Reduction of Invasive Pneumococcal Disease 3 Years After the Introduction of the 13-Valent Conjugate Vaccine in the Oxfordshire Region of England

Catrin E. Moore,1 John Paul,1,2 Dona Foster,1 Saeed A. Mahar,1 David Griffiths,1 Kyle Knox,1,3 Timothy E. Peto,1 A. Sarah Walker,1,a and Derrick W. Crook,1,a for the Oxford Invasive Pneumococcal Surveillance Group

1Nuffield Department of Medicine, University of Oxford,2Public Health England, Royal Sussex County Hospital, Brighton, and 3Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom

(See the editorial commentary by Tan on pages 999–1000.)

Background. The 7-valent pneumococcal conjugate (PCV7) vaccine’s impact on invasive pneumococcal disease (IPD) is well described, but few reports exist on the additional impact of the 13-valent vaccine (PCV13).

Methods. We calculated the IPD incidence across all ages in a surveillance project following implementation of PCV7 (in September 2006) and PCV13 (in April 2010) in children aged <2 years (11 hospitals; 4935 cases).

Results. The overall incidence decreased from 10 cases/100 000 persons per year in 1996–1997 to 8 cases/100 000 persons per year in 2007–2008 and 7 cases/100 000 in 2012–2013. Declines were greater in children aged <2 years (from 37 cases/100 000 in 1996–1997 to 29 and 14 cases/100 000 in 2007–2008 and 2012–2013, respectively). The incidence of IPD due to PCV7 serotypes decreased in all ages after PCV7 introduction (P < .001), whereas the incidence of IPD due to the additional 6 serotypes in PCV13 and to nonvaccine types (NVTs) increased in children aged ≥2 years (P < .001 for both comparisons). The incidence of IPD due to the 6 additional serotypes in PCV13 declined significantly after PCV13 introduction in all ages (P ≤ .01), and the incidence of IPD due to NVTs declined significantly in children aged ≥2 years (P = .003). In 2011–2013, the overall incidences of IPD due to PCV7 serotypes, the 6 additional serotypes in PCV13, and NVTs were 0.3, 2.8, and 4.4 cases/100 000; the incidences among children aged <2 years were 0.9, 2.4, and 10.8 cases/100 000, respectively.

Conclusions. The annual incidence of IPD due to vaccine serotypes (1–3 cases/100 000) among children aged <2 years and nontarget groups demonstrates the success of PCV7 and PCV13. A substantially higher incidence of IPD due to NVTs indicates the importance of ongoing surveillance and extension of vaccine polyvalency.

Keywords. Streptococcus pneumonia; pneumococcal conjugate vaccines; 7-valent pneumococcal conjugate vaccine; 13-valent pneumococcal conjugate vaccine; invasive pneumococcal disease; epidemiology.

Streptococcus pneumoniae is an important bacterial pathogen, causing a high burden of morbidity and mortality worldwide, with higher rates of invasive disease in children and elderly individuals. S. pneumoniae accounted for 33% of pneumonia-attributable deaths worldwide in 2011 [1]. Pneumonia remains a leading cause of death in children aged <5 years, with an estimated 1.3 million deaths in 2011; 81% of pneumonia-associated deaths occur in children aged <2 years [1]. Ninety-four different S. pneumoniae serotypes have been described. Available vaccines target serotypes that were prevalent in America and Europe when vaccines were developed, although these vary by age, disease syndrome, geographic region, and season [2].

Conjugate vaccines provide better protection than polysaccharide vaccines, particularly in younger individuals [3]. Following the successful introduction of
the 7-valent conjugate vaccine (PCV7; which contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) in the United States, this vaccine was introduced in the United Kingdom in September 2006, with doses at 2, 4, and 13 months of age, together with a catch-up campaign for individuals up to 2 years old [4]. Uptake rates of 92% and 87% were reported for 2 and 3 doses, respectively, in 2009 [5]. PCV7 was replaced by the 13-valent conjugate vaccine (PCV13; which contains the 7 PCV7 serotypes plus serotypes 1, 3, 5, 6A, 7F, and 19A) in the United Kingdom in April 2010. The polysaccharide vaccine (PPV) was introduced in the United Kingdom for individuals aged >80 years, in August 2003; those aged >70 years, in 2004; and those aged ≥65 years, in April 2005.

