Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study

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Summary

Background The seven-valent pneumococcal conjugate vaccine (PCV7) has reduced vaccine-type (VT) invasive pneumococcal disease but increases in non-vaccine-type (NVT) disease have varied between countries. We assess the effect of the PCV7 vaccination on VT and NVT disease in England and Wales.

Methods The study cohort was the population of England and Wales from July, 2000, to June, 2010. We calculated incidence rate ratios (IRRs) to compare incidences of VT and NVT disease before (2000–06) and after (2009–10) the introduction of PCV7. We used data from the national surveillance database. Cases included in our analysis were restricted to those confirmed by culture linked with isolates referred for serotyping at the national reference centre by laboratories in England and Wales. We adjusted for potential bias from missing data (serotype and age of patient) and changes in case ascertainment rates during the study period.

Findings 5809 cases of invasive pneumococcal disease were reported in 2009–10, giving an incidence of 10·6 per 100 000 population in 2009–10, which, when compared with the adjusted average annual incidence of 16·1 in 2000–06, gives an overall reduction of 34% (95% CI 28–39). VT disease decreased in all age groups, with reductions of 98% in individuals younger than 2 years and 81% in those aged 65 years or older. NVT disease increased by 68% in individuals younger than 2 years and 48% in those aged 65 years or older, giving an overall reduction in invasive pneumococcal disease of 56% in those younger than 2 years and 19% in those aged 65 years or older. After vaccine introduction, more NVT serotypes increased in frequency than decreased, which is consistent with vaccine-induced replacement. Key serotypes showing replacement were 7F, 19A, and 22F. Increases in NVT invasive pneumococcal disease were not associated with antimicrobial resistance.

Interpretation Despite much serotype replacement, a substantial reduction in invasive pneumococcal disease in young children can be achieved with PCV7 vaccination, with some indirect benefit in older age groups. Further reductions should be achievable by use of higher valency vaccines. Robust surveillance data are needed to properly assess the epidemiological effect of multivalent pneumococcal disease vaccines.

Funding Health Protection Agency.

Introduction

In September, 2006, the seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the UK with a vaccination schedule of 2, 4, and 13 months, and catch-up vaccination for children aged up to 2 years. On the basis of reports from the first few years of the PCV7 programme in the USA,[1] immunisation of infants in the UK was expected to reduce not only the incidence of invasive pneumococcal disease in vaccinated cohorts but also the overall burden of such disease in the unvaccinated population through herd immunity, generated by reduction in carriage of vaccine serotypes. Some increase in non-vaccine type (NVT) invasive pneumococcal infections, especially serotype 19A, has been reported in children and adults in the USA.[2,3] However, this increase has not been sufficient to offset the reduced incidence of vaccine type (VT) infections—reductions in total invasive pneumococcal disease have been recorded in all age groups. In populations aged 65 years or older, in which the burden of disease is high, a sustained reduction in overall invasive pneumococcal disease incidence of around 40% has been reported.[4]

However, experience with the indirect effects of the PCV7 programme elsewhere has been mixed, with increases in NVT infections largely offsetting the reduction in VT infections in some countries such as Spain, the Netherlands, France, and some indigenous populations in the USA and Australia.[5] The extent to which the recorded increases in NVT disease are real or the result of surveillance artifacts associated with changes in diagnostic or reporting practices after PCV7 was introduced is often unclear.[5] Baseline periods before PCV7 vaccination—from which estimates of percentage change in disease incidence are made—are of variable duration, completeness, and stability, and some populations are too small to produce robust estimates. Even when convincing evidence of true increases in NVT disease after vaccination exists, changes unrelated to vaccination, such as natural secular trends in specific serotypes or antibiotic pressure rather than vaccine-

