THE PROPORTION OF INVASIVE PNEUMOCOCCAL DISEASE AND PNEUMOCOCCAL PNEUMONIA IN UK ADULTS POTENTIALLY COVERED BY THE 13-VALENT AND NEXT-GENERATION HIGHER-VALENCY PNEUMOCOCCAL CONJUGATE VACCINES UNDER DEVELOPMENT

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BACKGROUND

- In 2006 the UK introduced a pneumococcal conjugate vaccine (PCV) that covered seven serotypes (PCV-7) for routine infant immunisation. This was replaced with a 13 valent PCV (PCV-13) in 2010 which is also used to vaccinate severely immunocompromised individuals *[1]*.
- Routine infant immunisation with both PCV-7 and PCV-13 has resulted in major reductions in the vaccine type (VT) pneumococcal disease burden in the UK across the age range due to direct and indirect (herd) protection *[2]*.
- PCV-13 has an adult indication but is currently not recommended for routine use in this capacity in the UK. At present all UK adults aged 65+ years and those considered at increased risk of pneumococcal infection are offered a single dose of the 23-valent plain pneumococcal polysaccharide vaccine (PPV23). Re-vaccination is recommended for patients with chronic renal disease and asplenia/splenic dysfunction *[1]*.
- UK data show PPV23 has only limited short term effectiveness against invasive pneumococcal disease (IPD) in older adults aged 65+ years with no evidence of any impact at the population level *[3]*. There is also a lack of consistent evidence showing PPV23 effectiveness against adult community acquired pneumonia (CAP) *[4]*.
- Post 2013/14 there has been a rapid increase in IPD in the UK that particularly affects older adults aged 65+years and is especially attributed to several PPV23non13 serotypes [2].
- Next generation higher valency PCVs (PCV-15 and PCV-20) that include PPV23non13 serotypes are now in advanced stages of development and are anticipated to shortly become available for use in adults *[5,6]*.
- The comparative serotype composition of currently available pneumococcal vaccines (PCV-13, PPV23) and next generation higher valency PCVs (PCV-15, PCV-20) is shown in Table 1.

METHODS

- PubMed was searched for recent peer reviewed publications describing the current epidemiology and pneumococcal disease burden in UK adults with insight by age group and individual pneumococcal serotype.
- The main objective was to determine the proportion of serotypes included in PCV-13, PCV-15 and PCV-20 currently causing pneumococcal disease using relevant contemporary adult pneumococcal disease data.

RESULTS

- Two key articles were identified. These contained routine national IPD surveillance data for adults aged 65+ years obtained in 2016/17 from England and Wales *[2]* and data from a study of hospitalised CAP in UK adults aged 16+ years living in Greater Nottingham from September 2013 to August 2018 where pneumococcal serotypes were identified using a urinary monoclonal antibody assay *[7]*. Greater Nottingham consists of the city of Nottingham and the adjoining urban areas of Nottinghamshire and Derbyshire in the East Midlands of England.
- In adults aged 65+ years the proportion of IPD due to serotypes included in PCV-13, PCV-15 and PCV-20 was 22%, 33% and 65% respectively in 2016/17 (Figure 1)
- Between 2013/14 and 2017/18 the overall proportion pneumococcal CAP in adults aged 16+ years due to the serotypes included in PCV-13, PCV-15 and PCV-20 was 35%, 40% and 66% respectively (36%, 39% and 64% in 2017/18) (Figure 2). Available data did not allow further stratification into narrower age bands.
- The majority of IPD in UK adults aged 65+y in 2016/17 caused by PCV-13 serotypes was due to serotype 3 (53% of PCV-13 type IPD, 12% of total IPD). Other notable PCV-13 serotypes were 19A (28% of PCV-13 type IPD, 6% total IPD) and 19F (6% of PCV-13 type IPD, 1% of total IPD). The remaining serotypes included in PCV-13 caused only 3% of the total IPD burden in those aged 65+years in 2016/17.
- Other serotypes not included in PCV-13 that contributed most notably to the total IPD burden in those aged 65+ years in 2016/17 were serotypes 8 (16%), 12F (9%), 22F (7%) and 9N (7%).
- Overall the serotype distribution observed for IPD in older adults aged 65+y and for pneumococcal CAP in adults aged 16+y was broadly similar.
- Serotypes 3, 8 and 12F were also prominent causes of pneumococcal CAP in adults aged 16+ years across the study period (17%, 16% and 5% respectively)
- All thirteen serotypes included in PCV-13 contributed to pneumococcal CAP in UK adults aged 16+years across the study period. Serotype 3 was especially prominent and increased across the study period (from 13% in 2013/14 to 19% in 2017/18)
- The proportion of adult pneumococcal CAP due to serotype 33F declined from 4.5% in 2013/14 to 0.3% in 2017/18.
- The additional serotypes included in PPV23 that are not currently included in any of the next generation PCVs (serotypes 2, 9N, 17F and 20) reflected:
  - 8% of total IPD burden in adults aged 65+ years in 2016/17 (mostly due to serotype 9N)
  - 6% of pneumococcal CAP in adults aged 16+ years across the study period (4% in 2017/18). This adult pneumococcal CAP burden was mainly caused by serotypes 9N, 17F and 20 with no single serotype dominating

