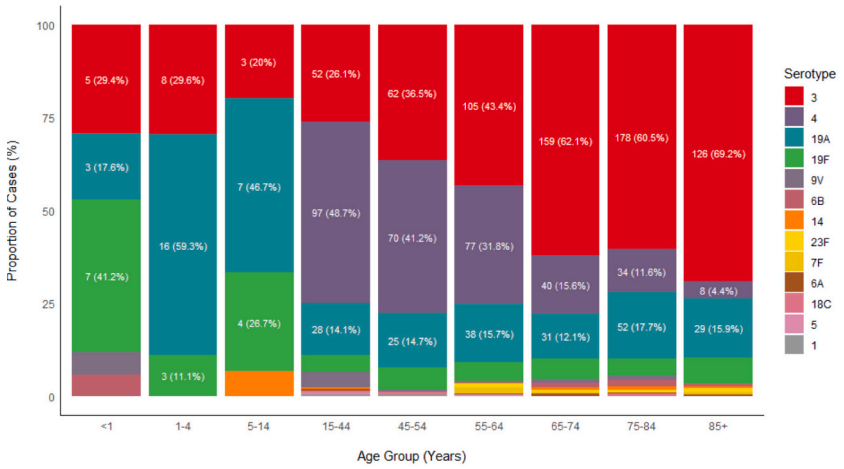
Of the 3942 aPCV21-serotype IPD cases, 2642 included serotypes

**Table 1**
Count and percentage of cases by vaccine serotype groups (PCV13, PCV20, aPCV21 and non-vaccine serotypes), age group and sex, July 2023 – June 2024.

| Characteristic | All serotypes; N (%) | Non-vaccine serotypes; n (%) | PCV13 /PCV20-only serotypes[a]; n (%) | PCV13/PCV20 and aPCV21 serotypes[b]; n (%) | PCV20 (non-PCV13) and aPCV21 serotypes[c]; n (%) | PCV20 and aPCV21 serotypes[d]; n (%) | aPCV21-only serotypes (non-PCV20)[e]; n (%) | All aPCV21 serotypes; n (%) |
|---|---|---|---|---|---|---|---|---|
| **All cases** | **4826 (100)** | **421 (8.7)** | **463 (9.6)** | **939 (19.5)** | **1703 (35.3)** | **2642 (54.7)** | **1300 (26.9)** | **3942 (81.7)** |
| **Sex** | | | | | | | | |
| Male | 2523 (100) | 236 (9.4) | 294 (11.7) | 497 (19.7) | 887 (35.2) | 1384 (53.3) | 609 (25.6) | 1993 (79.0) |
| Female | 2300 (100) | 185 (8.0) | 169 (7.3) | 441 (19.2) | 816 (35.5) | 1257 (53.1) | 689 (31.5) | 1946 (84.6) |
| Unknown | 3 (100) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 1 (33.3) | 2 (66.7) | 3 (100) |
| **Age (years)** | | | | | | | | |
| Median (IQR) | 68 (52–80) | 62 (58–83) | 56 (43–70) | 60 (56–81) | 65 (50–77) | 67 (52–79) | 72 (56–82) | 68 (54–80) |
| **Age Group** | | | | | | | | |
| <1 year | 88 (100) | 13 (14.8) | 9 (10.2) | 8 (9.1) | 37 (42.0) | 45 (51.1) | 21 (23.9) | 66 (75.0) |
| 1–4 years | 164 (100) | 21 (12.8) | 3 (1.8) | 24 (14.6) | 62 (37.8) | 86 (52.4) | 54 (32.9) | 140 (85.4) |
| 5–14 years | 80 (100) | 10 (12.5) | 5 (6.3) | 10 (12.5) | 32.0 (40) | 42 (52.5) | 23 (28.8) | 65 (81.3) |
| 15–44 years | 556 (100) | 30 (5.4) | 118 (21.2) | 81 (14.6) | 225 (40.5) | 306 (55.0) | 102 (18.3) | 408 (73.4) |
| 45–54 years | 456 (100) | 19 (4.2) | 83 (18.2) | 87 (19.1) | 158 (34.6) | 245 (53.7) | 109 (23.9) | 354 (77.6) |
| 55–64 years | 793 (100) | 50 (6.3) | 94 (11.9) | 148 (18.7) | 317 (40.0) | 465 (58.6) | 184 (23.2) | 649 (81.8) |
| 65–74 years | 917 (100) | 86 (9.4) | 63 (6.9) | 193 (21.0) | 339 (37.0) | 532 (58.0) | 236 (25.7) | 768 (83.8) |
| 75–84 years | 1028 (100) | 104 (10.1) | 63 (6.1) | 231 (22.5) | 306 (29.8) | 537 (52.2) | 324 (31.5) | 861 (83.8) |
| 85+ years | 744 (100) | 88 (11.8) | 25 (3.4) | 157 (21.1) | 227 (30.5) | 384 (51.6) | 247 (33.2) | 631 (84.8) |