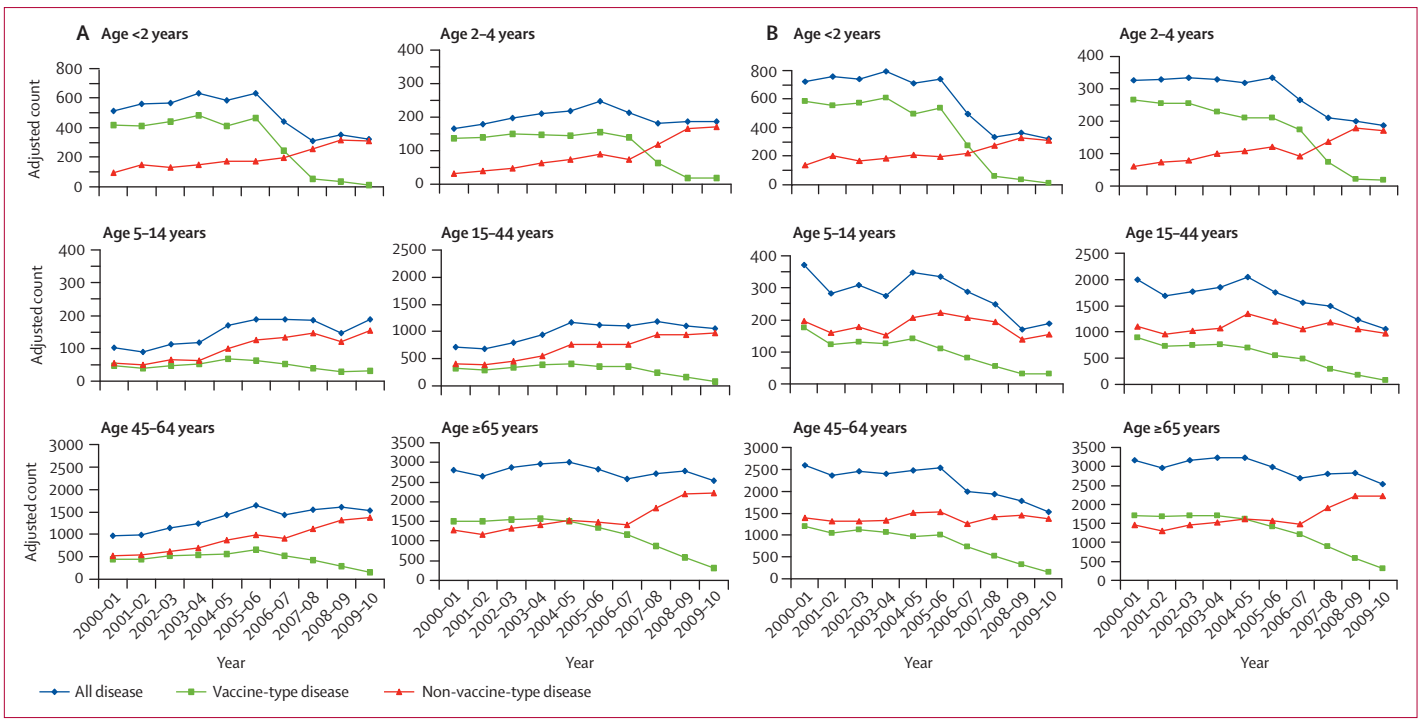

Figure 1: **Trends in Invasive pneumococcal disease in England and Wales (2000–10), by age group**
Without correction for underlying trends in case ascertainment (A). With correction for underlying trends in case ascertainment (B). Data are adjusted for missing serotype or age and for changes in population denominators.

induced serotype replacement, might be the cause.[6–8] Although vaccination schedules differ between countries—eg, between the UK and the USA, which uses a 2, 4, 6, and 12–15 month schedule—available data do not suggest that reported variations in NVT incidence are the result of such differences,[6] nor of the rapidity with which high vaccine uptake is achieved.

In 1996, in anticipation of the future availability of pneumococcal conjugate vaccines, enhanced national surveillance of invasive pneumococcal disease was established in England and Wales.[9] Before the introduction of PCV7, more than 5000 invasive pneumococcal infections were reported every year through the enhanced surveillance system, providing a robust baseline against which to assess the effect of PCV7 vaccination. We report the effect of the PCV programme on VT and NVT disease in vaccinated cohorts and in older, unvaccinated age groups, having controlled for possible changes over time in the sensitivity of our surveillance system. We also investigated changes in the incidence of individual serotypes to assess the extent to which such natural trends were affected by serotype replacement and to identify key replacing serotypes that are not covered by multivalent PCV vaccines.

Methods

Data collection

The study cohort comprised the population of England and Wales between July, 2000, and June, 2010 (about 54·8 million individuals). Since 1996, a dataset of all invasive pneumococcal infections reported in England and Wales has been created, by linking computerised laboratory reports given to the Health Protection Agency (HPA) and isolates referred to the HPA Respiratory and Systemic Infection Laboratory for serotyping.[9] This dataset consists of cases in which *Streptococcus pneumoniae* has been identified by culture, or more rarely by antigen detection or PCR, in a normally sterile site. Consistent with clinical practice in the UK, blood cultures and cerebrospinal fluid samples were almost exclusively obtained from patients who were admitted to hospital. Repeat samples from sterile sites within 30 days from the same individual were regarded as part of the same episode. Antimicrobial resistance results for penicillin and erythromycin are also available, together with some clinical information such as whether a patient had meningitis. Antimicrobial susceptibility testing was done according to British Society for Antimicrobial Chemotherapy guidelines.[10]

From January, 2006, PCR diagnosis was offered by the HPA on cerebrospinal fluid and pleural fluid samples from patients with suspected meningitis or empyema, with serotyping done with a pneumococcal polysaccharide antigen assay that detects 14 serotypes.[11] After the introduction of PCV7 vaccination in September, 2006, all patients with invasive pneumococcal disease in cohorts eligible for routine or catch-up vaccination were followed up for vaccination history and information on

	Average adjusted cases 2000–06 (raw*)	Average adjusted incidence 2000–06 (per 100 000 population)	Adjusted cases 2009–10 (raw*)	Adjusted incidence 2009–10 (per 100 000 population)	Incidence rate ratios (95% CI) 2009–10 *vs* 2000–06 (with trend adjustment)	Incidence rate ratio 2009–10 *vs* 2004–06 (no trend adjustment)
<2 years						
All	741 (510)	54·2	322 (322)	23·6	0·44 (0·39–0·49)	0·53
VT	558 (283)	40·8	12 (10)	0·9	0·02 (0·01–0·05)	0·03
NVT	183 (94)	13·4	310 (253)	22·7	1·68 (1·37–2·06)	1·81
2–4 years						
All	329 (182)	16·4	187 (187)	9·3	0·57 (0·49–0·67)	0·80
VT	238 (98)	11·9	17 (13)	0·8	0·07 (0·04–0·13)	0·11
NVT	90 (39)	4·5	170 (128)	8·5	1·82 (1·30–2·55)	2·08
5–14 years						
All	320 (136)	5·1	187 (187)	3·0	0·59 (0·48–0·72)	1·05
VT	134 (36)	2·2	33 (24)	0·5	0·25 (0·16–0·38)	0·50
NVT	185 (53)	3·0	155 (114)	2·5	0·82 (0·64–1·04)	1·37
15–44 years						
All	1850 (866)	8·3	1060 (1059)	4·7	0·57 (0·49–0·67)	0·93
VT	733 (186)	3·3	86 (70)	0·4	0·12 (0·07–0·21)	0·23
NVT	1117 (304)	5·0	974 (793)	4·3	0·85 (0·71–1·02)	1·28
45–64 years						
All	2471 (1114)	17·9	1528 (1526)	11·0	0·62 (0·58–0·66)	0·99
VT	1071 (270)	7·7	155 (122)	1·1	0·15 (0·12–0·18)	0·25
NVT	1400 (366)	10·1	1372 (1077)	9·9	0·96 (0·87–1·06)	1·48
≥65 years						
All	3125 (2620)	34·8	2531 (2528)	28·2	0·81 (0·75–0·88)	0·87
VT	1637 (772)	18·2	305 (252)	3·4	0·19 (0·14–0·25)	0·21
NVT	1488 (721)	16·6	2226 (1841)	24·8	1·48 (1·32–1·65)	1·48
All ages						
All	8835 (5428)	16·1	5816 (5809)	10·6	0·66 (0·61–0·72)	0·88
VT	4372 (1645)	8·0	608 (491)	1·1	0·14 (0·11–0·18)	0·20
NVT	4463 (1576)	8·1	5208 (4206)	9·5	1·19 (1·07–1·31)	1·46

