Trends in incidence of pneumococcal disease before introduction of conjugate vaccine: South West England, 1996–2005

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SUMMARY

Introduction of pneumococcal conjugate and polysaccharide vaccines into the United Kingdom's routine immunization programmes is expected to change the epidemiology of invasive pneumococcal disease (IPD). We have documented the epidemiology of IPD in an English region (South West) with high-quality surveillance data before these programmes were established. We analysed data on isolates of *Streptococcus pneumoniae* from blood and CSF between 1996 and 2005 from microbiology laboratories in the South West that were reported and/or referred for serotyping to the Health Protection Agency Centre for Infections. The mean annual incidence of IPD increased from 11·2/100 000 in 1996 to 13·6/100 000 in 2005 ($P < 0.04$). After adjusting for annual blood-culture sampling rates in hospitals serving the same catchment populations, an increase in annual incidence of IPD was no longer observed ($P = 1.0$). Variation in overall incidence between laboratories could also be explained by variation in blood culture rates. The proportion of disease caused by serotypes 6B, 9V and 14 decreased significantly ($P = 0.001$, $P = 0.007$, and $P = 0.027$ respectively) whereas that caused by serotype 4, 7F and 1 increased ($P = 0.001$, $P = 0.003$, and $P < 0.001$ respectively) between 2000 and 2005. The level of penicillin non-susceptibility and resistance to erythromycin remained stable (2% and 12% respectively). This study provides an important baseline to assess the impact of changing vaccination programmes on the epidemiology of IPD, thus informing future use of pneumococcal vaccines.

INTRODUCTION

Invasive pneumococcal disease (IPD) is associated with high morbidity and mortality, especially among the very young and the elderly [1, 2]. While several European countries have experienced an increasing incidence of infections with penicillin-resistant *Streptococcus pneumoniae*, others, especially those in northern Europe, have reported lower levels of resistance [3–6]. Understanding the epidemiology of IPD is important in the planning, implementation and evaluation of prevention strategies including vaccination.

Since 2003, the 23-valent pneumococcal polysaccharide vaccine (initially recommended in the

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United Kingdom for people at increased risk of pneumococcal disease [7]), has been recommended in the United Kingdom for use in all those aged >65 years. In England and Wales this recommendation was implemented in a stepwise manner from 2003, initially in those aged ⩾80 years and, then in those aged ⩾75 years, and finally for all those aged ⩾65 years from April 2005. Prior to the introduction of this policy the 23 serotypes included in the vaccine accounted for 96% of pneumococcal isolates causing serious infections in Britain [8].

In 2000, a 7-valent pneumococcal conjugate vaccine was licensed for children aged <5 years in the United States and recommended for routine use in children aged 2–23 months in the same year [9]. In 2002, this new vaccine was recommended for immunization of at-risk children aged <2 years in the United Kingdom, extended to at-risk children aged <5 years [7] in 2004 and included in the routine immunization schedule for children in the United Kingdom in September 2006 [10]. In the United States this vaccine has reduced the incidence of IPD due to vaccine serotypes in vaccinated and unvaccinated individuals including adults via herd immunity [11].

We undertook this study to describe the epidemiology of IPD in South West England (population 5 million), between 1996 and 2005. (The 23-valent pneumococcal polysaccharide vaccine, originally licensed for specific risk groups in 1989 in England, was extended in 2003 to include all individuals aged >65 years but implementation was phased in over 3 years with the inclusion of all individuals aged >65 years by April 2005.) The main objective was to provide a baseline for the interpretation of any changes arising from the new vaccination strategies. A second objective was to analyse temporal and geographic variation in IPD incidence.

