**Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales: a prospective national observational cohort study, 2000-2017**

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**Summary**

**Background**

Pneumococcal conjugate vaccines (PCVs) have significantly reduced the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes. Replacement disease with non-PCV serotypes, however, remains a concern. We describe the population impact of the 7-valent (PCV7) and 13-valent (PCV13) pneumococcal conjugate vaccines on IPD in England and Wales.

**Methods**

Using national IPD surveillance data for 2016/17, we compared incidence rate ratios (IRRs) against pre-PCV13 (2008/09-2009/10) and pre-PCV7 (2000/1-2005/06) baselines. We also estimated the number of IPD cases prevented since PCV introduction.

**Findings**

In 2016/17, overall IPD incidence (9.87/100,000; 5,450 cases) across all age groups was 37% lower (IRR, 0.63; 95%CI, 0.60-0.65) compared to the pre-PCV7 period (14.79/100,000; 8,167 cases) and 7% lower (IRR, 0.93; 95%CI, 0.89-0.97) than pre-PCV13 incidence (10.13/100,000; 5,595 cases). By 2016/17, PCV7-type IPD incidence across all age groups had fallen by 97% (0.24/100,000; IRR, 0.03; 95%CI, 0.02-0.04) compared to the pre-PCV7 period, while additional PCV13-type IPD declined by 64% (1.66/100,000; IRR, 0.36; 95%CI, 0.32-0.40) since PCV13 introduction. IPD incidence due to non-PCV13 serotypes doubled (7.97/100,000; IRR, 1.97; 95%CI, 1.86-2.09) since PCV7 introduction, and accelerated since 2013/14, especially serotypes 8, 12F and 9N, which were responsible for >40% of IPD cases by 2016/17. IPD incidence in <5 year-olds remained stable since 2013/14, with nearly all replacement disease occurring in adults. We estimated 38,366 IPD cases have been prevented in the 11 years since PCV7 introduction.

**Interpretation**

Both PCV7 and PCV13 have had a major impact in reducing the burden of IPD in England and Wales; recent rapid increases in some non-PCV13 serotypes, however, are compromising the benefits of the programme.

**Funding**

Public Health England

**Introduction**

Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes.1,2 Young children are the main carriers of *Streptococcus pneumoniae* and immunising this age-group not only protects them against pneumococcal disease but also provides indirect (herd) protection to the rest of the population through reduction in carriage and onward transmission of vaccine serotypes.3,4

The United Kingdom introduced the 7-valent PCV (PCV7) into the routine childhood immunisation programme in September 2006, at two, four and 12-13 months of age, alongside a 12-month catch-up programme for children aged <2 years.5 From April 2010, the 13-valent PCV (PCV13) replaced PCV7, with no catch-up.6 PCVs are also recommended for severely immunocompromised children and adults, in addition to the 23-valent pneumococcal polysaccharide vaccine (PPV23). Both PCV7 and PCV13 have consistently achieved immunisation coverage of >90% in the targeted age-groups, with large reductions in vaccine-type IPD across all age-groups.5,6 Within two years of PCV7 introduction, carriage studies found that children aged <5 years had a 93% lower odds of carrying a PCV7 serotype when compared to a previous carriage study conducted in 2001/02.4 The odds of carrying any of the extra six PCV13 serotypes increased by 38%, but declined by 95% within two years after PCV13 introduction.4

After both vaccine introductions, an increase in IPD due to non-PCV serotypes was observed. Four years after PCV7 introduction, IPD due to non-PCV7 serotypes increased across all age-groups by 19%.5 A similar increase of 25% was observed with non-PCV13 serotypes four years after PCV13 replaced PCV7.6 By the 2013/14 epidemiological year (running from July to June), despite an increase in IPD due to non-PCV13 serotypes, overall IPD rates had fallen by 56% and 32% compared to pre-PCV7 and pre-PCV13 baselines, respectively.6 For the first time since PCV introduction, however, IPD rates in <5 year-olds increased between 2012/13 and 2013/14, suggesting that the maximum benefit of the childhood PCV13 programme had been achieved.6 Here, we report age- and serotype-specific trends in IPD in England and Wales until the end of 2016/17, seven years after PCV13 introduction.

**Methods**

Public Health England (PHE) conducts national IPD surveillance in England and Wales as described previously.6 Invasive pneumococcal isolates are electronically reported by hospital laboratories to PHE and routinely linked – using personal identifiers common to both datasets – with isolates submitted to the PHE Reference Laboratory for confirmation and serotyping. Electronic reports are actively followed-up to ensure sample referral to the reference laboratory; improved automatic linkage and de-duplication processes were implemented in 2015. For serotyping, isolates were grown overnight in Todd Hewitt broth at 35°C with 5% CO2, harvested by centrifugation at 453 g for 30 min, then re-suspended in a small residual volume of broth and subjected to slide agglutination tests with standard antisera (Statens Serum Institut, Copenhagen, Denmark.7

PCV coverage in the UK has remained consistently high, with 94% receiving their primary immunisations by 12 months and 92% receiving their 12-month booster by 24 months of age.8 A single dose of PPV23 is offered to adults and children aged ≥2 years who are at increased risk of IPD,9 as well as older adults aged ≥65 years.10 IPD was defined as *S. pneumoniae* isolated from a normally sterile site. Repeat samples within 30 days from the same individual were regarded as part of the same episode. Non-culture pneumococcal PCR-testing is rarely performed by local hospital laboratories, is usually restricted to CSF and pleural fluid samples, and does not provide serotype. Because of this, PCR-confirmed cases (accounting for <4% of total IPD cases annually) were excluded from trends analyses.