Raw totals for VT and NVT add to less than all due to missing data on serotype. *Without adjustment for missing data (serotype or age of patient) or changes in population denominators and underlying trends in ascertainment. VT=vaccine type. NVT=non-vaccine type. 95% CIs are not given for 2009–10 *vs* 2004–06 because of insufficient data points to estimate over-dispersion caused by annual variations.

***Table 1*: Invasive pneumococcal disease in England and Wales, by age group, serotype, and date**

clinical presentation, thus improving ascertainment of cases with clinical symptoms of pneumococcal meningitis confirmed by blood culture only. Cases of invasive pneumococcal infection included in our analysis were restricted to those confirmed by culture. For analysis of meningitis cases, any cases ascertained solely as a result of the clinical information obtained from active follow-up of patients, or only from the referral information provided with invasive isolates sent for serotyping (for which recording of information on the laboratory systems has improved over time), were excluded. Serotypes 6A and 6C were routinely distinguished from each other from May, 2009, onwards, and have therefore been combined in this analysis. Full serotyping within serogroups in the HPA reference laboratory started in 2000. The study period thus spanned 10 years, 6 years of baseline before PCV7 vaccination from 2000–01 to 2005–06 and 4 years after PCV7 vaccination, from 2006–07 to 2009–10. Study years run from July to June.

The proportion of all culture-positive invasive pneumococcal infections that were serotyped increased from 50% in 2000–01 to 81% in 2009–10, with variation between age groups. In the same period, the proportion of cases with missing age data decreased from 4·4% to 0·1% and the population size increased in most age groups.[12] To correct for these changes, the raw number of yearly invasive pneumococcal infections with known age and serotype data were adjusted with the assumption that cases with missing data for age, serotype, or both had the same age and serotype distributions as those cases in which this information was known—the number of extra cases were then added to the raw numbers in each category. Numbers were then further adjusted to 2009–10 Office for National Statistics population denominators in each age group.[12] There was also an increasing trend in ascertainment of

	Average adjusted cases 2000–06 (raw*)	Average adjusted incidence 2000–06 (per 100 000 population)	Average adjusted cases 2008–10 (raw*)	Average adjusted incidence 2008–10 (per 100 000 population)	Incidence rate ratio (95% CI) 2008–10 *vs* 2000–06
<5 years					
All	107 (95)	3·18	49 (48)	1·44	0·56 (0·36–0·89)
VT	82 (59)	2·43	4 (4)	0·12	0·05 (0·02–0·15)
NVT	25 (18)	0·75	45 (44)	1·32	1·77 (1·27–2·47)
5–64 years					
All	88 (83)	0·21	84 (84)	0·20	0·95 (0·76–1·20)
VT	42 (28)	0·10	14 (13)	0·03	0·33 (0·21–0·52)
NVT	46 (30)	0·11	70 (64)	0·16	1·54 (1·22–1·95)
≥65 years					
All	39 (36)	0·43	32 (32)	0·35	0·82 (0·57–1·19)
VT	16 (11)	0·18	5 (5)	0·05	0·30 (0·10–0·96)
NVT	22 (15)	0·25	27 (25)	0·30	1·19 (0·84–1·69)

VT=vaccine type. NVT=non-vaccine type. 95% CIs are not given for 2009–10 *vs* 2004–06 because of insufficient data points to estimate over-dispersion cause by annual variations. *Without adjustment for missing data (serotype or age of patient) or changes in population denominators and underlying trends in ascertainment.

***Table 2*: Pneumococcal meningitis in England and Wales, by age group, serotype, and date**

cases during the period, as evidenced by a parallel increase in cases of other invasive bacterial infections reported to HPA, which continued up until 2009–10.[13] To correct for this increase, the average percentage annual change in total invasive pneumococcal infections from 2000–06 was calculated for each age group, and this was then used to retrospectively increase counts to the projected 2009–10 level of ascertainment. For example, in the age group of individuals aged younger than 2 years, a 3·8% increase was recorded in ascertainment per year, so for 2005–06 (4 years before 2009–10) an inflation factor of 1·16 ($1·038^4$) was used. Health Protection Agency has approval under PIAG Section 60 of the Health and Social Care Act 2001 (which has been subsumed into the National Information Governance Board for Health and Social Care with Section 60—now Section 251 of the NHS Act 2006) to process confidential information from patients for the purposes of monitoring the efficacy and safety of vaccination programmes.

Statistical analysis

Incidence rate ratios (IRRs) comparing 2009–10 incidence to the 2000–06 baseline incidence were calculated with Poisson regression. Overdispersion was allowed for, if present, by rescaling the SEs on the basis of the Pearson χ^2 test statistic and residual degrees of freedom. Raw counts were modelled with the inflation factors included in the model as an offset. To investigate the effect of the trend adjustment, IRRs were calculated, comparing 2009–10 counts with 2004–06 counts without adjustment for trends in ascertainment. The reason for use of 2004–06 counts is because these are the years closest to when the vaccine was introduced and because of the upward trend in case ascertainment from 2000 to 2006. Meningitis cases were analysed separately because ascertainment of these more serious manifestations of the disease were thought to be less likely to have changed over time. The proportion of cases that were serotyped over time was much the same between meningitis cases and all invasive pneumococcal disease cases.