[a] 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F.
[b] 3, 6A, 7F, 19A.
[c] 8, 10A, 11A,12F, 15B/C, 22F, 33F.
[d] 3, 6A, 7F, 8, 10A, 11A, 12F, 15B/C, 19A, 22F, 33F.
[e] 9N, 15A, 16F, 17F, 20, 23A, 23B, 24F, 31, 35B.

a) PCV13




b) PCV20

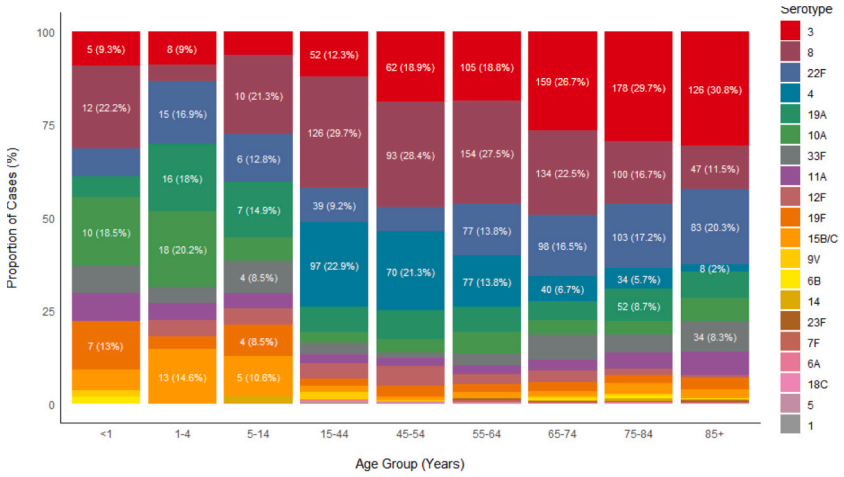



**Fig. 2.** Proportion of invasive pneumococcal disease (IPD) cases by age group and serotype covered by PCV13 and PCV20, July 2023–June 2024.

also covered by PCV20 (serotypes 3, 19A, 6A, 7F, 8, 22F, 10A, 33F, 11A, 12F, 15B/C). aPCV21, therefore, covered an additional 1300 (26.9% of cases with serotyped isolates).