**Data analysis**

Annual incidence was calculated by dividing the number of corrected cases by the population size for that year in England and Wales.11 The proportion of total isolates serotyped improved over time, from 48% in 2000/01 to 79% in 2005/06, 90% in 2009/10 and remained between 91% and 97% in subsequent years. Missing age (<1% of cases) and serotype information was corrected assuming that those reports had the same age and serotype distribution as those with complete data in that year. Changes in pre-PCV7 surveillance sensitivity over time were corrected by adjusting IPD incidence before 2009/10, according to the upward trend in age-specific total IPD rates seen in the pre-PCV7 period, as described previously.5 Since 2010, diagnostic microbiology laboratories in England and Wales are required under Health Protection Legislation to notify all confirmed IPD cases to Public Health England or Public Health Wales.6 Before 2010, reporting was voluntary. Consequently, pre-PCV7 trends were assumed to increase until 2009/10 and then stabilise thereafter. For example, pre-PCV7 IPD reports in <2 year-olds increased by 1·67% annually, so for 2005/06 (4 years before 2009/10), an inflation factor of 1.0167⁴=1∙07 was applied to the raw numbers for that year. Cases were stratified by PCV7-type (4, 6B, 9V, 14, 18C, 19F, and 23F), additional PCV13-type (1, 3, 5, 6A, 7F, and 19A) and non-PCV13 serotypes. A 10-valent vaccine (PCV10), which includes serotypes 1, 5 and 7F in addition to the PCV7 serotypes, is licensed and used in other countries. For the pre-PCV13 baseline, we averaged data for 2008/09 and 2009/10 because there was a relatively large increase in non-PCV13 IPD in <5 year-olds in 2008/9, which returned to the 2007/08 rate in 2009/10.6 Incidence rate ratio (IRR) was used to compare overall and age-specific changes in IPD incidence during 2016/17 (one year) with the average incidence during the two years prior to PCV13 introduction (2008/09-2009/10) and with the six pre-PCV7 baseline years (2000/01-2005/06) using Poisson regression on uncorrected counts with an offset for denominators (person-years), proportion of reports missing age or serotype each year, and the underlying trend correction factors. For the all-age analysis, age-group was included in the model to adjust for the changing age profile of the population over time. To account for extra-Poisson variability between years, the confidence intervals were inflated on the basis of the extra-Poisson variability seen in the 2000–06 corrected data (a period without interventions).

Cases prevented were estimated as the difference between the expected number of cases by age-group using the corrected trends in the absence of vaccination and the observed number of cases after the introduction of each vaccine. A P value of <0·05 was considered significant for overall and serotype group comparisons.

**Ethics approval**

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases (<http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made>). This includes PHE’s responsibility to monitor the safety and effectiveness of vaccines.

**Role of the funding source**

IPD surveillance is internally funded by PHE. The authors are responsible for the study design, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

**Results**

A total of 90,233 laboratory-confirmed IPD cases were reported in England and Wales over the 17-year surveillance period. The (uncorrected) number of IPD cases declined from a peak of 6,346 in 2005/06 to 4,053 in 2013/14, before increasing to 5,760 in 2016/17, when PCV7 serotypes accounted for 2.4% (n=134) of the 5,570 (96.7%) cases with serotyped isolates, the extra PCV10 serotypes 1.7% (n=96), the additional PCV13 serotypes 15.1% (n=842) and non-PCV13 serotypes 80.8% (n=4,498).

Compared to the pre-vaccine period (2000/01-2005/06), overall IPD incidence declined until 2013/14 to 7·12/100,000, before increasing to 9·87/100,000 in 2016/17 (Table 1, Figure 1). In 2016/17, IPD incidence across all ages was 37% lower (IRR, 0.63; 95%CI, 0.60-0.65) compared to the pre-PCV7 period but only 7% lower compared to the pre-PCV13 period (IRR, 0.93; 95%CI, 0.89-0.97). (Table 1). This was because the large reductions in vaccine-serotype IPD were offset by large increases in non-PCV13 IPD. In those aged <45 years, there were significant reductions in IPD compared with the pre-PCV13 baseline, ranging between 26% and 59%. In older age groups, where non-PCV13 increases were the largest, and reductions in PCV13-type IPD the smallest, IPD rates in 2016/17 were not significantly different from the pre-PCV13 baseline (Figure 2).

By 2016/17, PCV7-type IPD rates fell by 97% across all age-groups since PCV7 introduction (Table 1, Figure 1), with most cases occurring in ≥65 year-olds (74/134, 55%; mainly serotype 19F [n=40], serotype 14 [n=11] and serotype 6B [n=9]) and 45-64 year-olds (31/134, 23%; mainly serotypes 19F [n=15] and serotype 4 [n=9]). Only five PCV7-type IPD cases (4%) occurred in children aged <15 years (four 19F, one 23F).

IPD due to the additional PCV13 serotypes increased after PCV7 introduction and then declined when PCV13 replaced PCV7 in 2010 (Supplement Figure 1). Compared to 2008/09-2009/10 (incidence, 4·46/100,000), the incidence of IPD due to the extra PCV13-types declined to 1·45/100,000 in 2013/14 before increasing to 1·66/100,000 in 2016/17 (IRR, 0·36; 95% CI, 0·32-0·40) (Figure 1, Table 1). Whilst serotypes 1 (serotyped cases: 87 to 7) and 7F (237 to 89) continued to decline between 2013/14 and 2016/17, serotypes 3 (222 to 525) and 19A (202 to 310) increased. During the last three epidemiological years, 82% of serotype 19A IPD cases (704/857; age not known for 2 isolates) were in adults aged ≥45 years; serotype 19A IPD cases among ≥65 year-olds increased from 100 in 2013/14 to 178 in 2016/17, and from 56 to 84 cases among 45-64 year-olds. In <5 year-olds, serotype 19A IPD declined from a peak of 93 cases in 2009/10 to 7 in 2013/14 before increasing to 14, 13 and 12 cases in subsequent years. There were very few cases due to serotypes 5 (range, 0-8/year) and 6A (range, 7-16/year) during 2013/14-2016/17.

