Invasive pneumococcal disease: epidemiology in children and adults prior to implementation of the conjugate vaccine in the Oxfordshire region, England

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A 10-year invasive pneumococcal disease (IPD) enhanced surveillance project in the Oxfordshire region of the UK between 1996 and 2005 identified a total of 2691 *Streptococcus pneumoniae* isolates from all ages that provided a comprehensive description of pneumococcal epidemiology. All isolates were serotyped and those from children under 5 years of age were genotyped and a matched case-control study using adults hospitalized between 1995 and 2000 was performed to estimate the effectiveness of the pneumococcal polysaccharide vaccine in the local population. Fifty-one serotypes were isolated, with different age distributions. The overall incidence of IPD was 9.2 cases per 100 000 population per annum [95 % confidence interval (CI), 8.6–9.9] and that of meningitis was 0.7 per 100 000 population per annum (95 % CI 0.5–0.9). After adjusting for age, serotype 1 was found to be less likely to be associated with meningitis versus other IPD, compared with the most common serotype 14, whereas serotype 12F was more likely to cause meningitis than other IPD. There were significant temporal changes in IPD incidence of four serotypes, with decreases in serotypes 1, 12F and 14 and increases in serotype 8. A possible novel variant (from serotype 6A to 6B) was found using multilocus sequence typing analysis. From the matched case-control study of adults, the pneumococcal polysaccharide vaccine effectiveness was estimated to be 43 % (2–68 %), which did not change significantly after adjustment for pre-existing co-morbidities. The data provide a baseline against which the impact of the pneumococcal conjugate vaccine introduced in the UK in 2006 could be measured.

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INTRODUCTION

Streptococcus pneumoniae is a leading cause of childhood and adult morbidity, with 0.7–1 million children estimated to die annually from this disease (WHO, 1999, 2007).

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; MLST, multilocus sequence typing; OR, odds ratio; PCV7, pneumococcal conjugate vaccine 7-valent; PPV23, pneumococcal polysaccharide vaccine 23-valent; ST, sequence type.

Tables showing serotype-specific frequency over the study period and MLST profiles of isolates from children under 5 years of age are available as supplementary material with the online version of this paper.

Surveillance pre- and post-implementation of a heptavalent pneumococcal conjugate vaccine (PCV7) in the USA has demonstrated population-level benefits of such vaccines (Whitney *et al.*, 2003, 2006) and a realistic possibility exists that pneumococcal disease could decline substantially over the coming decades with increased uptake of PCV7 and/or conjugate vaccines currently in development.

Two pneumococcal vaccines are currently licensed in the UK. The first, licensed in 1989 and recommended for use in at-risk adults in 1992, is a polysaccharide vaccine (PPV23) containing antigens to 23 serotypes. Despite limited data showing varying efficacy (Conaty *et al.*, 2004;

Dear *et al.*, 2003; Fedson & Liss, 2004), PPV23 vaccine is currently recommended to be administered to adults over 65 years in the UK. The second vaccine (PCV7) was licensed in 2001 and was implemented in the childhood vaccine schedule in September 2006 (Dept Health, 2006) on the basis of direct and herd immunity effects on invasive pneumococcal disease (IPD) (Black *et al.*, 2000; Cutts *et al.*, 2005; Klugman *et al.*, 2003; O'Brien *et al.*, 2003).

Surveillance in the USA has shown continuing and significant changes in the distribution of pneumococcal serotypes causing IPD in the post-PCV7 era (Beall *et al.*, 2006; Byington *et al.*, 2005; Hanage *et al.*, 2007; Pai *et al.*, 2005). The incidence of IPD caused by PCV7 serotypes has declined among all ages in the USA; however, a gradual and continued rise in the incidence of disease due to non-vaccine serotypes has been observed, a trend also seen in carriage studies among vaccinated children (Dagan *et al.*, 2003; Hanage *et al.*, 2007; Huang *et al.*, 2005). These increases have not yet reached a comparable incidence level to those of the vaccine types. Changes in frequency of pneumococcal serotypes are thought to represent selection by the immune pressure of the vaccine on the population, but may also represent natural secular trends.

This paper reports a 10-year enhanced population-based pneumococcal surveillance in the Oxfordshire area of the UK, providing information on serotype and genotype distributions of pneumococci causing IPD prior to the introduction of PCV7. For the first time in the UK, the report also provides data on the effectiveness of PPV23 in the local adult population.