Numerous studies have reported pronounced decreases in the incidence of IPD due to serotypes covered in the vaccine following the introduction of PCV7 among children in both targeted and nontargeted populations [6–9]. However, there are also reports of increased rates of IPD due to serotypes not found in PCV7, with serotype replacement detrimentally impacting overall vaccine success [8, 10]. These studies were conducted before the introduction of PCV13: there are currently few published investigations of the impact of PCV13 or nontargeted types (NVTs) on IPD incidence [11].

Here, we investigate the IPD incidence in one United Kingdom region over 17 years (1996–2013), extending previous analyses by using updated data [6], and compare trends before the introduction of PCV7 to children aged <2 years, after PCV7 introduction but before PCV13 introduction, and after PCV13 introduction.

MATERIALS AND METHODS

Patient Population
Cases of invasive pneumococcal disease were identified from the Oxford Invasive Pneumococcal Surveillance Group; the study has been ongoing since January 1996 and covers a population of approximately 3 million people of all ages [12]. Ten hospital microbiology laboratories (Oxford University Hospitals, Stoke Mandeville Hospital, Milton Keynes General, Bedford Hospital, Kettering General, Royal Berkshire Hospital, Northampton General, Wycombe General, and Wexham Park) submitted isolates and available basic clinical information, using standardized case report forms, from 1996 onward. The network expanded to include Southampton General Hospital, from November 2005 onward, and the Royal Sussex County Hospital Brighton, from April 2009 onward. Acute care is almost exclusively provided by National Health Service (NHS) hospitals. However, laboratories in the region process samples from private hospitals, as well as from NHS hospitals and primary care. Invasive pneumococcal infections were defined as normally sterile samples (blood, cerebrospinal fluid, or joint fluid) from which S. pneumoniae was isolated. Available demographic information included age, sex, and clinical diagnosis, when made available to the laboratory. According to national data, approximately 2% of individuals (60 000) in the surveillance region are <2 years old [13]. Latest census data suggests 78% of Oxfordshire residents and 86% of England residents classify themselves as white [14]. As a component of Public Health England’s surveillance, limited patient data were available under section 251 of the NHS Act 2006.

Isolates
Isolates from participating laboratories were processed in accordance with standard microbiological techniques in a single laboratory in Oxford [12, 15–17]. Serotyping results were returned to maintain interest in participation. Isolate numbers were monitored annually, and hospitals were contacted regarding case ascertainment if variability increased. For quality control, all isolates were previously designated as nontypeable or as serotype 6A [6], and all rare serotypes (<8 isolates per serotype in our study) were retyped, resulting in serotype reassignment of 15 of 33 nontypeable strains, 20 of 141 serotype 6A strains, and 10 of 48 rare strains. Serotypes were termed vaccine serotypes, either PCV7 or PCV7 + 6 (for the additional serotypes contained in PCV13), and NVTs (for serotypes not covered by either vaccine). No isolates were received from 2 hospitals (Reading and Stoke Mandeville) in 2003–2005; the calculated incidence rates took account of this (see below).

Susceptibilities were determined for penicillin (using oxacillin), cefotaxime, chloramphenicol, erythromycin, and tetracycline in accordance with 2013 Eucast Guidelines (as testing used Iso-Sensitest agar) [16]. All strains determined as being penicillin resistant underwent minimum inhibitory concentration (MIC) testing for penicillin and ceftriaxone, using Etest (Biomerieux, France).