Serotype 3 IPD incidence fluctuated across the surveillance period, with the lowest incidence in 2013/14, followed by an increase in the next three years (Figure 3). In 2016/17, ≥65 year-olds were responsible for 65% (340/525) of serotype 3 IPD cases, followed by 45-64 (n=125, 24%) and 15-44 year-olds (n=34, 7%). These age-groups were responsible for nearly all the recent increase, although small year-on-year increases were also observed in <5 year-olds (7 to 19 cases) and 5-9 year-olds (1 to 4 cases).

**Non-PCV13 Serotypes**

IPD incidence due to non-PCV13 serotypes increased across all age groups after PCV7 introduction, and accelerated in the last three years (Figure 1 and 2). Among ≥65 year-olds, the increase was noticeable soon after PCV7 introduction, whilst among 45-64 year-olds and 15-44 year-olds increases only became apparent after PCV13 introduction, and especially in the last three years (Figure 2). In 2016/17, non-PCV13 serotypes were responsible for 78-88% of IPD cases in each age-group.

The individual non-PCV13 serotypes exhibited variable trends over time; some serotypes increased after PCV7 introduction and either continued to increase (23A, 23B, 16F, 31, 35B, 35F, 38), plateaued (22F) or declined (24F), whilst others increased mainly after PCV13 introduction (8, 12F, 9N, 15A, 15B/C) (Figure 4; Supplementary Figure 2). Vaccine-related serotype 6C IPD increased rapidly after PCV7 introduction until 2009/10, and then declined rapidly after PCV13 was introduced (Figure 3).

Three of the emerging serotypes (8, 12F and 9N) exhibited rapid increases in the last three years and are now responsible for more than 40% of total IPD cases; serotype 8 alone was responsible for 20% in 2016/17 (Table 2; Supplementary Figure 1). Eight of the ten most prevalent serotypes causing IPD in 2016/17 are included in the 23-valent pneumococcal polysaccharide vaccine (PPV23). These serotypes had variable contribution to IPD cases in different age groups (Table 2; Supplementary Table 1). The recent increase in IPD due to these additional PPV23 serotypes was also evident among ≥65 year-olds (Supplement Figure 3), despite a national PPV23 immunisation programme for 65 year-olds since 2003.

**Cases prevented**

Overall, we estimated 38,366 IPD cases were prevented since PCV7 introduction 11 years ago, even after taking into account serotype replacement disease after both vaccine introductions. There were 39,975 fewer cases due to PCV7 serotypes and 4,479 fewer cases due to PCV13 serotypes (after accounting for the 1,396 additional PCV13-serotype IPD cases after PCV7 introduction), compared to an estimated 6,088 increase in non-PCV13 IPD. During the PCV7 period (2006/7-2009/10), an estimated 9,735 cases were prevented, followed by 28,631 cases during 2010/11-2016/17. Overall, 9,116 cases were prevented in children (<15 year-olds) and 29,250 cases in adults (≥15 year-olds).

**DISCUSSION**

The UK was one of the first countries to replace PCV7 with PCV13 in April 2010. In England and Wales, the maximum benefit from the childhood PCV programme was achieved four years after PCV13 introduction. From 2013/14, IPD incidence increased in most age groups such that the overall IPD incidence in 2016/17 was only 7% lower than the pre-PCV13 baseline. Compared to the pre-PCV7 period, however, there was still a 37% reduction in overall IPD incidence. Children under 15 years continue to benefit hugely from the programme, with 72-81% and 36-59% lower IPD rates compared to the pre-PCV7 and pre-PCV13 periods, respectively. While PCV7-type IPD continued to decline, cases due to two of the six additional PCV13 serotypes, namely serotypes 3 and 19A, unexpectedly plateaued in 2013/14 and then increased, mainly in adult age-groups. The 6A component of PCV13 was expected to provide some cross-protection against 6C on the basis of immunogenicity studies, and this has been confirmed by the continuing decline in IPD due to this serotype in both children and adults. The overall decline in PCV13 type disease was, however, offset by an increase in non-PCV13 IPD, especially serotypes 8, 12F and 9N, since 2013/14. These increases were observed throughout England and Wales with no geographic or temporal clustering, as has been reported with some of these serotypes elsewhere.12 Overall, we estimate that nearly 40,000 cases of IPD have been prevented since PCV7 introduction 11 years ago, even after taking into account the additional cases due to serotype replacement disease.