METHODS

Descriptive and molecular epidemiology. *S. pneumoniae* cases were identified from an ongoing study by the Oxford Pneumococcal Surveillance Group, covering a population of approximately 3 million people. IPD cases were defined by isolation of *S. pneumoniae* from a normally sterile site [blood, cerebrospinal fluid or fluids (joint, pleural or ascitic)]. Demographics recorded for each isolate were date of birth, gender, diagnosis and isolate type. Diagnosis was classified as bacteraemia, meningitis (isolation from cerebrospinal fluid or blood culture with a clinical meningitis diagnosis), pneumonia or other.

S. pneumoniae isolates were cultured and identified using standard microbiological techniques. Penicillin resistance was determined by MIC using the British Society for Antimicrobial Chemotherapy guidelines for E-strips (Bio-Stat) (MacGowan & Wise, 2005). All isolates were serotyped using the Quellung reaction with serotype-specific antiserum (Statens Serum Institut).

Age-stratified incidence of IPD was estimated using estimates of mid-year population from the Office for National Statistics (<http://www.nomisweb.co.uk>; accessed May 2007). Poisson regression was used to estimate changes in serotype-specific incidence over time. Logistical regression was used to determine whether the IPD caused by any serotype was more likely to be meningitis.

Isolates from children of less than 5 years of age were characterized by multilocus sequence typing (MLST) as described by Enright & Spratt (1998). MLST data for 127 of these isolates have been reported previously (Brueggemann *et al.*, 2003). Allele and sequence type (ST)

designations were made using the MLST website (<http://www.mlst.net>). eBURST version 3 available on the MLST site was used to identify clonal complexes (Spratt *et al.*, 2004).

Case-control study. The case-control study for vaccine effectiveness used a subset of isolates collected from adults (16 years of age and over) between 1995 and 2000. Hospitalized controls were identified for all hospitalized cases of IPD during this period, matched for age (± 5 years), gender, date of admission (± 3 months) and General Practice, but irrespective of diagnosis. General Practice records for the matched controls and cases were retrieved and the following were recorded: date of PPV23 immunization, history of smoking, underlying disease (respiratory disease, cardiac disease, neoplastic disease, any other co-morbidity such as asplenia) and postal code. The index of deprivation was calculated using the Lower Layer Super Output Area code (available using the postal code via www.gigateway.org.uk). Ethical approval for the study was obtained from all participating hospitals and informed consent for participation was obtained from living subjects. The crude odds ratio (OR) was estimated using classical methods for matched studies and conditional logistic regression was used to calculate adjusted ORs. Vaccine effectiveness was estimated by 1 minus OR.

All statistical analysis was performed using Intercooled Stata 9 (StataCorp).

RESULTS AND DISCUSSION

Descriptive and molecular epidemiology

A total of 2907 isolates were received by the Oxford Pneumococcal Surveillance project between January 1996 and December 2005. Of these, 216 were subsequently excluded due to their failure to meet study criteria [not pneumococcus isolate ($n=51$); hospital not part of surveillance group ($n=54$); not an invasive isolate ($n=77$); duplicate isolate ($n=34$)], resulting in 2691 isolates for analysis.

Fifty-one serotypes were isolated in total (see Supplementary Table S1 available in JMM Online). Twenty-eight different serotypes were found in the under fives (446 isolates) and 44 in the 5–65 and over 65 age groups (955 and 1290 isolates, respectively). Over the 10-year surveillance period, 15 serotypes comprised 88% of the total isolate collection (serotypes 1, 3, 4, 6A, 6B, 7F, 8, 9V, 12F, 14, 18C, 19A, 19F, 22F and 23F). This was similar to published global data (Hausdorff *et al.*, 2000a). Differences in the rank order of serotypes by age-group (Table 1; similar to recent reports from 2000–2005; Ihekweazu *et al.*, 2007) reflect differences in the age distribution of IPD cases caused by different serotypes (Table 2), with the median age ranging from 5 years (serotype 18C) to 73 years (serotype 3) and also substantial differences across serotypes in the interquartile ranges (Table 2). This difference in age distribution has a major impact on vaccine coverage of the current and proposed vaccines for different age groups (Table 1).