Data Analysis
Data were analyzed using Stata, version 12.1 (StataCorp, College Station, TX). Changes in the incidence of IPD in each financial year from April 1996 to March 2013, overall and by serotype group (PCV7, PCV7 + 6, and NVT) before the introduction of PCV7 (September 2006) and before the introduction of PCV13 (April 2010) were compared by means of Poisson regression analysis, using annual population estimates derived from the United Kingdom Office for National Statistics [13]; analyses accounted for Southampton hospital joining the study halfway through a financial year and for periods when no isolates were submitted. Financial years (which begin in April and end in March) were used rather than years defined by the period from August to September, as published previously [6], to provide 3 full years of post-PCV13 observations. Continuous year-on-year trends were fitted, allowing the per annum trend to change in September 2006 (halfway through the financial year) and April 2010. Overall results were similar, incorporating a discontinuous instantaneous change in rate when new
hospitals joined in November 2005 and April 2009 or when restricting to hospitals submitting isolates throughout the study (data not shown). For categorical analyses by serotype, any serotypes containing <8 isolates across the entire study were grouped with other serotypes. Proportions were compared using the $\chi^2$ test or Fisher exact test (if <5% or <5 observations in any cell).

RESULTS

Isolates
A total of 5477 pneumococcal isolates were submitted from 1 April 1996 to 31 March 2013, of which 634 duplicate strains and noninvasive strains were excluded. Of the 4935 single invasive isolates remaining, 2325 (47.2%) were from females (16 [0.3%] were missing data on sex). Four hundred sixty isolates (9.3%) were from children aged <2 years (160 [34.8%] were from females); 57 (1.2%) were missing age data. Among individuals aged ≥2 years, the median age was 68.3 years (interquartile range [IQR], 48.2–81.5 years) and 62.8 years (IQR, 42.4–77.5 years) for females and males, respectively. A total of 4706 isolates (90.8%) were from the 9 main hospitals, 314 (6.1%) were from Southampton, and 160 (3.1%) were from Brighton. There was a seasonal pattern in incidence overall, with 1727 isolates (35.0%) recovered during January–March, compared with 578 (11.7%) during July–September.

A total of 51 serotypes (excluding 20 nontypeable isolates) were identified, 36 of which contained >8 strains. Over the study period, the 7 most frequently isolated capsular types accounted for 2616 isolates (53.0%) and were as follows: serotype 14 (586 isolates [11.9%]), 1 (400 [8.1%]), 8 (378 [7.7%]), 7F (361 [7.3%]), 19A (314 [6.4%]), 3 (301 [6.1%]), and 9V (276 [5.6%]; Supplementary Table 2). Disease was documented in 2918 patients (59.1%); of these, 1608 (55.1%) had bacteremia, and 1310 (26.5%) had meningitis. Meningitis accounted for a significantly greater proportion of documented diagnoses in children <2 years old (105/274 [38.3%]), compared with individuals aged ≥2 years (225/2613 [8.6%]); pneumonia accounted for a smaller proportion of cases among children aged <2 years, compared with the older group (13.5% vs 35.5%); and bacteremia accounted for a similar proportion (48.2% and 55.9%, respectively; overall $P < .0001$). There was no change in the burden of meningitis as a proportion of documented diagnosis over time among children aged <2 years (38% before PCV7 introduction, 41% after PCV7 introduction but before PCV13 introduction, and 35% after PCV13 introduction; $P = .87$).

Incidence of IPD During April 1996–March 2013
A total of 3030 isolates (61.4%) were recovered before PCV7 introduction (April 1996–August 2006), 942 (19.1%) were recovered during the period after PCV7 introduction and before PCV13 introduction (September 2006–March 2010), and 963 (19.5%) were recovered after PCV13 introduction (April 2010–March 2013).