METHODS

For this study, IPD refers to infection in which *S. pneumoniae* is isolated from blood or cerebrospinal fluid (CSF). Laboratories in England and Wales voluntarily report all clinically significant bacterial isolates of invasive disease to the Health Protection Agency Centre for Infections. Episodes in which *S. pneumoniae* is isolated from CSF or in blood with a clinical diagnosis of meningitis are categorized as pneumococcal meningitis. Each report corresponds to one patient episode of illness and contains information on patient date of birth or age, sex, reporting

laboratory, source of the specimen and antibiotic susceptibility. A second data source comprises the IPD isolates referred for serotyping to the HPA's Respiratory and Systemic Infection Laboratory (RSIL) from laboratories in England and Wales. Not all IPD isolates sent for serotyping to RSIL are reported to the HPA database and vice versa. Both data sources are routinely and regularly reconciled to produce a single national dataset of IPD cases (see http:// www.hpa.org.uk/infections/topics_az/pneumococcal/ default.htm) from which data for the South West was extracted for this study.

Microbiology laboratories in the South West supplied the annual number of blood cultures performed by each laboratory. To analyse geographical variation, we used laboratory catchment populations derived from primary-care usage data. Age group-specific incidence rates were calculated using national Census data. We measured incidence trends by means of negative binomial regression using case data from laboratories, and adjusting for laboratory catchment populations and blood cultures. Incidence trends by age group adjusting for laboratory catchment populations were also calculated.

IPD isolates referred for serotyping to RSIL were confirmed as pneumococci and serotyped using standard methods [12, 13]. Results of antimicrobial susceptibility testing were incorporated within the routine surveillance outputs from the participating laboratories, and the data are summarized on the basis of the susceptibility test reports issued to clinicians. Some of the isolates were also susceptibility tested at the Antimicrobial Resistance Monitoring and Reference Laboratory at the HPA Centre for Infections by determination of minimum inhibitory concentration (MIC). MICs were determined in air on diagnostic sensitivity test agar (Oxoid, Basingstoke, UK) containing 5% lysed horse blood (TCS Microbiology, Birmingham, UK) as described previously [14]. Isolates were categorized as susceptible or resistant using break-points recommended by the British Society for Antimicrobial Chemotherapy [15].

RESULTS

The annual incidence of IPD in South West England increased from 11·2/100 000 in 1996 to 13·6/100 000 in 2005 (trend of 1·014 per year, 95% CI 1·001–1·027, $P=0.04$, adjusted for population and laboratory catchment area; Table). There is no evidence to suggest this increase differs by age group ($P=0.28$). In

Table. *IPD isolates in the South West of England by year 1996–2005*

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
IPD	543	588	447	496	537	584	559	616	634	689
Cultures	102 772	105 974	108 788	112 611	113 620	122 200	134 683	143 339	140 123	153 335
South West population	4 841 545	4 875 973	4 901 316	4 935 669	4 975 091	4 934 162	4 959 593	4 999 287	5 038 200	5 067 794
IPD/100 000 pop.	11·2	12·1	9·1	10·0	10·8	11·8	11·3	12·3	12·6	13·6
Cultures/ 100 000 pop.	2123	2173	2220	2282	2284	2477	2716	2867	2781	3026

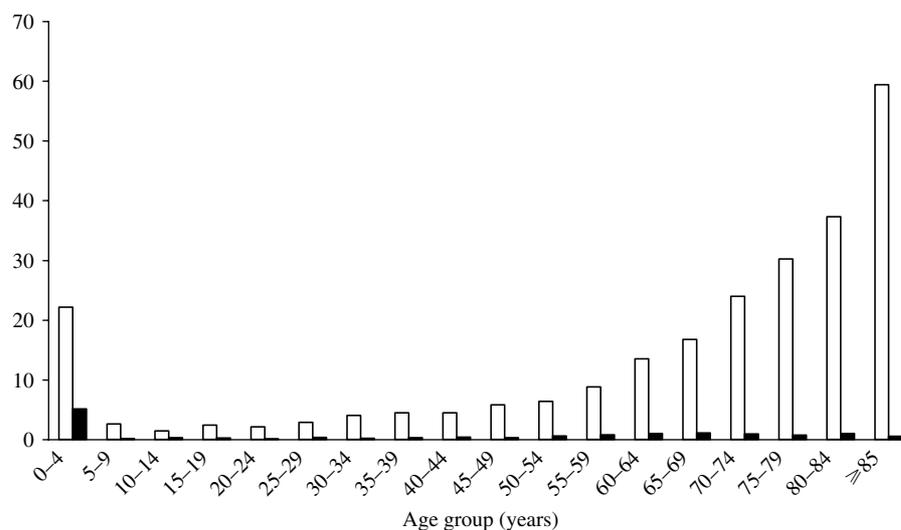IPD, Invasive pneumococcal disease.