Our national findings confirm a recent report of regional trends in North England.13 Other countries have also reported large declines in PCV13-type IPD, although the extent of replacement disease with non-PCV13 serotypes has been variable.14-21 Comparing the current UK situation with other countries, however, is difficult because most reports to date have been limited to the first three to four years after PCV13 implementation, a period when the increase in non-PCV13 IPD in England and Wales was not so marked. In the US, up until 2015, no increase in non-PCV13 IPD has been observed.22 In contrast, in Israel, where PCV13 gradually replaced PCV7 from November 2010, overall IPD incidence in ≥65 year-olds remained stable during 2012/13-2014/15 after an initial decline as the reduction in PCV13-type IPD was offset by a progressive increase in non-PCV13 IPD, which had an IRR was 1.85 (95% CI, 1.38–2.47) in 2014/15 compared with the pre-PCV13 baseline.19 Also, in Ireland, where PCV13 replaced PCV7 in December 2010, IPD incidence due to the serotypes covered by PPV23 only and non-PPV23 serotypes increased significantly by June 2016 (IRR 2·17 and 3·43, respectively), with no overall reduction in IPD from the pre-PCV13 baseline.15 Possible reasons for the variable impact of PCV13 on replacement disease include differences in emerging serotypes after PCV7 introduction potentially reflecting differences in longer term secular trends in individual non-PCV13 serotypes between countries, contribution of PCV13 serotypes to total IPD prior to PCV13 introduction, vaccination schedules and coverage, as well as differences in clinical practices for investigating and treating patients with suspected IPD, case ascertainment and surveillance methodologies.

Nasopharyngeal carriage studies after PCV7 introduction revealed complete replacement with non-PCV7 serotypes among vaccinated UK children and their family members.3 Notably, the additional PCV13 serotypes were responsible for only 14% of carried serotypes in 2008/09 (mainly serotypes 3, 7F and 19A) but 48% of invasive disease, indicating that these serotypes were highly invasive, i.e. had a high case:carrier ratio (CCR).3 Because the non-PCV13 serotypes identified in carriage had lower CCRs, the introduction of PCV13 was expected to further reduce IPD cases.3 At that time, however, it was already noted that some non-PCV13 serotypes causing IPD (e.g. 8, 12F and 22F) were rarely carried and, therefore, had high CCRs, raising concerns that these serotypes could potentially reduce the overall benefits of PCV13. Six years after PCV13 introduction, these three serotypes are indeed the most prevalent non-PCV13 serotypes causing IPD. Their impact on mortality, however, may be lower because of the negative correlation between invasiveness and case fatality rate;23 this is currently being assessed in our dataset.

In the UK, the maternal immunisation programme against pertussis began in October 2012 and was associated with lower serotype-specific pneumococcal antibody responses after primary immunisation in infants whose mothers were vaccinated antenatally.24 This could potentially affect the protection afforded for some PCV13 serotypes, but does not explain the recent increase in non-PCV13 IPD. Among the PCV13 serotypes, vaccine effectiveness estimate for 19A (67%; 95% CI, 33 to 84%) is lower than for other serotypes and non-significant for serotype 3 (26%; -69 to 68%);2 these two serotypes are also the most prevalent causes of vaccine failure in children.25 The fluctuating incidence of serotype 3 IPD throughout the surveillance period adds to the concerns that the vaccine does not provide any direct or indirect protection against this serotype.6,26 On the other hand, serotype 19A IPD cases declined rapidly across all age-groups after PCV13 introduction,5 but since 2013/14, there has been a small increase, particularly among ≥65 year-olds, indicating that this serotype continues to circulate six years after PCV13 introduction, as suggested by recent nasopharyngeal carriage studies in PCV13-immunised children.27 An additional infant priming dose may improve protection against PCV13-type IPD but, currently, the small number of cases nationally would not favour such a recommendation. In the US, where a three-dose infant priming schedule is used, PCV13-type IPD incidence in <5 year-olds has not declined since 2013.22

During the winter of 2014/15, when the aggressive increase in non-PCV13 IPD was first apparent, the UK experienced high influenza activity with poor protection offered by the influenza vaccine because of antigenic and genetic mismatch between circulating viruses and the vaccine strain.28 In 2013/14, too, the UK initiated the live attenuated influenza virus (LAIV) vaccination programme for young children. Both these factors could have led to an alteration in the nasopharyngeal microbiome,29 potentially altering the pneumococcal serotype profile in carriage and thus disease. It is difficult to speculate why this would only affect certain serotypes, unless these replacing serotypes, like the additional three PCV10 serotypes, had a predilection towards respiratory disease and were, therefore, preferentially affected by interactions with influenza.

In the UK, a PPV23 immunisation programme has been in place for 65 year-olds and at-risk individuals aged ≥2 years since 2003. Despite providing short-term individual protection against IPD, PPV23 given to >70% of ≥65 year-olds has not had any impact on disease incidence in the vaccine-eligible age-group; indeed, IPD due to many of the additional PPV23 serotypes increased after both PCV7 and PCV13 implementation in the childhood programme, despite elderly PPV23 vaccine coverage remaining constant in recent years.10.

The decline in IPD during the first four years after PCV13 replaced PCV7 was comparable to that observed after PCV7 introduction,6 but the subsequent increase since 2013/14 was unexpected. This will have a negative impact on health economic modelling for PCVs, especially because cost-effectiveness is largely driven by reductions in adults IPD through indirect protection as well as non-invasive pneumococcal disease, including community-acquired pneumonia and otitis media.30

**Strengths and Limitations**

The strength of this study lies in the long-term population-based surveillance, with a national reference laboratory that serotypes nearly all invasive isolates. Although we do not audit completeness of laboratory reporting, since 2010, there is a statutory requirement for diagnostic laboratories to report clinically significant infections to PHE; this process is now automated through electronic reporting. Our analysis is based on national surveillance and does not establish a causal relationship between the immunisation programme and observed trends. Changes in IPD due to specific serotypes, for example, may be due to secular trends, which could change in the future, without any intervention, as was observed with serotype 1 which declined after PCV7 introduction.5 We are currently following all IPD cases to assess disease severity and outcomes of IPD due to the emerging serotypes. This information will play a critical role when evaluating PCVs in future health economic models. Our study is limited to IPD cases and the greatest benefits will potentially occur through prevention of the large numbers of non-invasive pneumococcal infections.