For the analysis of all infections, VT infections, and NVT infections, six age groups were used (younger than 2 years, 2–4 years, 5–14 years, 15–44 years, 45–64 years, and 65 years or older), comparing 2009–10 IRR with the baseline IRR. To increase power for the analysis of changes in individual serotypes, and in a subset of patients with meningitis, data were analysed in three age groups (younger than 5 years, 5–64 years, and 65 years or older), and the years after PCV7 (2008–09 and 2009–10) were combined. For type-specific analyses, all serotypes that had an average of at least five reports per year during the study period were considered, and a 1% significance level was used because of the many comparisons made.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

After adjustment for missing age and serotype data, and changes in population size, we recorded a significant upward trend in the annual number of reports in each age group between 2000–01 and 2005–06, consistent with an underlying upward trend in ascertainment (figure 1). The average yearly increase in this period was 3·8% (95% CI 0·8–6·9%) in individuals younger than 2 years, 7·8% (6·3–9·2) in those aged 2–4 years, 15·4% (5·7–25·9) in those aged 5–14 years, 12·0% (5·8–18·5) in those aged

	Vaccine	Age <5 years			Age 5–64 years			Age ≥65 years		
		Average adjusted cases 2000–06 (raw*)	Average adjusted cases 2008–10 (raw*)	Incidence rate ratio (95% CI)	Average adjusted cases 2000–06 (raw*)	Average adjusted cases 2008–10 (raw*)	Incidence rate ratio (95% CI)	Average adjusted cases 2000–06 (raw*)	Average adjusted cases 2008–10 (raw*)	Incidence rate ratio (95% CI)
4	7v	36 (18)	3 (3)	0·08 (0·01–0·50)†	324 (88)	87 (64)	0·26 (0·17–0·39)†	174 (85)	48 (39)	0·27 (0·19–0·38)†
6B	7v	134 (63)	8 (7)	0·06 (0·04–0·10)†	139 (34)	48 (36)	0·37 (0·23–0·59)†	168 (79)	68 (55)	0·41 (0·29–0·57)†
9V	7v	57 (26)	2 (2)	0·03 (0·01–0·12)†	384 (97)	69 (51)	0·18 (0·12–0·28)†	307 (142)	66 (54)	0·22 (0·14–0·36)†
14	7v	310 (145)	3 (3)	0·01 (0·00–0·06)†	546 (139)	52 (38)	0·10 (0·06–0·17)†	543 (257)	89 (72)	0·16 (0·11–0·24)†
18C	7v	84 (40)	7 (6)	0·08 (0·06–0·12)†	162 (41)	52 (39)	0·33 (0·24–0·47)†	60 (29)	36 (29)	0·60 (0·41–0·88)†
19F	7v	115 (54)	15 (12)	0·13 (0·10–0·18)†	172 (44)	46 (34)	0·27 (0·19–0·38)†	119 (56)	61 (50)	0·52 (0·37–0·74)†
23F	7v	73 (35)	4 (3)	0·05 (0·02–0·12)†	191 (49)	49 (36)	0·25 (0·16–0·41)†	264 (125)	78 (63)	0·30 (0·21–0·42)†
1	13v	47 (24)	68 (54)	1·36 (0·78–2·39)	584 (178)	465 (346)	0·68 (0·39–1·19)	90 (48)	110 (89)	1·10 (0·60–2·02)
3	13v	17 (9)	30 (24)	1·66 (1·16–2·39)†	234 (59)	189 (141)	0·85 (0·64–1·14)	224 (111)	276 (225)	1·20 (1·04–1·40)
5	13v	3 (1)	5 (4)	1·83 (0·38–8·72)	11 (2)	20 (14)	2·31 (0·40–13·24)	0·4 (0·2)	5 (4)	14·68 (0·87–247·82)
6A/C	13v	40 (26)	19 (16)	0·47 (0·26–0·82)†	103 (26)	104 (78)	1·03 (0·85–1·26)	144 (69)	197 (160)	1·37 (1·18–1·60)†
7F	13v	24 (12)	104 (83)	4·31 (3·01–6·15)†	262 (76)	451 (339)	1·57 (1·16–2·14)†	86 (42)	187 (152)	2·13 (1·77–2·55)†
19A	13v	45 (21)	100 (79)	2·22 (1·68–2·93)†	130 (33)	233 (177)	1·87 (1·38–2·52)†	111 (55)	303 (247)	2·61 (1·89–3·62)†
8	NA	17 (8)	15 (12)	0·87 (0·70–1·09)	526 (134)	296 (221)	0·58 (0·49–0·68)†	216 (102)	166 (134)	0·78 (0·61–0·98)
9N	NA	6 (3)	3 (3)	0·50 (0·16–1·54)	93 (24)	61 (46)	0·66 (0·52–0·84)†	72 (34)	64 (52)	0·89 (0·72–1·09)
10A	NA	1 (1)	6 (5)	4·58 (1·44–14·56)†	26 (7)	26 (20)	1·01 (0·71–1·45)	13 (6)	18 (15)	1·41 (0·76–2·62)
11A	NA	4 (2)	8 (7)	2·13 (0·73–6·18)	56 (14)	53 (40)	1·02 (0·73–1·43)	49 (23)	73 (59)	1·50 (1·10–2·04)
12F	NA	6 (3)	8 (7)	1·45 (0·78–2·68)	155 (41)	115 (86)	0·73 (0·60–0·87)†	49 (24)	53 (43)	1·05 (0·73–1·51)
15A	NA	0 (0)	5 (4)	>10	7 (2)	16 (12)	2·36 (1·01–5·52)	13 (6)	31 (26)	2·46 (1·12–5·39)
15B	NA	6 (3)	13 (11)	2·14 (0·89–5·15)	22 (6)	26 (20)	1·25 (0·66–2·37)	15 (7)	33 (27)	2·23 (1·39–3·58)†
15C	NA	4 (2)	13 (11)	3·21 (1·48–6·97)†	13 (3)	18 (14)	1·49 (0·75–2·96)	8 (4)	17 (14)	2·04 (1·34–3·12)†
16F	NA	2 (1)	3 (2)	1·22 (0·25–5·96)	30 (7)	20 (15)	0·79 (0·39–1·60)	30 (14)	42 (35)	1·48 (0·97–2·25)
17F	NA	2 (1)	3 (2)	1·19 (0·34–4·17)	21 (6)	12 (9)	0·57 (0·31–1·04)	16 (8)	20 (17)	1·28 (0·64–2·54)
20	NA	2 (1)	2 (2)	1·09 (0·24–5·05)	73 (19)	33 (25)	0·47 (0·39–0·56)†	52 (24)	33 (27)	0·66 (0·49–0·89)†
21	NA	1 (1)	6 (5)	4·58 (1·25–16·8)	7 (2)	3 (3)	0·60 (0·15–2·31)	1 (1)	8 (7)	7·82 (2·29–26·73)†
22F	NA	9 (4)	30 (24)	3·25 (1·76–5·99)†	124 (31)	221 (164)	1·85 (1·35–2·54)†	125 (59)	258 (210)	2·09 (1·74–2·51)†
23A	NA	3 (1)	4 (3)	1·36 (0·49–3·77)	19 (6)	27 (21)	1·28 (0·80–2·05)	29 (15)	71 (58)	2·30 (1·65–3·23)†
23B	NA	1 (1)	7 (6)	6·77 (2·83–16·18)†	3 (1)	18 (14)	6·06 (1·57–23·45)	2 (1)	25 (21)	10·64 (3·75–30·16)†
24F	NA	2 (1)	3 (3)	1·75 (0·94–3·23)	6 (1)	6 (4)	1·04 (0·40–2·73)	6 (3)	15 (12)	2·44 (1·69–3·53)†
31	NA	0 (0)	0 (0)	0	14 (4)	18 (13)	1·20 (0·67–2·15)	15 (7)	25 (20)	1·62 (0·99–2·67)
33F	NA	12 (6)	19 (15)	1·61 (0·82–3·16)	40 (11)	64 (49)	1·58 (1·16–2·15)†	39 (19)	82 (67)	2·04 (1·58–2·63)†
34	NA	1 (0)	0 (0)	0	5 (2)	4 (3)	0·70 (0·31–1·55)	5 (2)	10 (8)	2·01 (1·12–3·61)
35B	NA	1 (1)	3 (3)	3·10 (1·07–9·00)	5 (1)	9 (7)	2·03 (1·09–3·77)	6 (3)	14 (12)	2·34 (1·14–4·81)
35F	NA	2 (1)	3 (2)	1·02 (0·56–1·86)	22 (6)	24 (19)	1·17 (0·69–2·01)	14 (7)	29 (24)	2·02 (1·20–3·38)†
38	NA	4 (2)	6 (5)	1·53 (0·75–3·10)	15 (4)	11 (8)	0·78 (0·37–1·63)	17 (8)	37 (30)	2·25 (1·20–4·22)