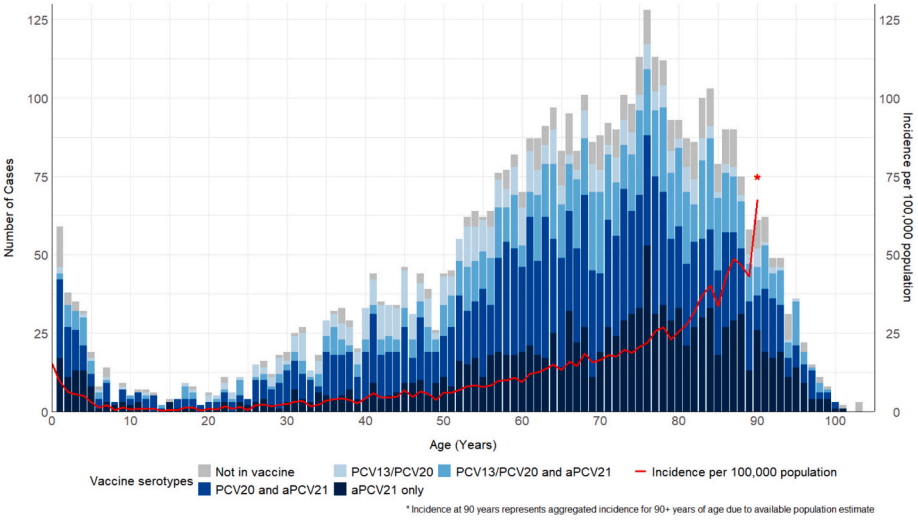



**Fig. 3.** Number and incidence per 100,000 population of invasive pneumococcal disease (IPD) cases by year of age and vaccine serotype groups (PCV13, PCV20, aPCV21 and non-vaccine serotypes), July 2023–June 2024.

### 3.5. Age distribution of cases by serotype group

The incidence of IPD was bimodal with a small early peak in infants (15.4 per 100,000), declining after the first year of life and then increasing exponentially from 50 years of age, reaching 67.5 per 100,000 at ≥90 years of age (Fig. 3).

When comparing the serotype distribution of cases by age group (Table 1), 4.2% (59/1402) of PCV13-serotype IPD cases were in children, 43.6% (611/1402) in adults and 52.2% (732/1402) in older adults. For PCV20-type IPD, the proportions would be 6.1% (190/3105), 42.2% (1311/3105) and 51.7% (1604/3105), respectively, whilst for aPCV21, the proportions would be 6.9% (271/3942), 35.8% (1411/3942) and 57.3% (2260/3942), respectively. Within each age group, however, the proportions of IPD cases due to the vaccine serotype groups were similar for all the three vaccines, with the serotypes in aPCV21 covering more than 70% of IPD cases, including in children (Fig. 4).

Additionally, aPCV21 would cover a high proportion of cases with different clinical manifestations compared with PCV13 (meningitis, bacteraemic pneumonia, septicaemia and other presentations) in children, as well as adults and older adults (Table 3). The vaccine could also potentially prevent a large proportion of deaths due to IPD which are mostly due to aPCV21 serotypes, in children (9/11, 81.1%), adults (74/102, 72.5%) and older adults (367/424, 86.6%) (Table 3).