**Conclusions**

The benefits of both PCV7 and PCV13 in preventing IPD cases in England and Wales are undeniable, with approximately 38,400 cases prevented during the first 11 years of the programme. Small increases in IPD due to non-PCV serotypes were observed after the introduction of both vaccines but, after four years of PCV13 use, IPD due to several non-PCV13 serotypes increased rapidly, for reasons as yet unknown. Most of the increase occurred in adults aged 45 years, particularly 65 year-olds who have the highest IPD incidence. Children continue to benefit greatly from the PCV13 programme and overall IPD incidence remains significantly lower than in the pre-PCV7 era. However, the recent increases in non-PCV13 IPD are compromising the benefits of the PCV programme and will need careful monitoring in the coming years. Higher valency PCVs should include these emerging serotypes whilst we await a universal pneumococcal vaccine.

**Research in context**

**Evidence before this study**

We searched PubMed for “pneumococcal conjugate vaccine”, “impact”, “indirect/herd protection”, “trends”, “serotype replacement”, “population” and “reduction/decline in invasive disease”. We searched for population-based studies reported in the English language that included all age groups and compared trends in vaccine-type and non-vaccine type invasive pneumococcal disease (IPD) before and after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13), published between January 2000 and June 2017. Countries with established national childhood PCV13 programmes have reported additional reductions in overall and PCV13-type IPD incidence and hospitalisation rates after vaccine introduction. IPD due to PCV7 serotypes continued to decline during the PCV13 period, with additional declines due to prevention of IPD caused by the extra PCV13 serotypes across all age groups through herd protection. The reduction in IPD incidence after PCV13 introduction was generally lower when compared to the same post-implementation period after PCV7 introduction. The overall increase in replacement disease due to non-PCV13 serotypes across all age groups has been variable, ranging from 0% to 106% up to 4 years after PCV13 introduction. Data on longer-term trends after PCV13 introduction in different settings are lacking.

**Added Value of This Study**

We analysed enhanced national surveillance data covering a population of 55 million people across England and Wales over 17 years, up to the seventh year after PCV 13 introduction. Whilst the introduction of PCV7 in 2006 and its replacement with PCV13 in 2010 have both resulted in significant reductions in IPD cases across all age groups through direct and indirect (herd) protection, we observed significant and unexpected changes after four years of PCV13 use, with rapid increases in IPD due to specific non-vaccine serotypes since 2013/14, notably serotypes 8, 9N and 12F. The increase in numbers of cases was predominantly in adults and especially those aged 65 years and over where IPD incidence is highest.. The three serotypes now account for more than 40% of all IPD cases, and are rarely found in carriage, indicating that they have are highly invasive. At the same time, IPD due to two of the six additional PCV13 serotypes, namely serotypes 3 and 19A, unexpectedly plateaued across all age groups since 2013/14 and then increased, mainly in the older adult age-groups. Six years after PCV13 introduction, the additional benefits of this higher-valent vaccine has been nearly abolished by replacement disease, although there remains a 34% reduction in overall IPD incidence compared to the pre-PCV7 baseline. Overall, however, we estimate that nearly 38,400 cases of IPD have been prevented in the 11 years since PCV7 introduction, even after taking into account the additional cases due to serotype replacement disease.

**Implications of the Available Evidence**

Pneumococcal conjugate vaccines have prevented large numbers of IPD cases over the past decade, with children continuing to benefit greatly from both PCV7 and its replacement with PCV13. The recent and unexpected rapid increase in IPD due to some highly-virulent, non-vaccine serotypes in England and Wales awaits confirmation in other settings with surveillance databases sufficiently large to monitor serotype-specific trends in IPD and with data that extend more than 5 years after PCV13 introduction. If confirmed elsewhere, our findings suggest that higher valency PCVs should include these rapidly emerging serotypes whilst we await a universal vaccine that is not serotype-dependent.

**Acknowledgements**

We thank Mel Kephalas and Rashmi Malkani of the Immunisation Department at PHE for the follow-up of unserotyped isolates. We are grateful to Pauline Waight who managed the pneumococcal surveillance prior to 2016. We thank Catrin Moore for reporting invasive pneumococcal disease cases in southern England serotyped by the John Radcliffe Hospital Oxford (Oxford, UK) laboratory. We also thank the staff at laboratories in England and Wales who referred isolates for serotyping and provided additional information on request.

**Author contributions**

SC was responsible for the management of the epidemiological surveillance data. SNL was the clinical lead for pneumococcal surveillance and wrote the first draft of the report. CLS and NKF were the scientific leads for the national reference laboratory surveillance activities. AD and NJA were responsible for the statistical analysis. All authors contributed to the data interpretation and read, commented on, and approved the final version of the report.

**Declaration of interests**

CLS and NKF as employees of the Respiratory and Vaccine Preventable Bacteria Reference Unit have received research funding from Pfizer and GlaxoSmithKline but receive no personal remuneration. SNL and RB do contract research for vaccine manufacturers (including GSK, Pfizer, and Sanofi Pasteur) on behalf of St George’s University of London and Public Health England (London, UK), respectively, but receive no personal remuneration. The Immunisation, Hepatitis, and Blood Safety Department has provided vaccine manufactures with postmarketing surveillance reports on vaccine preventable diseases, including pneumococcal infections, which the companies are required to submit to the UK Licensing Authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. EM, AD, and NJA declare no competing interests.