The overall IPD incidence in the Oxfordshire population was 9.2 cases per 100 000 per annum [95% confidence interval (CI), 8.6–9.9] and is consistent with previous reports in the UK (George & Melegaro, 2001; HPA, 2003; Melegaro *et al.*, 2006; Ihekweazu *et al.*, 2007). A seasonal pattern of disease, with a peak in the winter months, was

Table 1. Summary of IPD isolates 1996–2005 and pneumococcal vaccine coverage by age

PPV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F; PCV7 serotypes (carrier): 4, 6B, 9V, 14, 18C, 19F, 23F (CRM₁₉₇); PCV10 serotypes (carrier): 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F (*Haemophilus* protein D); PCV13 serotypes (carrier): 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A (CRM₁₉₇).

	All	<5 years	5–64 years	>65 years
Number of isolates (% of all isolates)	2691	446 (17 %)	955 (35 %)	1290 (48 %)
Number of males (% of group)	1388 (52 %)	281 (63 %)	514 (54 %)	593 (46 %)
IPD incidence (per 100 000 persons) [95 % CI]	9.2 [8.6–9.9]	24.3 [21.0–27.7]	4.1 [3.7–4.5]	32.2 [28.8–35.5]
Meningitis incidence (per 100 000 persons) [95 % CI]	0.7 [0.5–0.9]	5.7 [4.2–7.1]	0.3 [0.2–0.4]	1.0 [0.5–1.5]
Number of different serotypes identified	51	28	44	44
Rank serotype (number of isolates)				
1	14 (496)	14 (125)	1 (136)	14 (246)
2	9V (207)	6B (54)	14 (125)	9V (117)
3	1 (203)	18C (50)	8 (92)	3 (98)
4	23F (181)	19F (45)	9V (67)	23F (93)
5	8 (168)	23F (38)	4 (66)	6B (78)
6	6B (159)	9V (23)	7F (53)	8 (70)
7	3 (145)	19A (18)	23F (50)	4 (64)
8	4 (140)	6A (17)	12F/19F/3 (40)	19A (61)
9	19F (102)	1 (12)		1 (55)
10	19A (101)	4 (10)		6A (53)
Total isolates represented by top ten serotypes	72 %	88 %	74 %	72 %
Penicillin resistance	5 %	3 %	3 %	6 %
Erythromycin resistance	13 %	19 %	9 %	14 %
PPV23 coverage	2480 (92 %)	416 (93 %)	883 (92 %)	1181 (92 %)
PCV7 coverage	1273 (47 %)	345 (77 %)	403 (42 %)	669 (52 %)
PCV10 coverage	1724 (64 %)	368 (83 %)	600 (63 %)	756 (59 %)
PCV13 coverage	2062 (77 %)	410 (92 %)	684 (72 %)	968 (75 %)

observed (data not shown). As expected, the incidence of IPD also varied with age, with the highest rates being among young children and the elderly (Table 1). The overall incidence of meningitis was 0.7 per 100 000 per year (95 % CI 0.5–0.9), and was highest among the under five age group (Table 1). Serotype 14 accounted for the largest number of cases of IPD (8 % of total) and meningitis (9 % of total); compared with serotype 14, serotype 18C was significantly more likely to cause meningitis than other IPD [unadjusted OR=2.3 (95 % CI 1.3–4.2), $P=0.01$; Table 2], whereas serotypes 1 and 9V were less likely to cause meningitis [unadjusted OR=0.3 (0.1–0.7), $P=0.01$ and 0.4 (0.2–0.9), $P=0.02$, respectively]. Whilst this association was independent of age for serotype 1 [adjusted OR=0.3 (0.1–0.7), $P=0.01$], the age-adjusted effects of serotypes 18C and 9V were smaller and no longer statistically significant [adjusted OR=1.4 (0.7–2.5), $P=0.30$ and 0.5 (0.2–1.2), $P=0.13$, respectively]. Serotype 18C was more prevalent in children, the group most likely to get meningitis, and when the effect of age was included in a model predicting the risk of meningitis there was no additional impact of serotype 18C alone. An interesting finding was that a non-significant crude trend towards a higher chance of meningitis associated with serotype 12F [OR=1.5 (0.8–3.1), $P=0.24$] increased in magnitude and reached statistical significance after adjusting for the independent effect of age on the risk of meningitis [adjusted OR=2.3

(1.1–4.7), $P=0.03$]. Whilst there were more meningitis cases of serotype 12F than other IPD in all age groups, the biggest difference occurred in the 5–64 year group [6/40 (15 %) serotype 12F meningitis].