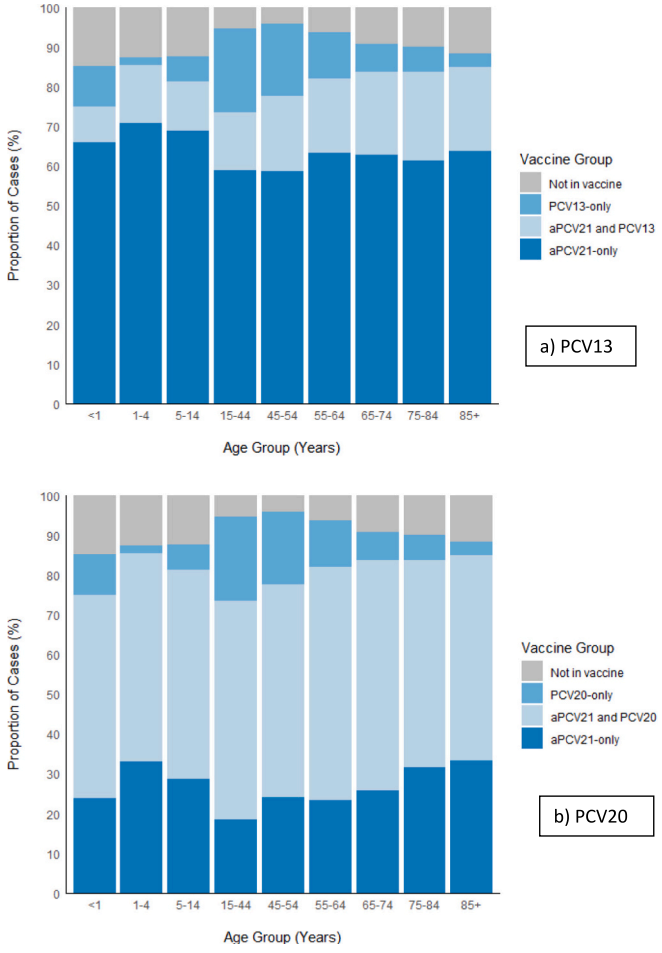



**Fig. 4.** Proportion of invasive pneumococcal disease (IPD) cases by age group and vaccine serotype group (PCV13, PCV20, aPCV21 and non-vaccine serotypes), by PCV13 and PCV20 coverage, July 2023–June 2024.

## 4. Discussion

### 4.1. Summary of findings

The novel adult PCV21 (aPCV21) has the potential to prevent a large proportion of IPD cases in older adults, with 84.0% (2260/2689) of all IPD cases with known serotype during 2023/2024 caused by aPCV21 serotypes among 65+ year-olds, who are currently the target population for universal adult vaccination. The serotype coverage of the vaccine would include 62.4% (1679/2689) of aPCV21-only IPD in addition to the 21.6% (581/2689) cases due to the four residual PCV13-serotypes that are also targeted by aPCV21 IPD in older adults during 2023/24. The vaccine would provide protection across the range of IPD clinical presentations and most IPD deaths in England. Notably, whilst total IPD cases and aPCV21-serotype IPD cases were highest in older adults, a smaller number but a similar proportion of cases could be prevented by the vaccine in younger adults and in children.

### 4.2. Compared to existing literature

In the United States, PCV13 was licensed for use in the routine childhood immunisation programme in 2010 and approved for adults aged ≥50 years in 2011. This was followed by a recommendation to incorporate PCV13 in series with PPV23 in the routine immunisation programme for those aged ≥65 years in 2014 [19]. This recommendation was contingent on a further assessment of emerging evidence on the results of the use of PCV13 in the paediatric routine immunisation programme, given that it was anticipated that the burden of disease among adults would reduce rapidly because of the indirect (herd) protection offered by the childhood PCV13 programme. This subsequently resulted in rescission of the offer of PCV13 and PPV23 for older adults in 2019 [20].

The US Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) now recommend aPCV21 as an option for adults aged ≥65 years, and adults aged 19–64 years with risk conditions currently eligible for PCV15 and PCV20 [21]. This was based on the observation that around 80% of serotypes in US adult cases with IPD were covered by aPCV21, of which 20–30% were only covered by aPCV21, with the remaining cases due to serotypes common to both aPCV21 and PCV20. aPCV21 was recommended as an option for eligible groups in addition to PCV20 and PCV15 from 24 June 2024.

### 4.3. Focus on new findings

Few countries recommended such an extensive PCV programme for adults and older adults because of the expected indirect benefits across the population resulting from the childhood programme. Evidence from the UK in the years following PCV13 introduction in the childhood programme (2010/11 to 2013/14) [4] and in other countries [2,22] showed a large reduction in PCV13-serotype disease across all age groups following PCV13 introduction without the need for PCV recommendations for older adults and at-risk populations.