DISCUSSION

- Despite strong indirect protection induced by the UK routine infant PCV-13 immunisation programme *[2]* a significant burden of adult pneumococcal disease persists in the UK that could potentially be addressed by directly vaccinating older adults with PCV-13.
  - This is largely due to a small number of vaccine serotypes (19A, 19F and most notably 3)
  - This is possibly because correlates of protection vary by serotype and those serotypes requiring higher thresholds of protection (i.e. serotypes 3, 19A, 19F) may induce only more limited levels of herd protection through routine infant PCV-13 programmes *[8]*.
  - The extent to which this may be an issue for additional serotypes included in next generation higher valency PCVs is unknown at present but remains a possibility
  - Directly vaccinating older adults with next generation higher valency PCVs may therefore be needed to optimally address the pneumococcal disease burden in this age group. Relying on herd immunity alone induced by a paediatric programme may result in a persisting adult disease burden due to certain serotypes where herd immunity is more limited.
- The ability of PCVs to specifically protect against serotype 3 disease is attracting debate *[2]*. However, a recent analysis of data from a large randomised controlled clinical trial suggests that PCVs that include serotype 3 will provide some direct protection in adults against serotype 3 CAP. PCV-13 efficacy against serotype 3 pneumonia in adults aged 65+years was 61.5% (95%CI 17.6-83.4) *[9]*.
- Compared to PCV-13 the serotype composition of higher valency PCVs reflect increasing proportions of serotypes currently causing adult pneumococcal disease in the UK, particularly when serotypes that have recently been rapidly increasing in the UK (e.g. serotypes 8 and 12F) are included.
- At present the serotypes included in PCV-20 reflect a large proportion (~65%) of the adult pneumococcal disease burden in the UK
- Using UK data inclusion of serotypes 22F and 33F only provides a moderate increase compared to PCV-13
- The additional serotypes in PPV23 that are not included in any next generation PCVs currently cause a small proportion of adult pneumococcal disease in the UK (8% of IPD in 2016/17, 4% of pneumococcal CAP in 2017/18).
- In the UK serotype 9N has been an increasing cause of IPD post 2013/14 but is not included in a next generation PCV at present. In the UK serotype 9N IPD affects older individuals and those with underlying co-morbidities and is associated with a higher mortality compared to other serotypes *[10]*. Serotype 9N is a candidate serotype to consider including in future higher valency PCVs in addition to other serotypes that may subsequently emerge as important causes of pneumococcal disease.

FIGURES

Figure 1. The number and proportion of IPD cases due to serotypes included in PCV-13, PCV-15 and PCV-20 in adults aged 65+ years living in England and Wales in 2016/17

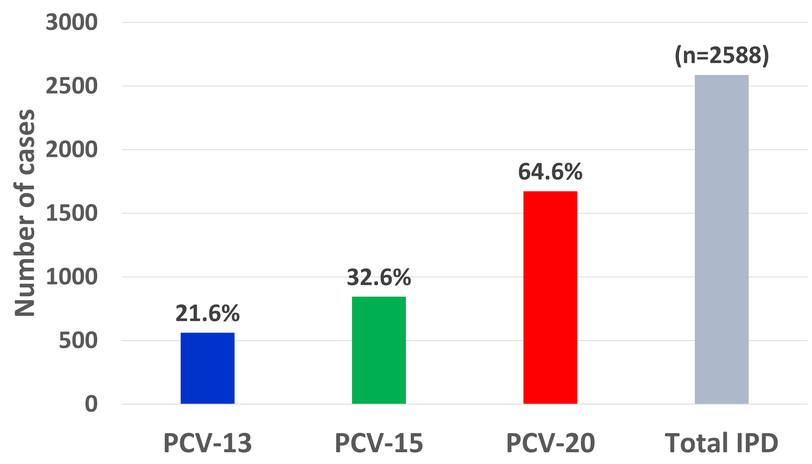
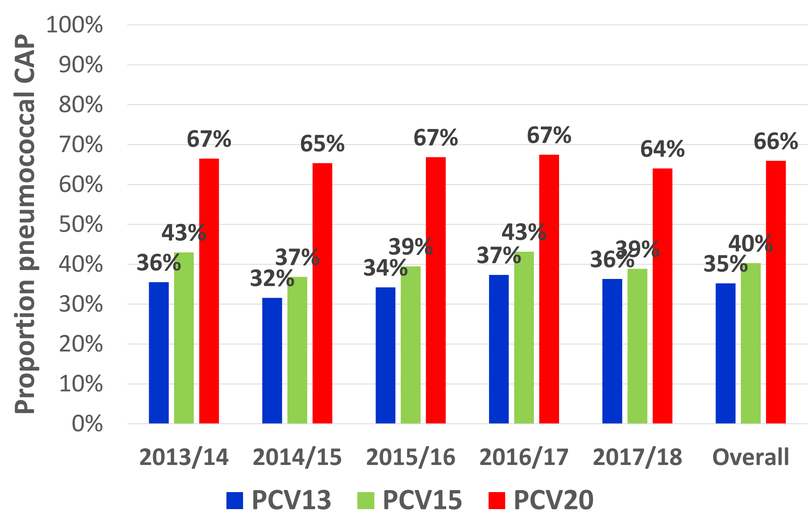


Figure 2. The proportion of PCV-13, PCV-15 and PCV-20 community acquired pneumococcal pneumonia in adults aged 16+ years in Greater Nottingham between 2013/14 and 2017/18



CONCLUSIONS

- ***Directly vaccinating UK adults with PCV-13 could potentially address a significant proportion of the contemporary adult pneumococcal disease burden***
- ***The serotypes included in higher valency next generation PCVs (PCV-15 and PCV-20) reflect increasing proportions of the current adult pneumococcal disease burden in the UK, with ~65% of the burden attributed to those serotypes included in PCV-20***

TABLES

	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A	22F	33F	10A	15B	8	11A	12F	2	9N	17F	20
PPV23	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■
PCV-13	■	■	■	■	■	■	■	■	■	■	■	■	■											
PCV-15	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■									
PCV-20	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■				

Table 1. The comparative serotype composition of currently available pneumococcal vaccines (PCV-13, PPV23) and next generation higher valency PCVs (PCV-15, PCV-20)

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