Variation in the disease manifestation of pneumococcal serotypes has been recognized previously for meningitis (Hausdorff *et al.*, 2000b). Our observation that serotype 12F significantly increases the chance of meningitis versus other IPD is the first such report. The specific pathogenic factors that determine such an association are not clear and would need further investigation. Although serotype 12F has one of the highest attack rates for IPD (Sleeman *et al.*, 2006), curiously serotype 1 has an even higher attack rate whilst having a low association with meningitis. Therefore, it would appear that the meningitis causing potential of a strain is not simply associated with attack rate for IPD. Serotype 12F is not included in the proposed higher-valency conjugate vaccine formulations. Even though the incidence of this serotype in IPD has decreased (Table 2, see below), it is prudent to consider it as one that may potentially account for a larger proportion of disease in the future.

Three serotypes showed major and significant changes ($P<0.001$) in serotype-specific incidence between 1996 and 2005 using Poisson regression; serotypes 1 and 12F decreased in incidence and serotype 8 increased in incidence (Table 2, Fig. 1). Serotype 14 also showed an overall reduction during

Table 2. Serotype-specific age distribution, impact on meningitis and changes in IPD incidence over time

IQR, Interquartile range; RR, relative risk. Serotypes are ordered by total numbers (all ages).

Serotype	Median age in years (IQR)	Cases of meningitis/ total IPD (%)	OR* of serotype causing meningitis versus other IPD compared with serotype 14		Mean annual change in incidence			
			Unadjusted [95 % CI]	<i>P</i>	Adjusted† [95 % CI]	<i>P</i>	RR per year [95 % CI]	<i>P</i>
14	65 (5–81)	45/496 (9 %)	1.0		1.0		0.9 [0.9–1.0]	0.003
9V	69 (50–81)	8/207 (4 %)	0.4 [0.2–0.9] 0.02		0.5 [0.2–1.2] 0.13		1.0 [0.9–1.0]	0.2
1	46 (26–66)	6/203 (3 %)	0.3 [0.1–0.7] 0.01		0.3 [0.1–0.7] 0.01		0.8 [0.8–0.9]	<0.001
23F	67 (32–80)	17/181 (9 %)	1.0 [0.6–1.9] 0.90		1.1 [0.6–2.1] 0.67		1.0 [1.0–1.1]	0.5
8	61 (38–73)	10/168 (6 %)	0.6 [0.3–1.3] 0.21		0.8 [0.4–1.8] 0.66		1.1 [1.1–1.2]	<0.001
6B	64 (2–80)	15/159 (9 %)	1.0 [0.6–1.9] 0.89		0.9 [0.5–1.7] 0.70		1.1 [1.0–1.1]	0.02
3	73 (57–83)	7/145 (5 %)	0.5 [0.2–1.1] 0.10		0.9 [0.4–2.0] 0.73		1.0 [0.9–1.0]	0.6
4	61 (42–79)	6/140 (4 %)	0.4 [0.2–1.1] 0.07		0.6 [0.2–1.5] 0.27		0.9 [0.9–1.0]	0.04
19F	50 (2–72)	18/133 (14 %)	1.6 [0.9–2.8] 0.13		1.3 [0.7–2.4] 0.41		1.0 [1.0–1.1]	0.5
19A	70 (42–82)	6/102 (6 %)	0.6 [0.3–1.5] 0.30		0.8 [0.3–1.9] 0.56		1.0 [0.9–1.0]	0.4
18C	5 (2–63)	19/101 (19 %)	2.3 [1.3–4.2] 0.01		1.4 [0.7–2.5] 0.30		0.9 [0.9–1.0]	0.2
7F	49 (26–71)	8/94 (9 %)	0.9 [0.4–2.0] 0.86		0.9 [0.4–2.1] 0.84		1.0 [0.9–1.1]	1.0
6A	72 (38–84)	8/91 (9 %)	1.0 [0.4–2.1] 0.93		1.1 [0.5–2.6] 0.77		1.0 [0.1–1.1]	0.3
12F	62 (42–76)	11/83 (13 %)	1.5 [0.8–3.1] 0.24		2.3 [1.0–4.7] 0.03		0.8 [0.7–0.8]	<0.001
22F	71 (57–82)	4/57 (7 %)	0.8 [0.3–2.2] 0.61		1.4 [0.5–4.2] 0.55		1.0 [0.9–1.0]	0.8
Other serotypes	67 (43–79)	26/331 (8 %)	0.8 [0.5–1.4] 0.54		1.2 [0.7–2.0] 0.54		–	–
Total	63 (33–79)	214/2691 (8 %)	–		–		–	–

*Serotype 14 was used as the reference strain for the logistic regression model. ORs for serotypes with significant ($P<0.05$) effect on meningitis in adjusted or unadjusted model are underlined.