Fig. 1. Invasive pneumococcal disease (IPD) in the South West of England by year 1996–2005, by age group. □, IPD (all)/100 000; ■, meningitis/100 000.

the <5 years age group the annual incidence increased from 20·8/100 000 in 1996 to 26·3/100 000 in 2005 and in those aged >65 years it changed from 32·5/100 000 to 31·0/100 000. The highest annual age-specific attack rates were seen in age groups <5 years and >65 years (mean 22·8/100 000 and 31·2/100 000) (Fig. 1). The male:female ratio was 1·1:1. The average incidence of IPD by laboratory catchment population ranged from 8·6–18·7/100 000 (Table). A stable seasonal pattern, with increased incidence in winter months was seen throughout the study period. The numbers of IPD cases reached a low during August and peaked in December and January when numbers were 3–5 times higher.

Adjusting annual IPD incidence by annual blood-culture sampling rates removed evidence of an increasing trend (trend of 1·000 per year, 95% CI 0·984–1·016, $P = 1·0$, adjusted for population, laboratory catchment area and annual blood-culture sampling rates). The 10-year incidence of IPD by catchment population was also associated with

blood-culture sampling rates ($P < 0·001$), i.e. laboratories serving populations with higher IPD incidence were also found to have higher blood-culture sampling rates (Fig. 2).

Of all isolates, 394 (6·9%) were from cases of pneumococcal meningitis. The mean annual incidence of meningitis was 0·8/100 000 population (all ages). No discernible trend was observed for pneumococcal meningitis over the study period ($P = 0·136$). Of all the meningitis cases, 24·5% occurred in patients aged <1 year.

Serotype distribution

The proportion of invasive isolates with serotype information rose steadily from 39% in 1996 to 77% in 2005, compared with a mean change of 35–67% for the other English regions. Analysis of serotype distribution was restricted to the 6 years between 2000 and 2005 when serotype information was available for at least 50% of isolates. Fifty-four different serotypes
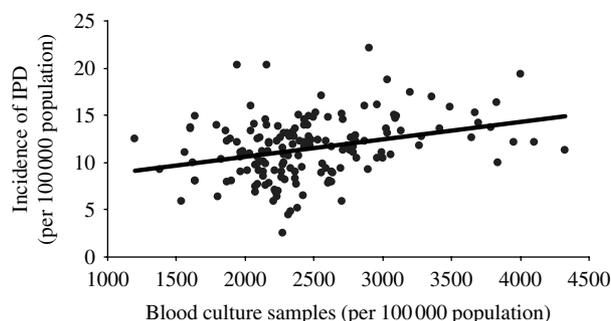
Fig. 2. Relationship between rate of invasive pneumococcal disease (IPD) and blood culture per 100 000 population in the South West of England by laboratory and year, 1996–2005.

were detected in this 6-year period. There was significant variation in pneumococcal disease caused by the different serotypes in these 6 years ($P < 0.001$). The proportion of disease caused by serotypes 6B, 9V and 14 decreased significantly ($P = 0.001$, $P = 0.007$, and $P = 0.027$ respectively) whereas that caused by serotypes 4, 7F and 1 increased ($P = 0.001$, $P = 0.003$ and $P < 0.001$ respectively) (Fig. 3).