**Table 1: Number of cases (corrected^ and raw\*) and incidence of invasive pneumococcal disease in 2016/17 compared with the baseline average of 2008/09 to 2009/10 (2008-10) by age and serotype grouping**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Age (years)* | *Serotype* | *2000-06 corrected (raw) cases* | *2000-06 incidence per 105* | *2008-10 corrected (raw) cases* | *2008-10 incidence per 105* | *2016/17 corrected (raw) cases* | *2016/17 incidence* *per 105* | *IRR 2016/17 vs·* *2000-06* | *95% CI \*\** | *IRR*  *2016/17 vs:*  *2008-10* | *95% CI* |
| **<2** | **All cases** | **686 (525)** | **49·00** | **302 (297)** | **21·59** | **195 (195)** | **13.90** | **0.28** | **0.23-0.35** | **0.64** | **0.51-0.82** |
|  | PCV7 | 501 (286) | 35·78 | 20 (19) | 1·44 | 1 (1) | 0.07 | 0.00 | 0.00-0.04 | 0.05 | 0.01-0.91 |
|  | PCV13only | 100 (58) | 7·12 | 174 (160) | 12·44 | 22 (21) | 1.54 | 0.22 | 0.11-0.40 | 0.12 | 0.06-0.23 |
|  | Non-PCV13 | 85 (48) | 6·10 | 108 (99) | 7·70 | 172 (167) | 12.28 | 2.01 | 1.55-2.70 | 1.59 | 1.18-2.15 |
| **2-4** | **All cases** | **304 (189)** | **15·31** | **154 (147)** | **7·76** | **80 (88)** | **4.02** | **0.26** | **0.19-0.36** | **0.52** | **0.37-0.73** |
|  | PCV7 | 216 (101) | 10·88 | 15 (14) | 0·78 | 2 (2) | 0.10 | 0.01 | 0.00-0.06 | 0.12 | 0.01-0.98 |
|  | PCV13only | 59 (29) | 2·98 | 98 (90) | 4·96 | 11 (12) | 0.57 | 0.19 | 0.08-0.43 | 0.12 | 0.05-0.27 |
|  | Non-PCV13 | 29 (13) | 1·46 | 40 (36) | 2·02 | 66 (70) | 3.35 | 2.29 | 1.47-3.72 | 1.66 | 1.04-2.70 |
| **5-14** | **All cases** | **315 (146)** | **4·93** | **144 (135)** | **2·25** | **59 (63)** | **0.92** | **0.19** | **0.13-0.27** | **0.41** | **0.27-0.61** |
|  | PCV7 | 129 (38) | 2·01 | 26 (23) | 0·41 | 2 (2) | 0.03 | 0.02 | 0.00-0.12 | 0.08 | 0.01-0.61 |
|  | PCV13only | 131 (47) | 2·05 | 82 (72) | 1·29 | 9 (9) | 0.14 | 0.07 | 0.03-0.17 | 0.11 | 0.04-0.29 |
|  | Non-PCV13 | 56 (16) | 0·87 | 35 (31) | 0·55 | 48 (47) | 0.75 | 0.85 | 0.55-1.52 | 1.36 | 0.78-2.34 |
| **15-44** | **All cases** | **1853 (878)** | **8·19** | **1065 (1004)** | **4·71** | **783 (778)** | **3.46** | **0.42** | **0.37-0.47** | **0.74** | **0.65-0.83** |
|  | PCV7 | 725 (190) | 3·20 | 122 (99) | 0·54 | 25 (24) | 0.11 | 0.04 | 0.02-0.06 | 0.21 | 0.11-0.39 |
|  | PCV13only | 588 (172) | 2·60 | 566 (467) | 2·50 | 95 (90) | 0.42 | 0.16 | 0.11-0.20 | 0.17 | 0.12-0.23 |
|  | Non-PCV13 | 541 (142) | 2·39 | 376 (311) | 1·66 | 662 (625) | 2.93 | 1.22 | 1.09-1.47 | 1.76 | 1.50-2.06 |
| **45-64** | **All cases** | **2380 (1120)** | **17·12** | **1483 (1393)** | **10·67** | **1485 (1587)** | **10.69** | **0.62** | **0.57-0.67** | **1.00** | **0.92-1.10** |
|  | PCV7 | 1024 (277) | 7·36 | 219 (179) | 1·57 | 30 (31) | 0.21 | 0.03 | 0.01-0.05 | 0.14 | 0.08-0.24 |
|  | PCV13only | 577 (170) | 4·15 | 634 (530) | 4·56 | 232 (241) | 1.67 | 0.40 | 0.30-0.46 | 0.37 | 0.30-0.45 |
|  | Non-PCV13 | 779 (207) | 5·60 | 631 (528) | 4·54 | 1224 (1272) | 8.80 | 1.57 | 1.44-1.81 | 1.94 | 1.72-2.19 |
| **≥65** | **All cases** | **3063 (2650)** | **34·23** | **2482 (2443)** | **27·74** | **2588 (3035)** | **28.93** | **0.85** | **0.80-0.89** | **1.04** | **0.98-1.11** |
|  | PCV7 | 1587 (792) | 17·73 | 413 (359) | 4·61 | 65 (74) | 0.73 | 0.04 | 0.03-0.06 | 0.16 | 0.11-0.22 |
|  | PCV13only | 621 (325) | 6·94 | 927 (813) | 10·36 | 494 (562) | 5.52 | 0.79 | 0.67-0.88 | 0.53 | 0.46-0.61 |
|  | Non-PCV13 | 855 (426) | 9·55 | 1142 (1001) | 12·76 | 2030 (2310) | 22.68 | 2.37 | 2.21-2.61 | 1.78 | 1.63-1.94 |
| **All ages \*\*\*** | **All cases** | **8167 (5609)** | **14·79** | **5595 (5426)** | **10·13** | **5450 (5760)** | **9.87** | **0.63** | **0.60-0.65** | **0.93** | **0.89-0.97** |
| PCV7 | 4191 (1704) | 7·59 | 809 (692) | 1·46 | 131 (134) | 0.24 | 0.03 | 0.02-0.04 | 0.16 | 0.12-0.20 |
| PCV13only | 1852 (804) | 3·35 | 2466 (2134) | 4·46 | 918 (938) | 1.66 | 0.43 | 0.39-0.47 | 0.36 | 0.32-0.40 |
|  | Non-PCV13 | 2124 (862) | 3·85 | 2320 (2008) | 4·20 | 4401 (4498) | 7.97 | 1.97 | 1.86-2.09 | 1.80 | 1.69-1.92 |