†Adjusted for age ($P<0.001$). No additional effect of gender.

the study ($P=0.003$) (Fig. 1). The significant decline in incidence of serotype 1 occurred predominantly during 1999 and 2000 with levels being relatively constant after this or possibly increasing from a minimum in 2002. The incidence of serotype 12F decreased between 1996 and 2003, with a slight increase in 2004. Serotype 8 demonstrated a steady increase over 10 years and serotype 14 fluctuated, with a rise in incidence followed by a fall. The reasons for secular changes in the incidence of different serotypes are not fully understood, although changes in incidence of some serotypes have been reported; for example, similar to our study, decreases in serotype 14 disease between 2000 and 2005 have been reported recently in the UK (Ihekweazu *et al.*, 2007), although that study also found increases in serotype 4, 7F and 1 and decreases in 6B and 9V disease over this shorter period, which were not replicated by our longer study. The variation in serotype 1 incidence may be consistent with periods of epidemic spread and outbreaks (Dagan *et al.*, 2000; Gratten *et al.*, 1993; Henriques Normark *et al.*, 2001; Konradsen & Kaltoft, 2002). Serotypes 12F and 8 have both been reported to cause outbreaks (Birtles *et al.*, 2005; CDC, 2005; Hoge *et al.*, 1994), although no outbreaks of either were investigated during this surveillance period, which could account for the changes in incidence detected.

It is possible that outbreaks and increases in incidence may be associated with genotype; for example, ST306 was associated with an increase in incidence of IPD caused by serotype 1 in

Fig. 1. IPD incidence for serotypes that changed significantly over 1996–2005. (a) Significant decline (solid line, serotype 1; dotted line, serotype 12F; dashed line, serotype 14). (b) Significant increase (dotted line, serotype 8).

Sweden (Henriques Normark *et al.*, 2001). MLST characterization of serotype 1 in children in the Oxfordshire region has identified this European clone (ST306) in isolates after 2003. This genotype has also been isolated from children during 2006 and 2007, a period in which an increase in incidence of serotype 1 has been seen (D. W. Crook, unpublished data). Pre-2003, ST227 was the predominant genotype in Oxfordshire with no ST306 isolates detected in children or adults (Brueggemann & Spratt, 2003). Further analysis is needed to assess whether epidemic expansion of specific genotypes associates with periodic changes in the incidence of serotype 1. The possibility that the increase in serotype 8 could be accounted for by a single genotype was investigated during this study. Eighty-one serotype 8 isolates (from a total of 168, 50 % from each year) were typed and no change in clonal type over time was found (results not shown). Therefore, the increase in the incidence of serotype 8 could not be explained by the emergence of a specific genotype. The pneumolysin gene has been studied recently and a shared non-haemolytic allele has been reported from both serotype 8, ST53 and serotype 1, ST306 (Jefferies *et al.*, 2007; Kirkham *et al.*, 2006). Whether the recent emergence of this gene variant can account for these increases in incidence will require further investigation.

Long-term epidemiological studies are important to determine whether the changes in serotype-specific IPD incidence occur in other serotypes. Some changes in serotype incidence have been reported over longer time periods than that of our study (Akduman *et al.*, 2006; Feikin & Klugman, 2002); therefore, a 10-year observation period may be insufficient to demonstrate subtle or infrequent changes in frequency of other serotypes, particularly rarer ones. However, the fact that we have documented significant changes in the incidence of four serotypes over the study period in Oxfordshire indicates a dynamic pneumococcal population. This means that any IPD serotype-specific variability that may arise in the Oxfordshire region as a result of vaccine implementation must be considered against this changing background.