7v=seven-valent pneumococcal conjugate vaccine. 13v=13-valent pneumococcal conjugate vaccine. NA=not applicable. *Without adjustment for missing data (serotype or age of patient) or changes in population denominators and underlying trends in ascertainment. †Indicates a significant (p<0·01) increase or decrease in incidence between 2000–06 and 2008–10.

***Table 3*: Incidence rate ratios for serotype-specific invasive pneumococcal disease in England and Wales by age group and date**

15–44 years, 11·5% (8·5–14·6) in those aged 45–64 years, and 1·4% (–1·4 to 4·2) in those aged 65 years or older. The yearly annual increase in number of reports in all individuals younger than 5 years was 5·3% (3·0–7·6) and in all individuals aged 5–64 years was 12·2% (8·0–16·6). Figure 1 shows the adjusted yearly cases with the trend correction.

The percentage change in the adjusted number of invasive pneumococcal infections (100×[IRR–1]), allowing for the upward trend in ascertainment, shows significant reductions in the total number cases in all age groups, with a total reduction across all age groups of 34% (95% CI 28–39) in 2009–10 compared with the average annual incidence in 2000–06 (table 1). The magnitude of the overall reduction in invasive pneumococcal disease incidence between 2000–06 and 2009–10 varies between age groups, largely because of differences in the percentage change in NVT serotypes—we recorded no change in the incidence of infection with NVT serotypes in individuals aged