\* Case numbers may differ slightly from previous publications because of improved linkage, automated de-duplication, additional serotyping data, surveillance questionnaire returns, and small changes in case inclusion criteria.

\*\* The IRR was calculated for the corrected incidence at the two time points; 95% confidence interval inflated from a Poisson interval based on over-dispersion of 2.1 seen from modelling 2000-06 pre-PCV7 invasive pneumococcal disease data.

^ corrected for proportion serotyped, missing age, denominator compared to 2009/2010 and for the trend in total IPD up to 2009/10 (after which no trend correction was applied).

\*\*\* Age-standardised incidence and IRR are reported for ”all ages” group

IRR: incidence rate ratio, CI: confidence interval, PCV7: serotypes in the 7-valent pneumococcal conjugate vaccine (PCV7), PCV13only: serotypes in the 13-valent pneumococcal conjugate vaccine (PCV13) but not the PCV7 vaccine, non-PCV13: serotypes that are not in PCV13.

**Table 2.** Mo**st prevalent serotypes causing IPD by age group during the 2016/17 epidemiological year in England and Wales.** Serotypes, 3, 19A and 7F are covered by the 13-valent pneumococcal conjugate vaccine (PCV13).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Serotype** | **<5 years** | **5-64 years** | **65+ years** | **All ages \*** |
| 8 | 33 (10.0%) | 621 (27.2%) | 463 (15.7%) | 1,120 (20.1%) |
| 12F | 47 (14.2%) | 408 (17.9%) | 275 (9.3%) | 730 (13.1%) |
| 3 | 23 (6.9%) | 159 (7.0%) | 340 (11.5%) | 525 (9.4%) |
| 9N | 9 (2.7%) | 159 (7.0%) | 207 (7.0%) | 375 (6.7%) |
| 22F | 17 (5.1%) | 141 (6.2%) | 216 (7.3%) | 375 (6.7%) |
| 19A | 13 (3.9%) | 119 (5.2%) | 178 (6.0%) | 310 (5.6%) |
| 15A | 18 (5.4%) | 63 (2.8%) | 152 (5.2%) | 234 (4.2%) |
| 33F | 17 (5.1%) | 57 (2.5%) | 106 (3.6%) | 180 (3.2%) |
| 10A | 27 (8.2%) | 58 (2.5%) | 90 (3.1%) | 176 (3.2%) |
| 23B | 21 (6.3%) | 43 (1.9%) | 71 (2.4%) | 135 (2.4%) |
| 23A | 3 (0.9%) | 30 (1.3%) | 89 (3.0%) | 122 (2.2%) |
| 11A | 5 (1.5%) | 36 (1.6%) | 71 (2.4%) | 112 (2.0%) |
| 15B/C | 26 (7.9%) | 28 (1.2%) | 45 (1.5%) | 99 (1.8%) |
| 16F | 2 (0.6%) | 32 (1.4%) | 57 (1.9%) | 91 (1.6%) |
| 24F | 11 (3.3%) | 24 (1.1%) | 55 (1.9%) | 91 (1.6%) |
| 7F | 4 (1.2%) | 45 (2.0%) | 40 (1.4%) | 89 (1.6%) |
| 35B | 9 (2.7%) | 19 (0.8%) | 59 (2.0%) | 87 (1.6%) |
| Other | 46 (13.9%) | 241 (10.6%) | 433 (14.7%) | 720 (12.9%) |
| Total | **331** | **2,283** | **2,947** | **5,571** |

\* age not known in 10 cases

**Figure 1. Corrected trends in IPD incidence in England and Wales.** The vertical lines labelled PCV7 and PCV13 denote introduction of the 7-valent and 13-valent pneumococcal conjugate vaccines into the national childhood immunisation programme, respectively.

PCV7: IPD due to the serotypes included in the 7-valent pneumococcal conjugate vaccines; PCV13 only: IPD due to the additional 6 serotypes included in the 13-valent pneumococcal conjugate vaccines; NVT: serotypes responsible for IPD that are not included in the 13-valent pneumococcal conjugate vaccines

**Figure 2. Corrected trends in age-group specific IPD incidence in England and Wales.** The vertical lines labelled PCV7 and PCV13 denote introduction of the 7-valent and 13-valent pneumococcal conjugate vaccines into the national childhood immunisation programme, respectively. Note the different scales on the vertical axis.

PCV7: IPD due to the serotypes included in the 7-valent pneumococcal conjugate vaccines; PCV13 only: IPD due to the additional 6 serotypes included in the 13-valent pneumococcal conjugate vaccines; NVT: serotypes responsible for IPD that are not included in the 13-valent pneumococcal conjugate vaccines

**Figure 3. Corrected overall and age-group specific trends in IPD incidence due to the additional PCV13 serotypes and PCV13-related serotype 6C seven years after PCV13 introduction in England and Wales.** The vertical lines labelled PCV7 and PCV13 denote introduction of the 7-valent and 13-valent pneumococcal conjugate vaccines into the national childhood immunisation programme, respectively. Note the different scales on the vertical-axis.

