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Invasive pneumococcal infection in South and West England

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SUMMARY

Variation in the incidence of invasive pneumococcal disease across South and West England, in 1995, was measured through a survey of microbiology laboratories. A 100% response rate was achieved. The incidence by laboratory varied between 5·2 and 20·4 per 100000 catchment population ($P < 0{\cdot}001$). Adjusting for pneumococcal vaccine uptake rate in over 65 year olds, hospital admission rates, blood culture system used and for the age and sex structure of the population, did not account for this variation. When blood culture sampling rates were included in a logistic regression model, the variation between laboratories was much less and of lower statistical significance ($P = 0{\cdot}019$). Higher rates of blood culture sampling were associated with a higher incidence of invasive pneumococcal disease. Consistently high sampling should be encouraged because a higher diagnostic rate should result in more selective prescribing of antibiotics, and secondly because improved ascertainment of severe pneumococcal infections is a prerequisite for the evaluation of new pneumococcal conjugate vaccines.

INTRODUCTION

Invasive pneumococcal disease remains a major cause of morbidity and mortality worldwide. *Streptococcus pneumoniae* is the commonest cause of community acquired pneumonia and a common cause of bacteraemia in the UK [1]. Since the introduction of *Haemophilus influenzae* type b vaccine, *S. pneumoniae* has become the second commonest cause of bacterial meningitis [1].

In England and Wales, the annual number of reports of pneumococcal bacteraemia and meningitis increased considerably between 1982 and 1992 (1600 and 3734 reports respectively) [2]. Similar increases in pneumococcal bacteraemia have been reported in Sweden [3, 4], and Denmark [5], but not in Finland [6]. The incidence of pneumococcal bacteraemia also increased over a 12-year period in South Carolina, USA [7]; the authors attributed much of this temporal variation to increased blood culture sampling rates. Geographical variation in incidence was noted in England and Wales [2], and was thought to be due to differences in efficiency of reporting infections. An

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audit of reporting invasive pneumococcal infections, within part of South and West England, over a 6-month period, also found geographical variation within the region and confirmed some incompleteness of reporting.

This study was undertaken to measure the incidence of invasive pneumococcal infection throughout South and West England, during a 12-month period, and to examine reasons for variations between individual laboratories within the region. In addition the frequency of serotype and antibiotic resistance was investigated. This was performed as part of enhanced surveillance of severe pneumococcal infections, prior to the introduction of new conjugate pneumococcal vaccines.

POPULATIONS, MATERIALS AND METHODS

For the purpose of this study, South and West England comprised the following health authorities: Cornwall & Isles of Scilly, South & West Devon, North & East Devon, Somerset, Avon, Gloucestershire, Herefordshire, Wiltshire, Dorset, Southampton & South West Hampshire, North & Mid Hampshire, Portsmouth & South East Hampshire, Isle of Wight. This corresponds to the NHS South and West Region plus Herefordshire, with a population of approximately 6·5 million.

All NHS microbiology laboratories and Public Health Laboratories within South and West England, and the Royal Hospital Haslar (Ministry of Defence), were asked for information on invasive pneumococcal disease occurring (i.e. date of specimen) between 1 January 1995 and 31 December 1995. Data were requested on patient details (identifier, age, sex, residence), specimen (date, source), pneumococcal isolate (serotype, antibiotic susceptibility), and total number of blood cultures received (by age and sex). The type of blood culture system was also requested. Duplicate specimens from the same patient were excluded from analysis, as were specimens from people who lived outside South and West England. The data from Haslar (Gosport) and Portsmouth laboratories were combined for the purpose of the analysis, as were the data from Poole and Bournemouth.

Consultants in Communicable Disease Control were asked for data on catchment populations for acute medical admissions relating to each laboratory, and age-sex breakdown of resident populations. The regional pharmaceutical adviser provided data, by health authority, on pneumococcal immunizations in >65 years age group, for 1994/5. The numbers of finished consultant episodes in geriatric and medical specialities were obtained for each NHS acute trust from KC70 returns for 1995/6.

Hospital episode rate was defined as the number of consultant episodes in geriatrics and medicine per 1000 catchment population during 1995/96. Vaccine uptake rate was defined as the number of doses of pneumococcal vaccine prescribed for people aged over 65 years, during 1994/5, per 1000 population in that age group. Analysis of immunization uptake was confined to over 65 year olds, since this age group was at greatest risk of disease and was more likely to show differences in incidence related to immunization.