There was no evidence of change in penicillin resistance over the study period, the rate being constant at 5 % of isolates (Table 1). All isolates were intermediately penicillin-resistant (MICs, 0.16–1.5 $\mu\text{g ml}^{-1}$) with the exception of one isolate with a MIC of 2 $\mu\text{g ml}^{-1}$ (a serotype 9V isolate that was susceptible to other antibiotics tested). Erythromycin resistance also remained constant at 13 %. Resistance to other antibiotics was low: chloramphenicol 0.4 % ($n=12$), cefotaxime 0.4 % ($n=12$) and tetracycline 3 % ($n=55$). Only 1.2 % of isolates were resistant to two antibiotics and 0.7 % ($n=21$) were resistant to three (all resistant to penicillin). Of these 21, 17 (80 %) were serotypes represented in the 7-valent vaccine [the others being serotypes 15A (2), 6A (1) and a non-typeable serotype]. The prevalence of antibiotic resistance in Oxfordshire remains low compared with other European countries (Beekmann *et al.*, 2005) and the USA.

Four hundred and forty-six clinical isolates were collected from children aged less than 5 years, 428 strains of which

were genotyped using MLST (see Supplementary Table S2 available in JMM Online). Ninety-nine STs were identified, 43 of which occurred only once (including nine novel STs). The eBURST v. 3 algorithm identified 16 clonal complexes, eight of which included >10 isolates (Table 3). All the major clonal complexes included one predominant genotype and one or two major serotypes, except for one that contained three serotypes (19F, 19A and 15 B/C). One possible novel variant was found, namely a variant of ST65 that expressed a serotype 6B capsule. This is consistent with a capsular switch that is usually regarded to arise by recombination as described for serotype 19A (Pai *et al.*, 2005). However, given that 6A and 6B capsular sequences only differ by a single nucleotide difference in the *wciP* gene (Mavroidi *et al.*, 2004), it is possible that the change occurred by point mutation. Nonetheless, this observation emphasizes the phenomenon of capsular switching in nature, although in this case the switch was from a serotype not in PCV7 to one which is. This study provides a baseline of genotypic data among paediatric isolates, against which any alterations that may occur in the population after vaccine implementation will be monitored.

Case-control study

The effect of the PPV23 vaccination programme in adults was estimated using a case-control study carried out between 1995 and 2000, before the recommended age-based vaccination programme started. The study included 352 hospitalized IPD cases and 352 matched controls. There was no difference in the mean ages (cases: mean, 70.4 years; controls, 70.9 years), deprivation score (cases: mean, 10.8; controls, 11.7) or gender (48 % males in both groups), and the distribution of IPD serotypes was similar to those in Table 1 (90 % of serotypes isolated from the cases were contained in the PPV23 vaccine compared with 92 % in the whole surveillance period). Thirty-five cases (10 %) and 50 controls (14 %) had received PPV23 more than 1 month prior to the episode of IPD, giving a crude vaccine effectiveness of 43 % (2–68 %; $P=0.04$). The uptake of the vaccine was low at this time nationally, the percentage of over 65 years being vaccinated rising from <10 to 20 % over the study period (Noakes *et al.*, 2006). There was little difference in effectiveness after adjustment for the three most common pre-existing co-morbidities (respiratory disease, cardiac disease and neoplastic disease) or the presence of any pre-existing co-morbidity (Table 4). The PPV23 vaccine effectiveness as estimated in this study is similar to those of other reports (Conaty *et al.*, 2004; Musher *et al.*, 2006). When the variable 'time since vaccination' was stratified by more than or less than 1 year, there was no evidence of heterogeneity in vaccine effectiveness ($P=0.7$). The duration of PPV23 protection is not clear and could not be estimated from this study.

The introduction of PCV7 will make it difficult to assess the effectiveness of PPV23 using UK IPD epidemiological data after 2006. Although PCV7 is administered to children, there is evidence of a herd effect in adults in

Table 3. Summary of MLST data obtained from IPD samples from children under 5 years of age

ST65 has not been reported previously in serotype 6B. STs in italics are new to this study. Clonal complexes are indicated by superscript letters – the proposed founder is in bold. The clonal complexes for the major STs were: a: $n=81$, serotype 14, ST9; b: $n=47$, serotype 9V or 19F, ST162; c: $n=44$, serotype 18C, ST113; d: $n=40$, serotype 14, ST124; e: $n=18$, serotype 23F, ST311; f: $n=19$, serotype 19A or 15BC, ST199; g: $n=12$, serotype 6A, ST65; h: $n=16$, serotype 6B, ST176. The remaining clonal complexes had between two and seven strains (not shown).