Overall, IPD incidence was declining slightly but significantly before PCV7 introduction by 2% per annum ($P < .001$; Figure 1A, Table 1, and Supplementary Table 1), with a mean of 9 cases/100 000 persons for all patients, 8/100 000 for those aged ≥2 years, and 42 cases/100 000 for those aged <2 years. Although the overall IPD incidence declined by 18% per annum among children aged <2 years after PCV7 introduction ($P < .001$), the incidence increased by 7% per annum in individuals aged ≥2 years ($P < .001$), leading to an overall increase of 5% per annum in the entire population ($P < .001$). The incidence only started to decline at the population level and in those aged ≥2 years after the introduction of PCV13 (by 16%–18% per annum; $P < .001$, for both comparisons). The IPD incidence remained stable following PCV13 introduction in children aged <2 years (estimated per annum increase, 10%; $P = .49$) but with very few cases following the substantial IPD declines with PCV7 introduction (only 15 IPD cases each year in children aged <2 years for 2011–2012 and 2012–2013; results were similar when the hospitals which joined in 2005/2006 were excluded [data not shown]). Following the introduction of PCV7, the incidences due to each serogroup were fairly stable in all ages, although there was evidence of a peak in incidence in children aged <2 years for 2011–2012 and 2012–2013; results were similar in older children and adults (Figure 1B). The lowest incidence was observed in individuals 6–17 years of age, and the highest incidences were observed in individuals aged <2 years or >65 years.

Incidence of IPD Due to PCV7 Serotypes, PCV7 + 6 Serotypes, and NVTs
As expected, the patterns of incident IPD due to PCV7 serotypes, PCV7 + 6 serotypes, and NVTs were qualitatively different (Figure 2, Table 1, and Supplementary Table 1). Before PCV7 introduction, the incidences due to each serogroup were fairly stable in all ages, although there was evidence of a peak in incidence in children aged <2 years between 1999–2002, driven by a prolonged outbreak of serotype 14 disease, and some evidence that the incidence due to the PCV7 + 6 serogroup was declining by 2% per annum in individuals aged ≥2 years, from a peak at the start of the study.

The most striking difference between groups of serotypes was observed following the introduction of PCV7, with IPD due to these strains declining by 76% per annum and 41% per annum in children aged <2 years and individuals aged ≥2 years, respectively, from September 2006 through April 2010 ($P < .001$; Figure 2 and Table 1). IPD due to PCV7 + 6 serotypes and NVTs increased significantly in individuals ≥2 years during the same period (by 29% per annum and 21% per annum, respectively; $P < .001$ for both). Smaller and nonsignificant increases in IPD due to PCV7 + 6 serotypes and NVTs were...
also observed in children aged <2 years (7% per annum for both; $P = .63$ and $P = .61$, respectively). Thus, in children aged <2 years, in whom PCV7 serotypes accounted for the vast majority of IPD cases before 2006 (76%), the substantial decline in the IPD incidence due to PCV7 serotypes outweighed the modest increases in IPD incidence due to both PCV7 + 6 serotypes and NVTs, leading to a modest decline in the overall incidence (Figure 1A). In contrast, in individuals aged ≥2 years, for whom PCV7 serotypes accounted for a smaller proportion (50%) of IPD cases before 2006, the increase in incidence due to PCV7 + 6 serotypes and NVTs after PCV7 introduction reversed the reductions in the IPD incidence due to PCV7 serotypes, leading to a modest increase in incidence overall.