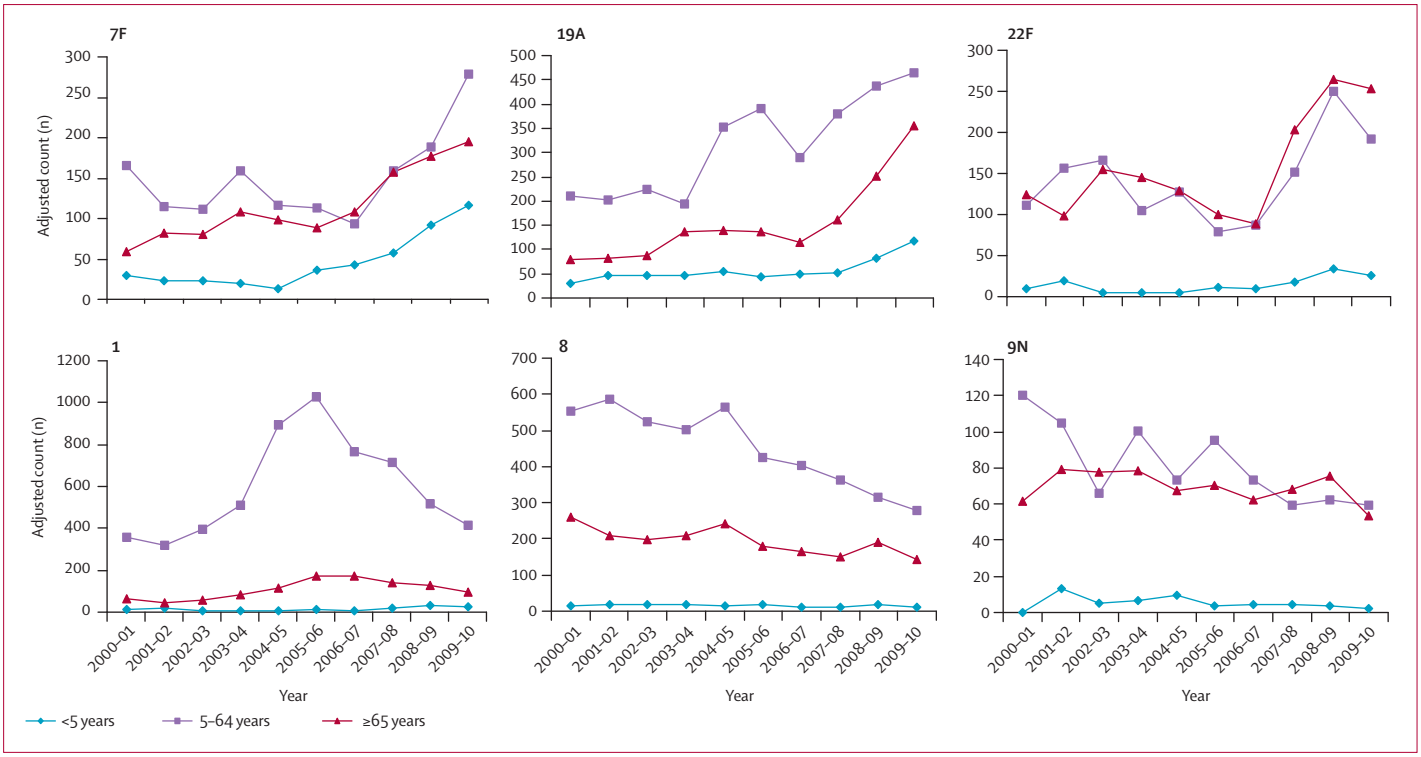

Figure 2: **The effect of PCV7 vaccination on the prevalence of specific *Streptococcus pneumoniae* serotypes, by age group**

5–64 years, but significant increases in all other age groups (table 1).

Data for the subset of patients with pneumococcal meningitis is shown in table 2. There was no evidence of an upward trend in the numbers of meningitis cases before PCV7 vaccination after accounting for changes in population size and missing serotype and age data, so a trend adjustment was not included. We recorded an increase in the number of meningitis cases due to NVT serotypes in individuals aged younger than 5 years and those aged 5–64 years (table 2).

We recorded a significant reduction between 2000–06 and 2008–10 in the adjusted incidence of all seven PCV7 serotypes in all age groups (table 3). During the same period, the incidence of invasive pneumococcal infections due to serotype 6A/6C significantly decreased in individuals younger than 5 years, did not change in those aged 5–64 years, and significantly increased in those aged 65 years or older (table 3). We recorded significant increases in all age groups for serotypes 7F, 19A, and 22F (table 3; figure 2). These three serotypes, together with serotypes 1 and 8 were the most prevalent in 2009–10 in individuals aged 5 years or older. In children younger than 5 years, we recorded significant increases in the incidence of invasive pneumococcal infections due to serotypes 3, 10A, 15C, and 23B. In individuals aged 65 years or older, we recorded increases in cases due to serotypes 15B, 15C, 21, 23A, 23B, 24F, 33F, and 35F, of which the incidence of 33F also increased in individuals aged 5–64 years.

Apart from the PCV7 serotypes, other serotypes showing a decrease in one or more age groups after PCV7 introduction were 8, 9N, 12F, and 20. For serotype 1, although no significant reduction was seen after PCV7 vaccination was introduced, in individuals aged 5–64 or 65 years or older, there was clear evidence of a cyclical change in incidence during the 10-year study period in these age groups (figure 2). In individuals aged 5–64 years, serotype 1 accounted for 17% of the serotyped cases in 2009–10 compared with 35% in 2005–06. For individuals aged 65 years or older, serotype 1 accounted for only 4% of the serotyped cases in 2009–10 and 11% in 2005–06. Overall, we recorded more increases than decreases in the number of cases due to non-PCV7 serotypes after PCV7 vaccination was introduced: in individuals aged younger than 5 years, seven non-PCV7 serotypes increased and one decreased; in those aged 5–64 years, four non-PCV7 serotypes increased and four decreased; and in those aged 65 years or older, 12 non-PCV7 serotypes increased and one decreased (table 3).