Until the recent licensure of PCV20, the UK and other countries recommended a single dose of PPV23 for older adults when they turned 65 and for 2–64 year-olds with underlying conditions that increased their risk of IPD. The use of PPV23 aims to provide additional protection against IPD as it contains 11 more serotypes than PCV13 but it is known to have a lower effectiveness and to provide shorter duration of protection than PCVs [23,24]. Following a national tender in the UK, PCV20 will replace PPV23 in early 2026 for these cohorts [25], and is expected to be more effective in preventing IPD caused by serotypes contained in PCV20 than PPV23. Unlike the United States where all older adults are eligible for the vaccine from 65 years of age, the nationally-funded pneumococcal immunisation programme will replace the single PPV23 dose currently offered to a single annual cohort of adults when they turn 65 years (and not every adult from 65 years of age) and to at-risk

**Table 3**
Count and percentage of cases by vaccine serotype groups (PCV13, aPCV21 and non-vaccine serotypes), broad age group, presentation and deaths (with 7-day case fatality rate [deaths/total cases by group]), July 2023 – June 2024.

| | | Presentation | | | | | | Deaths |
|---|---|---|---|---|---|---|---|---|
| Age group | Vaccines group | Meningitis, n (%) | Bacteraemic Pneumonia, n (%) | Other, n (%) | Septicaemia, n (%) | Unknown, n (%) | Total | n (% [7-day CFR*]) |
| 0–14 | PCV13-only | 5 (29.4) | 5 (29.4) | 2 (11.8) | 2 (11.8) | 3 (17.6) | 17 (100) | 0 (0) |
| | aPCV21 and PCV13 | 24 (57.1) | 8 (19.0) | 2 (4.8) | 4 (9.5) | 4 (9.5) | 42 (100) | 2 (4.8) |
| | aPCV21-only | 72 (31.0) | 91 (39.7) | 7 (3.1) | 25 (10.9) | 34 (14.8) | 229 (100) | 7 (3.1) |
| | Not in vaccine | 13 (29.5) | 16 (36.4) | 5 (11.4) | 4 (9.1) | 6 (13.6) | 44 (100) | 2 (4.5) |
| **Total** | | 114 | 120 | 16 | 35 | 47 | 332 | **11 (3.3)** |
| 15–64 | PCV13-only | 148 (50.3) | 15 (5.1) | 83 (28.2) | 34 (11.6) | 14 (4.8) | 294 (100) | 16 (5.4) |
| | aPCV21 and PCV13 | 179 (56.8) | 13 (4.1) | 57 (18.1) | 33 (10.5) | 33 (10.5) | 315 (100) | 23 (7.3) |
| | aPCV21-only | 608 (55.6) | 72 (6.6) | 164 (15.0) | 161 (14.7) | 88 (8.1) | 1093 (100) | 51 (4.7) |
| | Not in vaccine | 42 (42.4) | 10 (10.1) | 15 (15.2) | 22 (22.2) | 10 (10.1) | 99 (100) | 12 (12.1) |
| **Total** | | 977 | 110 | 319 | 250 | 145 | 1801 | **102 (5.7)** |
| 65+ | PCV13-only | 84 (55.3) | 16 (10.5) | 20 (13.2) | 26 (17.1) | 6 (3.9) | 152 (100) | 22 (14.5) |
| | aPCV21 and PCV13 | 354 (60.8) | 32 (5.5) | 111 (19.1) | 76 (13.1) | 9 (1.5) | 582 (100) | 126 (21.6) |
| | aPCV21-only | 1022 (60.8) | 128 (7.6) | 235 (14.0) | 238 (14.2) | 58 (3.5) | 1681 (100) | 241 (14.3) |
| | Not in vaccine | 167 (60.1) | 28 (10.1) | 34 (12.2) | 41 (14.7) | 8 (2.9) | 278 (100) | 35 (12.6) |
| **Total** | | 1627 | 204 | 400 | 381 | 81 | 2693 | **424 (15.7)** |

* includes post-mortem samples up to 14 days after date of death.

individuals aged <65 years [6]. Currently, the UK childhood immunisation programme continues to include PCV13 and, therefore, those receiving PCV20 because of their age and/or risk conditions will benefit directly from vaccination against the additional serotypes it contains that are not included in PCV13. Following the next tender for the childhood pneumococcal immunisation programme, however, PCV20 could replace PCV13, which will not only provide direct protection against IPD caused by the seven additional PCV20 serotypes in children, but will also provide indirect protection for older children, adults and older adults, which would reduce the net direct benefit of the protection offered by the PCV20 programme for 65 year-olds and at-risk individuals aged <65 years. As such, the added value of PCV20 in the latter population would then decline substantially.