Figure 1. The incidence of invasive pneumococcal disease over the study period overall (A) and by age group (B). The vertical lines represent the introduction of the 7-valent pneumococcal conjugate vaccine (in September 2006) and the 13-valent pneumococcal conjugate vaccine (in April 2010). Higher than normal rates of influenza-like illnesses were observed during 2009–2010 and 2010–2011.
Table 1. Year-on-Year Trends in the Incidence of Invasive Pneumococcal Disease Relative to the Introductions of 7-Valent Pneumococcal Conjugate Vaccine (PCV7) and 13-Valent Pneumococcal Conjugate Vaccine (PCV13)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, No.</td>
<td>Year-on-Year IRR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>All serotypes</td>
<td>3030</td>
<td>0.98 (.97–.99)</td>
<td>.001</td>
</tr>
<tr>
<td>Age ≥2 y</td>
<td>2645</td>
<td>0.98 (.98–.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>342</td>
<td>0.98 (.96–1.00)</td>
<td>.08</td>
</tr>
<tr>
<td>PCV7 serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥2 y</td>
<td>1304</td>
<td>0.98 (.97–1.00)</td>
<td>.03</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>255</td>
<td>0.97 (.94–1.01)</td>
<td>.20</td>
</tr>
<tr>
<td>PCV7+6 serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥2 y</td>
<td>669</td>
<td>0.99 (.97–1.01)</td>
<td>.34</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>49</td>
<td>1.03 (.95–1.11)</td>
<td>.51</td>
</tr>
<tr>
<td>NVTs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥2 y</td>
<td>672</td>
<td>1.00 (.98–1.02)</td>
<td>.70</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>38</td>
<td>1.06 (.98–1.15)</td>
<td>.13</td>
</tr>
<tr>
<td>Serotype 9N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>55</td>
<td>1.07 (1.00–1.16)</td>
<td>.07</td>
</tr>
<tr>
<td>Age ≥2 y</td>
<td>53</td>
<td>1.06 (.99–1.15)</td>
<td>.11</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>2</td>
<td>1.24 (.80–1.90)</td>
<td>.34</td>
</tr>
<tr>
<td>Serotype 22F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>63</td>
<td>1.03 (.96–1.09)</td>
<td>.40</td>
</tr>
<tr>
<td>Age ≥2 y</td>
<td>62</td>
<td>1.03 (.97–1.10)</td>
<td>.34</td>
</tr>
<tr>
<td>Age &lt;2 y</td>
<td>1</td>
<td>0.81 (.49–1.34)</td>
<td>.42</td>
</tr>
<tr>
<td>Serotype 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotype 6B</td>
<td>172</td>
<td>1.02 (.98–1.07)</td>
<td>.29</td>
</tr>
<tr>
<td>Serotype 6A</td>
<td>83</td>
<td>1.09 (1.02–1.16)</td>
<td>.01</td>
</tr>
<tr>
<td>Serotype 6C</td>
<td>26</td>
<td>0.92 (.83–1.01)</td>
<td>.10</td>
</tr>
</tbody>
</table>

A P value of <.05 was considered statistically significant.
Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NA, not applicable; NVT, nonvaccine serotype; PCV7 + 6, 6 serotypes included in PCV13 but not PCV7.
* One case occurred in 2011, and 2 cases occurred in 2012, leading to a positive incidence trend overall.

Of interest, similar incidence trends were observed for PCV7 + 6 serotypes after the introduction of PCV13 in April 2010, with significant declines of 64% per annum (P = .01) and 46% per annum (P < .001) in children aged <2 years and individuals aged ≥2 years, respectively. The incidence of IPD due to PCV7 serotypes remained unchanged in individuals aged ≥2 years (P = .85), with the numbers in children aged <2 years remaining small (3 cases). However, whereas introduction of PCV7 was accompanied by rises in the incidence due to PCV7 + 6 serotypes and NVTs, there was evidence of a decrease in incidence due to NVTs following the introduction of PCV13 in individuals aged ≥2 years (19% per annum; P = .003), with a nonsignificant decline of a similar magnitude in children aged <2 years (15%; P = .54). The incidence of IPD due to NVTs was 4.4 cases/100 000 and 10.8 cases/100 000 for all ages and children aged <2 years, respectively, in 2011–2013.

Changes in the serotype-specific incidence of IPD were consistent across age groups (Figure 3A–C). In particular, declines in the incidence of IPD due to PCV7 + 6 serotypes after PCV13 introduction occurred in all ages but were especially noticeable in those <2 and >65 years of age, as were increases in the incidence due to NVTs after PCV7 introduction. Results were similar in hospitals joining the study after 2004 (data not shown).