Among the key serotypes that increased significantly after PCV7 vaccination, there was no evidence of an association with a change in antimicrobial resistance to either penicillin or erythromycin. Although for serotype 19A we recorded an increase in penicillin non-susceptibility (resistant plus intermediate resistance)

	Penicillin				Erythromycin			
	Patient younger than 5 years		Patient aged 5 years or older		Patient younger than 5 years		Patient aged 5 years or older	
	Isolates tested	Non-susceptible isolates	Isolates tested	Non-susceptible isolates	Isolates tested	Non-susceptible isolates	Isolates tested	Non-susceptible isolates
2000–04	46	0	160	1 (0·6%)	38	1 (2·6%)	152	7 (4·6%)
2004–05	17	2 (11·8%)	84	1 (1·2%)	17	2 (11·8%)	73	3 (4·1%)
2005–06	12	1 (8·3%)	98	2 (2·0%)	10	3 (30·0%)	87	3 (3·4%)
2006–07	18	1 (5·6%)	76	4 (5·3%)	15	1 (6·7%)	64	4 (6·3%)
2007–08	20	2 (10·0%)	154	7 (4·5%)	16	2 (12·5%)	140	6 (4·3%)
2008–09	40	6 (15·0%)	223	11 (4·9%)	30	3 (10·0%)	196	8 (4·1%)
2009–10	58	6 (10·3%)	361	15 (4·2%)	41	1 (2·4%)	276	14 (5·1%)

Data are n and n (%). Epidemiological years run from July to June.

Table 4: **Susceptibility of isolates of *Streptococcus pneumoniae* (serotype 19A) to penicillin and erythromycin between 2000 and 2010**

during the study period, this increase first occurred before the introduction of PCV7 vaccination (table 4). For 7F and 22F there was negligible antimicrobial resistance to either penicillin or erythromycin during the entire study period—of 1643 antimicrobial tests done for serotype 7F, two were non-susceptible to penicillin and 11 were non-susceptible to erythromycin, and of 1147 tests done for serotype 22F, one was non-susceptible to penicillin and eight were non-susceptible to erythromycin.

Discussion

Our analyses show clear evidence of herd immunity after PCV7 vaccination, with decreases in all vaccine serotypes in all age groups. However, this decrease is partly offset by an increase in NVT disease. Such increases are likely to be attributable to vaccine-induced serotype replacement because we recorded more increases in the prevalence of non-PCV7 serotypes after introduction of the PCV7 vaccine than we did decreases, and because we recorded no obvious relation between increases in NVT disease and trends in antimicrobial resistance. Cases of serotype 6A/6C infection decreased in vaccinated cohorts but increased in individuals aged 65 years or older. Although evidence exists that PCV7 vaccination provides some cross protection against serotype 6A but not 6C,[14] we were unable to distinguish between serotype 6A and 6C for the whole study period, so could not confirm this occurrence in our study cohort.

Our analyses confirm the existence of natural secular changes in the incidence of specific serotypes (eg, 1, 8, and 9N). The decrease in 9N could be attributable to within-group cross protection from the 9V component of PCV7. However, existing data do not suggest serological cross-reactivity exists between serotypes 9N and 9V.[4,15] In our dataset, the effect of these natural changes masked the likely true extent of serotype replacement rather than falsely contributing to it, especially for serotype 1 in the 5–64 year age group. For example, when assessing the incidence of pneumococcal meningitis, which is not commonly caused by serotype 1, a significant increase in invasive pneumococcal infections due to NVT serotype was recorded in the 5–64 year age group (table 2).

The corrections we made to the raw numbers to adjust for changes in completeness of reporting make several assumptions. First, was that the age distribution and serotype distribution of cases for which these data were not known were much the same as for cases for which these data were known, which seems a reasonable assumption. Second, was that the upward trend in the number of reported infections before PCV7 vaccination was introduced is attributable to improved ascertainment of cases and would have continued after PCV7 vaccination was introduced. Evidence for this assumption comes from trends in other bacteraemias (eg, *Escherichia coli*) reported to HPA via the same surveillance system, and for which there has been no public heath intervention. Upward trends in the incidence of such bacteraemias began before the time of PCV7 vaccination and continued until 2009–10,[13] which was possibly attributable to an increase in blood culturing rates or improved laboratory practice and efficiency of reporting. Indeed, there have been active attempts by the HPA to improve laboratory reporting in the past decade.[16] Although the adjustments we made to account for these secular trends in case ascertainment provide the best estimate available from the data, inevitable uncertainty exists around these adjustments that could result in either an overestimate or underestimate of the benefits of PCV7. For suspected pneumococcal meningitis cases, for which a cerebrospinal fluid sample or blood culture should be standard clinical practice, we recorded no upward trend before the introduction of PCV7 vaccination, suggesting that the upward trends in other bacteraemia reports are attributable to changes in blood culturing practice. Without accounting for this change in ascertainment, we recorded only a 20% reduction in the total number of invasive pneumococcal infections in children aged 2–4 years (compared with a 43% reduction when

accounting for these changes), and no overall effect in the 15–64 year age groups (table 1), despite the cyclical decrease in incidence of serotype 1 after PCV7 vaccination was introduced.

Nevertheless, even with these corrections and natural decreases in some non-PCV7 serotypes, the increase in NVT infections in England and Wales is greater than was reported in the USA.[4] Active Bacterial Core surveillance (ABCs) data from the USA show a change in the incidence of NVT infections in children younger than 5 years from 16·8 per 100 000 population in 1998–99 to 22·1 per 100 000 population in 2006–7, an increase of only 32% (panel).[4] In England and Wales, the increase in NVT infections in children younger than 5 years was already substantially greater by the fourth year of the programme (table 1). Unlike the invasive pneumococcal disease surveillance system in England and Wales and many other countries where most patients with invasive pneumococcal disease are admitted to hospital, the ABCs system includes a substantial proportion of data from children who had not been admitted to hospital (68% of those younger than 5 years in 1998–99),[4] resulting in a substantially higher prevalence of invasive pneumococcal disease of 98·7 per 100 000 population in the USA compared with 31·8 per 100 000 population in England and Wales. When the ABCs data are restricted to children younger than 5 years who had been admitted to hospital, the incidence of all infections before PCV7 vaccination (31·4 cases per 100 000 population) was much the same as it was in England and Wales, but the increase in NVT disease 7 years into the programme (102%) was larger than it was after 4 years in England and Wales (77%)—with an incidence of NVT disease of 22·1 cases per 100 000 population in the USA compared with 14·3 cases per 100 000 population in England and Wales. However, ABCs data seemed to show a decrease in the number of patients with NVT infections who were not admitted to hospital, which, although not a significant decrease, was consistent with a reduction in blood culturing rates in this population after PCV introduction.