**Figure 4. Corrected overall and age-group specific trends in IPD incidence due to the main replacing serotypes seven years after PCV13 introduction in England and Wales.** The vertical lines labelled PCV7 and PCV13 denote introduction of the 7-valent and 13-valent pneumococcal conjugate vaccines into the national childhood immunisation programme, respectively. Note the different scales on the vertical-axis.

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Figure 1

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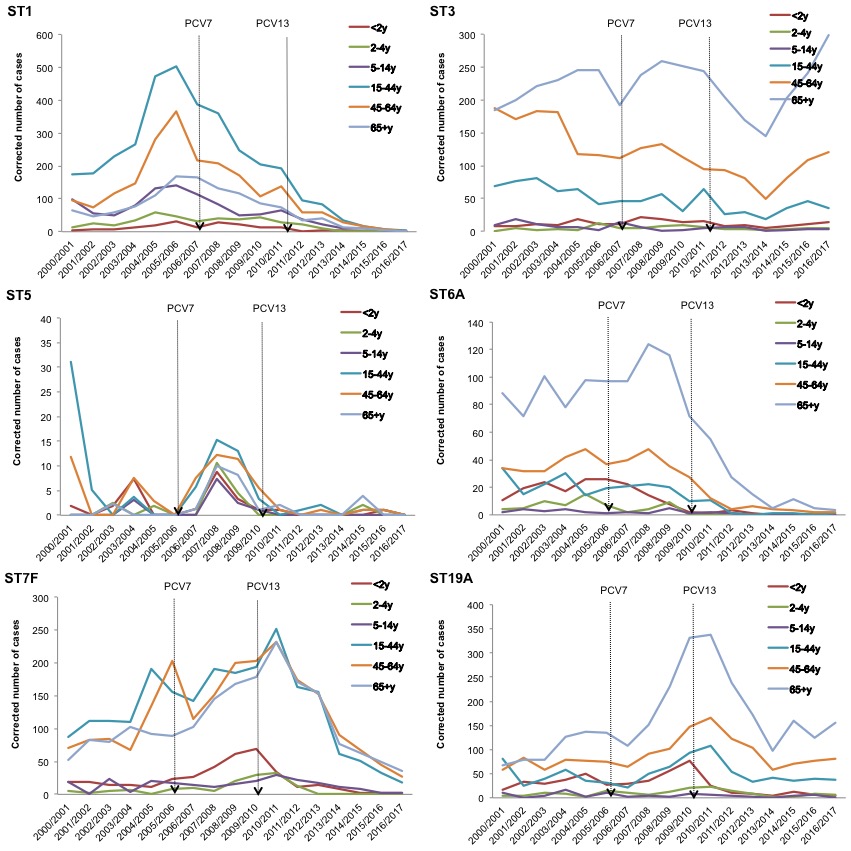
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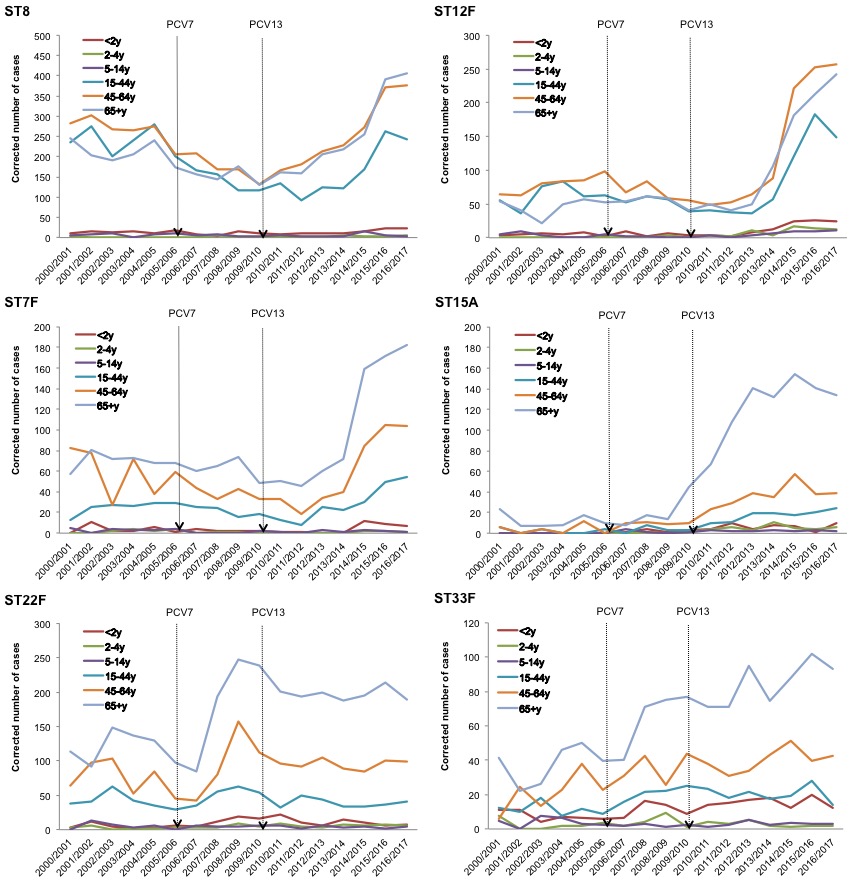
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figure 4



Supplement Figure 1



Supplement Figure 2