Data on vaccination were available for all 24 children aged <2 years with IPD caused by a vaccine serotype after the introduction of the conjugate vaccines (Table 2). Of 9 children with IPD due to PCV7 serotypes after PCV7 introduction, 4 were not vaccinated (3 were too young), 2 did not receive the complete vaccine schedule (only 1 dose), and 3 experienced vaccine failure. Of the 15 children aged <2 years with IPD caused by the additional serotypes in PCV13 after its introduction, 4 were too young to be vaccinated, 3 received an incomplete vaccine.
schedule (1 dose of PCV13), and 6 and 2 with IPD due to serotypes 19A and 7F, respectively, were vaccinated with PCV7 before infection and would not have been protected (Table 2).

**Changes in the Incidence of IPD Caused by NVT Serotypes**
We characterized 38 different serotypes not covered in the current PCV13 vaccine (1609 isolates [32.6%]). The 10 most frequent NVTs were serotypes 8, 22F, 12F, 33F, 9N, 11A, 6C, 23A, 15A, and 20 for all ages (Supplementary Table 2). Serotype 23B was first observed in 2009; all other NVTs were isolated across the study period. Interestingly, the incidence of IPD due to serotype 6C increased significantly after PCV7 introduction \( (P < .001) \); there was marginal evidence supporting a declining incidence after PCV13 introduction (estimated decline, 82% per annum \( [P = .10] \); Table 1 and Figure 4). The incidence of disease due to serotype 9N decreased by 8% per

---

**Figure 2.** The incidence of invasive pneumococcal disease, according to serotype, among children aged <2 years (A) and individuals aged ≥2 years (B). The vertical lines represent the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7; in September 2006) and the 13-valent pneumococcal conjugate vaccine (PCV13; in April 2010). Abbreviations: CI, confidence interval; NVT, nonvaccine type.
Figure 3. The incidence of invasive pneumococcal disease (IPD), according to age group. A, Incidence of IPD due to serotypes in the 7-valent pneumococcal conjugate vaccine (PCV7), by age group. B, Incidence of IPD due to the 6 additional serotypes in the 13-valent pneumococcal conjugate vaccine (PCV13), by age group. C, Incidence of IPD due to nonvaccine serotypes, by age group. The vertical lines represent the introduction of the PCV7 (in September 2006) and the PCV13 (in April 2010).
annum ($P = .58$) after PCV7 introduction and by 34% per annum after PCV13 introduction ($P = .05$; Table 1). In contrast, significant increases in incidence over the study period were seen for serotypes 10A, 15A, 22F, 23A, 23B, 24F, 33F, 38, and 8. In particular, the incidence of IPD due to serotype 22F increased by 75% per annum in all ages after PCV7 introduction ($P < .001$; Table 1), with an outbreak in 2009, after which the incidence decreased by 19% per annum ($P = .01$).

**Resistance**

Oxacillin susceptibility was recorded for 4923 isolates (99.8%), with 232 (4.7%) resistant to the oxacillin disc. Following the Eucast guidelines, 6 meningitis strains (2.6%) were resistant to penicillin by MIC testing. A further 7 nonmeningitis strains (3.0%) would be reported as penicillin resistant (6 with MICs of 2 and 1 with an MIC of 3). None of 110 isolates tested exhibited ceftriaxone resistance, but 1 meningitis strain had an MIC of 1.5, suggesting reduced susceptibility. See the Supplementary Materials for details of the susceptibility to other antibiotics tested and the increasing incidence of erythromycin-resistant IPD driven by serotype 15A.