For pneumococcal meningitis the increase in NVT cases in children younger than 5 years in the USA was 78%,[4] which was much the same as that seen in England and Wales (77%; table 2) and is consistent with a similar level of ascertainment for this more serious manifestation of the disease in the two countries' surveillance systems.

The overall incidence of invasive pneumococcal disease in individuals aged 65 years or older who have been admitted to hospital in the USA[4]—56·7 cases per 100 000 population before PCV7 vaccination was introduced and 34·8 cases per 100 000 population after PCV7 vaccination was introduced—was higher than in England and Wales, possibly indicating differences in blood culturing practice between countries. In southwest England, interhospital variations in incidence of invasive pneumococcal infections in individuals aged 65 years or older differed by as much as four times, which was largely attributable to differences in blood culturing rates.[18] The increase in NVT disease in individuals aged 65 years or older in the USA was 32% by 2006–07[4] compared with 48% in England and Wales by 2009–10.

***Panel:* Research in context**

Systematic review

We searched PubMed with the search terms "pneumococcal conjugate vaccine", "impact after introduction", "herd immunity", "trends", "serotype replacement", "effects after introduction", and "reductions in invasive disease".

We searched for population-based surveillance studies that had data for all age groups and provided incidence rates for vaccine-type and non-vaccine-type invasive pneumococcal disease for at least 3 years after the introduction of the seven-valent pneumococcal conjugate vaccine (PCV7), with at least 2 years of baseline data before PCV7 vaccination was introduced. The most robust was the Active Bacterial Core surveillance (ABCs) system in the USA, which collated invasive pneumococcal disease data from eight geographic regions (around 3000 cases per year) and reported results for up to 7 years after the introduction of PCV7 vaccination.[3] However, unlike other countries' surveillance systems, a substantial proportion of paediatric patients in the ABCs are not admitted to hospital, raising questions about changes in surveillance sensitivity after the introduction of PCV7 vaccination. Data for invasive pneumococcal disease from before PCV7 vaccination are only reported for 2 years, limiting the ability to adjust for trends in ascertainment.

Interpretation

Ours is the first large population-based study of the effect of PCV7 on invasive pneumococcal disease in all ages that has attempted to adjust for changes in case ascertainment with time. Our findings show the complexity of interpreting disease trends in a changing clinical, diagnostic, and surveillance environment. Serotype replacement was more aggressive than reported in the USA by Pilishvili and colleagues,[3] although when comparisons were based on data from patients who were admitted to hospital, the percentage and absolute increases in non-vaccine type disease in children were much the same in the two countries. Despite much serotype replacement, a substantial reduction in invasive pneumococcal disease of sufficient severity to warrant hospital admission can be achieved in children with PCV7 vaccination, with additional indirect benefits in older age groups. The incidence of pneumococcal meningitis was reduced by nearly half in children younger than 5 years. Further reductions should be achieved by switching to higher valency vaccines for which the potential for serotype replacement is likely to be less than with PCV7.[17] The extent to which our findings can be extrapolated to populations such as those in developing countries where carriage and invasive pneumococcal disease incidence rates are much higher than in the USA and Europe, and where the coverage of prevalent serotypes by PCV7 is lower, is not clear.

The incidence of VT disease decreased by 90% in the USA and by 81% in England and Wales, indicating similar herd immunity effects after allowing for the fact that the USA programme has been in operation for longer. The greater increase in NVT disease in individuals aged 65 years or older in England and Wales at an earlier stage of the programme could be because of subtle serotype-specific differences in invasive pneumococcal disease between countries, differences in case ascertainment, or possibly natural secular changes unrelated to vaccination.

Our findings indicate that serotype replacement in the USA and England and Wales in the paediatric population is much the same when like-with-like comparisons are made (ie, analysis of data from only those patients who have been admitted to hospital). They draw attention to the complexity of interpreting invasive pneumococcal disease data from different countries, and of comparing the effect of programmes at different stages of maturity and with surveillance systems targeting different populations of patients. Future analyses should account for changes in the sensitivity of surveillance systems over time, and sufficient baseline data from before vaccine introduction should be used to identify secular changes in individual serotypes and their likely effect on the incidence of NVT disease. In 2010, both the UK[19] and the USA[20] introduced a 13-valent pneumococcal conjugate vaccine in place of PCV7, providing cover for an additional six serotypes including 19A and 7F, which are important replacing serotypes. Understanding the effect of such higher-valency vaccines will need robust surveillance systems and knowledge of the invasiveness potential of non-PCV serotypes, as measured by their prevalence in carriage compared with their prevalence in invasive pneumococcal disease, an aspect of surveillance that has hitherto been largely overlooked.[5,17,21]

Contributors

EM, PAW, and RCG established the national enhanced surveillance system. MPES and RCG were responsible for serotyping of isolates. PAW was responsible for data management. PAW and NJA analysed the data. EM and NJA drafted the paper. All authors had access to the data and commented on and approved the final version.

Conflicts of interest

RCG and MPES have received assistance to attend scientific meetings from Wyeth (Pfizer) and GlaxoSmithKline, and their laboratory has received research funding from Wyeth (Pfizer) and GlaxoSmithKline. EM, PAW, and NJA declare that they have no conflicts of interest.

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