Serotype	Major ST	No. of major ST isolates (%)	Minor STs (n)	Singleton STs
14	9^a	73 (60 %)	124^d (37), 15 ^a (6)	11 ^a , 24 ^a , 129, 409, 1109 ^d
6B	138	27 (54 %)	176^h (14)	65, 95, 315, 327, 386, 402 ^h , 465, 469 ^h , 2227
18C	113^c	29 (62 %)	114 ^c (4), 121 ^c (4), 308 ^c (3), 119 (2)	110 ^c , 1073 ^c , 2115, 2237 ^c , 2239 ^c
19F	162^b	22 (54 %)	309 (5), 420 (2), 459 (2), 476 (2)	43, 199, 251, 312 ^b , 314 ^b , 426, 654, 2228
23F	36	17 (49 %)	311 ^e (16)	81, 440
9V	162^b	17 (74 %)	156 ^b (3)	163 ^b , 407 ^b , 2235 ^b
19A	199^f	11 (61 %)	173 (3)	416, 419 ^f , 1201, 2229 ^f
6A	65 ^g	9 (53 %)	—	42^e , 313, 398, 457, 460 ^g , 470, 1360 ^g , 1390
1	227	9 (75 %)	306 (2)	300
4	246	4 (36 %)	205 (3), 206 (2), 247 (2)	—
7F	191	10 (100 %)	—	—
3	180	6 (86 %)	—	458
8	53	4 (67 %)	—	944, 2234
33F	673	3 (50 %)	60 (2)	2230
15B/C	199^f	4 (80 %)	—	411 ^f
9N	66	2 (67 %)	—	834
12F	218	2 (67 %)	—	223
21	193	—	—	—
16F	—	—	—	30, 2238
NT*	—	—	—	124, 1475
5	—	—	—	289
20	—	—	—	235
22F	—	—	—	455
23A	—	—	—	438 ^e
35B	—	—	—	198
38	—	—	—	393

*Non-typeable.

the USA, where there has been a reduction in the overall incidence of IPD in adults (Lexau *et al.*, 2005; Whitney *et al.*, 2003). This reduction was caused by a drop in incidence of the serotypes contained within the conjugate vaccine, whereas the incidence of serotypes contained only within the

23-valent polysaccharide vaccine did not change. This overall herd effect for PCV7 in the USA (28 % decline in adults aged over 50 years; Lexau *et al.*, 2005) is similar to the estimate of direct PPV23 vaccine effectiveness found in our study. If the conjugate vaccine reduces adult pneumococcal

Table 4. PPV23 vaccine effectiveness

Patient history	No. of cases (% of total)*	No. of controls (% of total)*	OR†	Percentage vaccine effectiveness†
Pneumococcal vaccine	35 (10 %)	50 (14 %)	0.57	43 % [2 to 68]
Respiratory disease	88 (25 %)	62 (18 %)	0.49	51 % [13 to 73]
Cardiac disease	147 (42 %)	181 (51 %)	0.62	38 % [−9 to 65]
Neoplastic disease	72 (20 %)	77 (22 %)	0.57	43 % [2 to 68]
Any co-morbidity	272 (77 %)	285 (81 %)	0.59	41 % [−3 to 66]
Smoking	165 (53 %)	145 (47 %)	0.53	47 % [7 to 70]

*The total number of cases and controls was the same (352).

†OR for vaccinated versus not vaccinated and corresponding percentage vaccine effectiveness (estimated by 1 minus OR): unadjusted followed by adjusted for respiratory, cardiac, neoplastic, any co-morbidity and smoking, respectively.

disease via the herd effect in the UK, a careful re-evaluation of the PPV23 vaccination programme will be needed, taking into account how much more disease PPV23 will potentially prevent and at what cost.

The continuous enhanced surveillance in the Oxfordshire area since 1996 represents a valuable set of serotype data with which to monitor vaccine impact. The effect in the UK of implementing the PCV7 vaccine rapidly and achieving a high uptake in a very short time, in contrast to the USA where the uptake was more gradual, may have a different impact on the pneumococcal population that continued surveillance will now reveal. Increasing the understanding of the secular changes of *S. pneumoniae* and the potential of different serotypes to cause disease in different age groups may assist in determining the importance of these population effects.

Ethical approval (Central Oxford Research Ethics Committee: C98.249; South Bucks Local Research Ethics Committee: AK/AM/REC 565; Northampton Medical Research Ethics Committee: RS/MS/01/96; East Berkshire Research Ethics Committee: 2087-2; and Milton Keynes Local Research Ethics Committee: ARF/MKLREC/31/01).

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