**DISCUSSION**

Investigation of the IPD incidence in southern England over 17 years, covering the introduction of 2 pneumococcal conjugate vaccines into the childhood immunization schedule for children aged <2 years, illustrates the complex dynamics of this bacterial pathogen. Overall IPD incidence has decreased by approximately 20%, compared with the prevaccine era. The introductions of PCV7 and PCV13 were both followed by similar pronounced declines in IPD caused by serotypes covered by these vaccines in the target population (children aged <2 years), with convincing
but somewhat smaller herd effects against these serotypes also demonstrated in individuals aged ≥2 years. Furthermore, we found evidence that PCV7 introduction was accompanied by replacement of PCV7 serotypes with other serotypes causing disease \( (P < .001) \). Because of the lower coverage of PCV7 among older persons, a small but significant increase in the overall IPD incidence was thus observed after PCV7 introduction. In contrast, we found no evidence of replacement of the additional 6 serotypes in PCV13 with other NVTs after PCV13 introduction. Thus, the introduction of PCV13 was associated with decreases in IPD in individuals aged ≥2 years and the population as a whole, in comparison to the introduction of PCV13, when the greatest benefit was seen in children aged <2 years. The uptake of the PCV primary immunization course \( (\text{ie}, 2 \text{ doses of PCV before 12 months of age}) \) was reasonably high, supporting this association. Vaccine uptake for children aged <1 year and those aged <2 years in England was 83.7% and 81.5%, respectively, in 2007–2008; this has increased annually and was 94.2% and 91.5%, respectively, in 2011–2012 \[17,18\]. In comparison, PPV uptake in those aged >65 years was 68.3% in 2011–2012 (66.6%–70.5% through 2007–2011).

The reasons underlying the significant replacement we observed following only PCV7 but not PCV13 introduction are unclear. Hypotheses include saturation of the ecological niche or a greater effectiveness of PCV13 in preventing infections due to NVTs. Evidence against the latter hypothesis is that both vaccines are conjugated to an identical protein (CRM197) at the same concentration and that both are administered in the same way. Apart from the inclusion of 6 additional serotypes in PCV13, the only difference between this vaccine and PCV7 is that PCV13 also includes 0.02% polysorbate 80 excipient \[19\]. Recent studies comparing children receiving PCV7 to those receiving PCV13 have not found differential reductions in nasopharyngeal colonization with most serotypes common to PCV7 and PCV13 or with serotype 3 (in PCV13 only) \[19–21\]. However, reports are conflicting. In 1 study, PCV13 was associated with a significantly lower serotype 19F acquisition and prevalence and with concomitantly higher geometric mean levels of immunoglobulin G (IgG), compared with PCV7 \[19\]. No such difference in IgG levels was observed in another, smaller study \[11\].

Our limited data on vaccine failure supports the hypothesis that the vaccines do not fully protect against serotype 3 infection, as 2 children who received 2 doses of PCV7 and a single dose of PCV13 subsequently had IPD due to serotype 3. Previous Active Bacterial Core (ABC) Surveillance data also suggested that the incidence of IPD due to serotype 3 was not reduced in children but may be reduced in adults aged 18–49 years \[22\]. Therefore, a single catch-up dose of either vaccine may not be protective for all individuals. Two IPD cases due to serotype 19F following incomplete vaccination with PCV7 in our study also tentatively support suggestions by Dagan et al \[19\] that PCV7 does not protect well against serotype 19F infection.

As expected, NVTs now compose more than two-thirds of IPD cases, albeit with an overall incidence that is approximately 20% lower than before PCV7 introduction. Although relative increases are similar, absolute increases in the incidence of IPD caused by NVT serotypes in 2012–2013, compared with that during 1996–1997, were most notable in individuals at greatest underlying risk, namely children aged <2 years and individuals aged >65 years. However, absolute increases were also apparent in individuals aged 50–64 years, as reported elsewhere \[20\].

Two groups of specific serotypes demonstrated at least some evidence for cross-reactivity between vaccine serotypes and NVTs. The incidence of IPD due to serotype 6B decreased rapidly following PCV7 implementation in children aged <2 years and individuals aged ≥2 years. In contrast to the ABC cohort, the incidence of IPD due to serotype 6A declined beginning approximately 1 year after PCV7 implementation (Figure 4), possibly suggesting herd rather than vaccine protection. The incidence due to serotype 6C increased significantly following PCV7 implementation before declining after PCV13 implementation, suggesting no cross-reactivity or herd protection from 6B in PCV7 recipients but some protection from 6A in PCV13 recipients. We also found a decrease in incidence due to serotype 9N after PCV7 introduction and after PCV13 introduction, similar to Millar et al \[7\]. Both vaccines contain serotype 9V, but neither contain serotype 9N, and there is not currently thought to be any serological cross-reaction between the 2 serotypes. Although the current observation may reflect a natural change in the population rather than a vaccine effect, the similarity between trends in the incidence of IPD due to serotypes 9N and PCV7 serotypes is striking (Table 1); if confirmed in non-United Kingdom cohorts, it could indicate broader protection against this serotype.