The most common serotypes in all ages were 14, 1, 9V, 23F, 8, and 4. In those aged < 5 years, the most common serotypes were 14, 6B, 19F, 18C and 1. The 7-valent conjugate vaccine contains serotypes corresponding to 248/341 (73%) known serotypes causing IPD in this age group. The most important serotypes causing illness and not included in the 7-valent conjugate were serotypes 1, 19A, 6A, and 7F, responsible for 17% of invasive infections. In those aged > 65 years, the most common serotypes were 14, 23F, 9V, 3, and 6B. In this age group, 90% of the serotypes causing illness were contained in the 23-valent polysaccharide vaccine compared with 58% of serotypes in the 7-valent vaccine.

Antimicrobial susceptibility

Antimicrobial susceptibility data for erythromycin and penicillin were available for 74% and 82% of isolates between 1996 and 2005. The availability of antimicrobial resistance results reported through routine surveillance improved steadily from 1996, rising from 52% to 87% for penicillin and from 51% to 84% for erythromycin. The proportions of strains resistant to erythromycin and penicillin non-susceptible remained similar between 1996 and 2005 (mean 12·0% and 1·8% respectively). Of the 248 invasive infections in < 5-year-olds caused by serotypes contained in the

7-valent conjugate vaccine, 21% were resistant to erythromycin (mainly serotype 14), compared with 6% due to serotypes not in the vaccine ($P = 0.002$). There was no difference in the equivalent proportions non-susceptible to penicillin.

DISCUSSION

This paper sets out a 10-year baseline of high-quality surveillance data from an English region to interpret changes in the epidemiology of IPD following recent changes to routine vaccination programmes in the United Kingdom. The 5693 isolates from the South West reported to the national enhanced surveillance system accounted for 10% of isolates in England and Wales during the same period [16]. Although the incidence of IPD increased significantly over the study period, this could be explained by an increase in the rate of blood culture sampling. Similarly, higher rates of blood culture sampling were associated with higher incidence by laboratory catchment population, consistent with findings of Smith et al. [17]. The rate of blood culture sampling should therefore be taken into account in any evaluation of the impact of vaccination programmes.

In common with other reports, IPD exhibited distinct winter seasonality in all areas in the South West, and over all the years investigated [18]. This seasonal fluctuation in the incidence of IPD has been attributed to exposure to winter viruses (e.g. influenza and respiratory syncytial virus) [19] and to temperature [20]. The higher incidences seen in the 1996–1997 and 1999–2000 seasons might have been related to the peaks of influenza seen in those seasons [21]. A recent study by Hussain et al. showed that there were no significant seasonal differences in the prevalence of carriage of S. pneumoniae [22].

Across Europe, differences in the incidence of IPD have been well documented. These can be explained to varying extents by patient and health-care factors such as blood culture practice and pre-admission antibiotic administration [23], as well as wide variations in surveillance systems [24]. In periods of changes in vaccination policy, surveillance needs to take these factors into consideration when evaluating changes in incidence trends.