An adult-specific PCV targeting serotypes different from those in PCV20 could, therefore, be beneficial. The 10 serotypes in the aPCV21 that are different to PCV20, for example, are responsible for 30% of cases among those aged ≥65 years. Any such direct protection would be in addition to the PCV20-serotype IPD cases prevented through the indirect protection afforded by a childhood PCV20 programme, but would be limited to the eligible cohort of 65 year-olds and at risk individuals aged <65 years.

Using the most recent mid-year population estimates for England, 624,637 individuals would be offered the vaccine when they turn 65 years. During 2023/24, there were 83 IPD cases with serotyped isolates in 65 year-olds, including 49 aPCV21-only cases that would potentially be covered with an aPCV21 programme for older adults (numbers needed to vaccinate [26], 12,747, assuming 100% vaccine uptake among 65 year-olds). In the second year of the programme, two age cohorts (65 and 66 year-olds) would be protected by the programme. Protection would be cumulative as the programme matures and would depend on the duration of protection offered by aPCV21 in the eligible population. Additionally, protection relies on high vaccine uptake as the vaccine would only provide direct protection because pneumococci belonging to the aPCV21 serotypes would continue to circulate in the population since carriage and transmission is primarily driven by young children [27].

An added concern with using aPCV21 in older adults is that the vaccine does not protect against serotype 4 IPD. This is important in the context of a recent resurgence in serotype 4 IPD, which has been reported among adults experiencing homelessness and adults reporting drug use in the United States, Canada [21,28,29] and adults working in shipyards in Northern Europe [30]. In the US, the ACIP guidelines specifically recommend the use of a PCV containing serotype 4 (e.g. PCV20 or PCV15 in conjunction with PPV23) in geographical areas with high serotype 4 prevalence for eligible individuals with underlying conditions or risk factors such as homelessness and injecting drug use.

In the UK, an expansion of serotype 4 was noted in recent years [13], nearly all in adults. During 2023/24, serotype 4 accounted for 7.4% of all IPD cases overall and was the most common PCV13 serotype among adult cases aged 15–64 years (39.9%, 244/611 of PCV13-serotype cases in this age group) with no cases in children, compared to just 24 isolates of serotype 4 overall in 2019/2020 [13]. Monitoring IPD caused by this serotype will be important for future decisions on PCV use in children and adults.

Another problem with aPCV21 use for adults only is that newer generation vaccines, including PCV24, PCV30 and PCV31 which are currently being developed for the childhood PCV immunisation programme, will include many of the serotypes contained in aPCV21. With the overlap in serotype coverage likely to increase with these newer generation PCVs, the indirect effects of future childhood immunisation programmes will gradually reduce the direct benefits of an adult-only aPCV21 immunisation programme.

### 4.4. Implications of findings

aPCV21 is an innovative approach to tackling serotype replacement disease. If unlimited resources were available, offering aPCV21 to all adults could reduce IPD burden by up to 80%. Most countries, however, offer a restricted pneumococcal immunisation programme targeting primarily at-risk younger adults and offering a single dose of vaccine to older adults reaching a target age, which is 65 years in the UK. Such a programme would offer a limited immediate impact on overall IPD burden, which increases exponentially from 50 years of age, but the benefits would accumulate because one additional cohort will be offered the vaccine each year.

Importantly, however, although case numbers in children remain substantially lower than in older adults, the proportion of IPD cases caused by aPCV21 serotypes is similar. Vaccinating children with aPCV21, although not currently licensed for this age group would not reduce IPD incidence substantially in children because of the direct

protection offered by the vaccine but, by preventing carriage acquisition and onward transmission of aPCV21 serotypes, would also lead to a large reduction in IPD caused by the aPCV21 serotypes across all age groups, including older adults, because of the indirect effects of such a childhood immunisation programme.