There are several limitations to our study. Although the surveillance has continued over a prolonged period, it is based in 1 United Kingdom region, representing approximately 5% of the population. Published data from Public Health England (covering the whole United Kingdom) are similar, suggesting our region is reasonably representative. Because only 3 years of surveillance data were available after PCV13 implementation, subsequent trends may differ. Clinical information was limited; information on clinical diagnosis was not always available to the submitting laboratory, and more-severe manifestations (ie, meningitis) may have been preferentially reported, accounting for the higher-than-expected burden of meningitis in our youngest age group. Other than possible cases of vaccine failure, vaccine status was not universally available. Last, our study did not examine circulating carriage strains from the region over the same period. Therefore, it is unclear whether changes in serotype-specific incidences observed in the study result from an impact of the new vaccines on the overall carriage prevalence.
of the invasive serotypes or result from their innate invasiveness; a separate study is needed to confirm either hypothesis. However, as the diagnostic methods and case ascertainment have remained unchanged throughout the prolonged study period, it is likely that our observations represent a true change in *S. pneumoniae* epidemiology.

There was no change in penicillin resistance during our study period; similarly, >90% of strains isolated in 2011 remained susceptible to penicillin in a US study [21]. We found clear evidence of a strain-specific impact on the incidence of erythromycin-resistant IPD, an important phenotype in the United Kingdom, where macrolides, including clarithromycin, are used in patients with β-lactam allergy. Although there was a substantial decline in the incidence of erythromycin-resistant IPD after PCV7 introduction, owing to the serotypes covered by PCV7, this is now increasing again (particularly in individuals aged ≥2 years). In our study, erythromycin resistance is limited to a small number of serotypes (eg, 6C, 15A, 23A, and 35B), and this increase is in predominantly due to serotypes not contained in any vaccine, most commonly serotype 15A.

Our data to date suggest that PCV13 may be more effective than PCV7 in reducing IPD, because of the former’s inclusion of 6 additional serotypes and its prevention of replacement by NVT strains. Given the risk of replacement posed by the substantial pool of NVTs present in the population, serotype-specific surveillance of IPD should be continued to monitor the efficacy of PCV13.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

**Acknowledgments.** We thank Bedford Hospital NHS Trust (Simantee Guha), Kettering General Hospital NHS Foundation Trust (Manjula Natarajan), Milton Keynes Hospital NHS Foundation Trust (Lakshmi Ragunathan and Mansoor Razi), Northampton General Hospital NHS Trust (Minas Minassian and Tony Bentley), Brighton and Sussex University Hospitals NHS Trust (John Paul), Royal Berkshire NHS Foundation Trust (Andrew Stacey and Shabnam Iyer), Buckinghamshire Healthcare NHS Trust (David Waghorn, Ruby Devi, and Jenny O’Driscoll), University Hospital Southampton NHS Foundation Trust (Grane Jones), Heathwood and Wessex Park Hospitals NHS Foundation Trust (Mike McIntyre and Albert Lessing), and Oxford University Hospitals NHS Trust (Ian Bowler), for contributing isolates and data to the Oxford Pneumococcal Surveillance Project over the last 17 years and making this study possible; and all of our collaborators, specifically Pauline Kaye, Mary Slack, and Rashmi Malkani at Public Health England, for the information they provided about vaccine uptake in younger children.

**Financial support.** This work was supported by Pfizer (research grant to the Oxford Pneumococcal Surveillance Project) and the Oxford NIHR Biomedical Research Centre.

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