Although vaccination in those aged ⩾ 65 years was only recommended in the United Kingdom in 2003, primary-care physicians had already been advised to immunize certain high-risk patients. With a reported efficacy against invasive disease of about 65% [25],
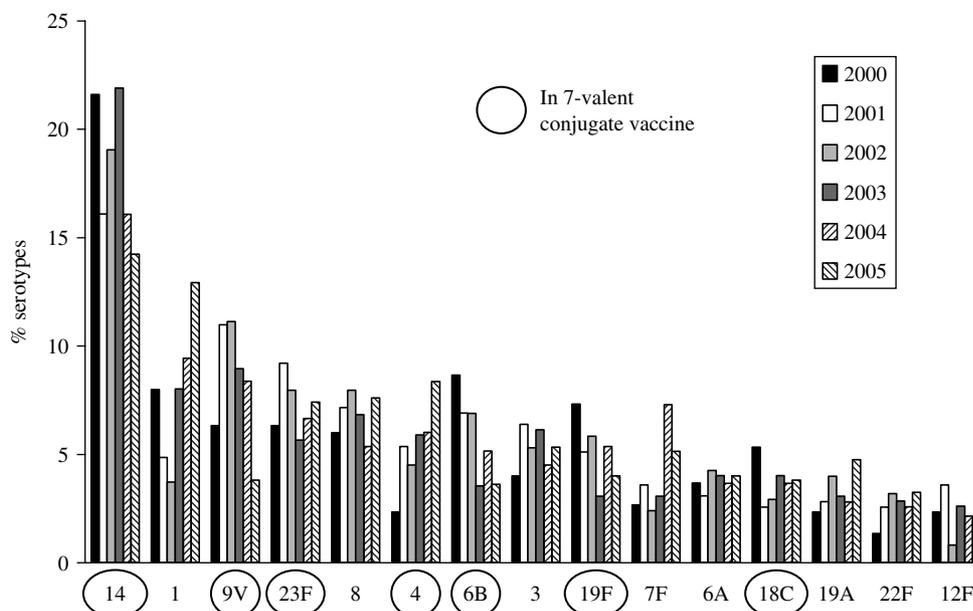
Fig. 3. Top 15 occurring serotypes of invasive pneumococcal disease in all age groups in the South West of England 2000–2005 by year.

good surveillance data is essential in showing an effect of the introduction of the vaccine at a population level. While the protective efficacy of this vaccine for the growing population of adults aged >65 years has been shown, its limited protective effect on non-invasive disease has led to some controversy about its overall impact at the population level [26]. Pneumococcal polysaccharide vaccine (PPV) uptake in the >65 years age group was 64·4% nationally by April 2006 [27]. No reduction in IPD incidence in older age groups was seen between 2003 and 2005 in our study, the last 2 years of which overlaps with the stepped introduction of the PPV programme for the elderly in 2003.

On the other hand, there is a growing body of evidence supporting the beneficial effects of the conjugate pneumococcal vaccine. In the United States, from 1998 to 2003, the incidence of IPD associated with serotypes contained within the 7-valent conjugate vaccine decreased by 94%, and by 75% overall [28]. The data contained in our study and further surveillance data will enable the elicitation of similar evidence from our setting.

Resistance to antimicrobials used in the treatment of IPD is of continuing concern. Nationally, penicillin non-susceptibility rates vary between regions from a low of 3% in South West in 1999 compared to a high of 11% in London [18]. Our results show that rates of resistance to erythromycin and penicillin

non-susceptibility have remained stable and resistance patterns did not vary geographically in the South West region over recent years. The relatively high level of resistance to erythromycin that we found is also reflected in the national dataset and reinforces the unreliability of macrolides as empirical monotherapy for suspected pneumococcal infections. Among the potential benefits of the introduction of the 7-valent conjugate vaccines to the vaccination schedule in the United Kingdom includes a possible reduction in the incidence of macrolide and penicillin resistance, since the vaccine covers the majority of antibiotic-resistant pneumococci. Such reductions have been reported in the United States where the vaccine was introduced in 2000 [29].

At least 90 pneumococcal serotypes have been recognized to date, but only a small proportion of these serotypes are commonly associated with IPD [30]. All three serotypes that showed a significant reduction in incidence and one that showed an increase are included in the 7-valent conjugate vaccine. These changes occurred before the introduction of this vaccine into the routine childhood vaccination programme. Continued surveillance of the distribution of pneumococcal serotypes causing invasive disease permits the evaluation of the impact of such vaccines, as well as providing early warning of the emergence of non-vaccine serotypes as causes of invasive disease [31]. The high level of erythromycin resistance

among serotypes contained in the conjugate vaccine suggests that this vaccine may reduce the level of such resistance, both in children and through herd immunity in older populations. Some herd immunity in adults following introduction of conjugate vaccine in childhood is expected, but the limited impact of polysaccharide vaccination on pneumococcal disease in the elderly means that the use of conjugate vaccines in this age group may yet prove a cost-effective public health intervention.

APPENDIX

South West Pneumococcus Study Group

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