Therefore, an alternative strategy could be to offer infants two different PCVs as part of the routine immunisation schedule. This could potentially include one or two priming PCV13 or PCV20 as well as aPCV21 doses followed by a booster of each of the two vaccines in the second year of life. An alternative strategy might be to retain the current infant PCV13 schedule and offer aPCV21 at 12 and 18 months of age with the primary aim of providing indirect protection, not only for older children and adults, but also for infants under 1 year of age who would otherwise not be directly protected by the vaccine. The overlapping serotypes in PCV13 (or a future higher-valent PCV for children) and aPCV21 would only serve to boost immunogenicity for the common serotypes.

Adding a separate aPCV21 schedule in addition to the current PCV in the childhood immunisation programme would also help overcome some of the problems of 'immunogenicity creep' [31], whereby maximum serotype-specific antibody concentrations decline with increasing number of serotypes added to PCV. The effect could potentially lower individual-level protection against some of the vaccine serotypes, or alternatively, provide less protection against carriage which would translate into lower indirect protection at the population-level.

### 4.5. Strengths and limitations

A strength of this analysis is the use of a long-term well-established surveillance system for IPD in England, with high ascertainment of confirmed cases and completion of surveillance questionnaires. The offer of a free serotyping service through the UKHSA national reference laboratory also ensures consistent methodology to support national surveillance. A limitation of the national surveillance is that it only includes invasive cases and, therefore, we did not assess the impact of the different vaccines on non-invasive pneumococcal infections, including pneumonia, sinusitis and otitis media, which make up a higher proportion of the pneumococcal disease cases. Additionally, we did not analyse cases by comorbidity status, and it is possible that the distribution of serotypes causing pneumococcal disease in healthy individuals differ from the distribution of serotypes causing disease in those with underlying conditions. Our conclusions, though relating primarily to IPD, should also be applicable to non-invasive pneumococcal disease given that a large proportion of such cases are likely to be caused by serotypes included in aPCV21.

## 5. Conclusion

Higher valent PCVs have the potential to further reduce the burden of IPD across all age groups in England. A recently licensed PCV for adults, aPCV21, would provide protection against additional pneumococcal serotypes but only to those who are vaccinated. However, given that the additional serotypes in aPCV21 are responsible for a similar proportion of IPD cases across all age groups, use of such a vaccine in the childhood immunisation programme has the potential to provide both direct and indirect protection across the population.

## CRediT authorship contribution statement

**Aryan Nikhab:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Tara Patel:** Formal analysis, Data curation. **Graeme Rooney:** Writing – review & editing, Data curation. **Sobia Wasti:** Writing – review & editing, Data curation. **Fariyo Abdullahi:** Writing – review & editing, Data curation. **Joshua C. D'Aeth:** Writing – review & editing, Data curation. **Seyi Eletu:** Writing – review & editing, Data curation. **David Litt:** Writing – review & editing, Data curation. **Shamez N. Ladhani:** Writing – review & editing, Writing – original draft, Conceptualization.

## Ethics

UKHSA has legal permission to process confidential information for the purpose of national surveillance of communicable diseases without individual patient consent (Regulation 3 of Health Service Regulations 2002) and so ethics committee approval is not required.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Immunisation and Vaccine Preventable Diseases Division has provided vaccine manufacturers with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy (SNL, AN, GR, SW, TP, FA). A cost recovery charge is made for these reports. SNL performs contract research on behalf of St. George's University of London (SGUL) and the UK Health Security Agency (UKHSA) for pharmaceutical companies including vaccine manufacturers but receives no personal remuneration. The Respiratory and Vaccine Preventable Bacteria Reference Unit has received grant funding from vaccine manufacturers for investigator-led research projects on pneumococcal surveillance (DL, JCD, SE). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

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

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