The blood culture sampling rate was defined as number of blood culture sets received per 100000 catchment population.

Invasive pneumococcal infection was defined as the isolation of *S. pneumoniae* from blood and/or CSF cultures. Infection at other 'normally sterile' sites was not classified as invasive unless blood cultures were also positive. We did not differentiate between community acquired and hospital acquired infections.

Antibiotic susceptibilities were determined according to individual laboratory protocols. All laboratories participate in the United Kingdom's National External Quality Assurance Scheme, including identification and susceptibility testing of *S. pneumoniae*.

Serotyping was performed on pneumococcal isolates submitted to the Respiratory and Systemic Infection Laboratory at the Central Public Health Laboratory, London.

Statistical methods

The incidence data was modelled in the statistical package GLIM 4 [8] using logistic regression. Analyses were carried out on overall incidence and incidence by age and sex as follows.

All areas were initially compared by overall incidence. The effects of vaccine uptake rate, blood culture sampling rate, blood culture system and admission rates (medical and geriatric) were then tested for significance individually and within a multivariable model. The effect of laboratory was then examined after adjusting for all significant factors. This analysis required the exclusion of two laboratories (one without vaccine uptake rate and one without blood culture sampling rate).

Incidence was then examined by age and sex for each laboratory and modelled. Factors included in this model were age, sex and blood culture sampling rate. Inter-laboratory variation was then examined after adjusting for these factors. This analysis required the exclusion of two laboratories (both missing information on age of cases).

RESULTS

All 26 NHS and PHLS microbiology laboratories in South and West England participated in the study. During 1995, a total of 668 invasive pneumococcal infections were identified; an overall incidence of 10·3 infections per 100000. There were highly significant variations in incidence between individual laboratories, ranging from 5·2–20·4 per 100000 population ($P < 0{\cdot}001$) (Table 1).

The sex was specified for 641 patients, of whom 358 (56%) were male and 283 (44%) female. Females were at lower risk of invasive infection than males (8·9 *vs*. 12·0 per 100000) with an odds ratio (OR), after adjusting for age, of 0·58 (95% CI, 0·5–0·69).

The age was available for 620 patients. The incidence in patients aged < 1 year was high (33·2 per 100000) falling to a nadir in the 15–24 year group (1·9 per 100000) (Fig. 1). It remained relatively low until after the age of 45 years when it rose rapidly to reach a peak (44·7 per 100000) in those aged ⩾ 75 years.

The monthly distribution of 612 invasive pneumococcal infections, for which date of specimen was recorded, showed significant seasonal variation ($P < 0{\cdot}01$) (Fig. 2). The lowest number of cases occurred during July–September (average 3·5% of all cases, per month) with a distinct peak in December (16·5% of all cases). At other times of the year the number of cases was relatively constant. This seasonal variation was the same in the elderly (> 65 years) and in non-elderly (⩽ 65 years) patients.

The median hospital episode rate was 70·3/1000 (range 22·1–126·2/1000). The median vaccine uptake rate was 37·4/1000 (range 21·3–60·7/1000). The yield for blood cultures varied from 3·2 to 7·5/1000 cultures (Table 1). Of the blood culture systems in use, 9 laboratories had BacTAlert, 7 had Bactec, 3 Signal and 3 Sentinel.

Of 644 invasive infections where specimen site was recorded, *S. pneumoniae* was isolated from blood only in 603 (94%), from CSF only in 19 (3%) and from both blood and CSF in 22 (3%).

Antibiotic susceptibilities were not reported for all isolates of *S. pneumoniae*. Reduced susceptibility or full resistance to penicillin occurred in 13 (2·3%) of 568 isolates tested and resistance to erythromycin occurred in 41 (7·6%) of 537 isolates tested. Resistance to both antibiotics was reported in only one isolate. Antibiotic susceptibilities showed no statistically significant variation between laboratories, with the exception of one (Truro) which had a high proportion of isolates that were resistant to erythromycin (9/33, 27·3%; $P = 0{\cdot}0004$). There was no statistically significant variation in antibiotic susceptibility by age group of patient or month of specimen.

Information on serotype was available for 209 (31%) of the isolates of *S. pneumoniae* (Table 2). Serotype 14 was the most common accounting for 20% of isolates. The serotypes for 202 (97%) of the isolates are encompassed within the current 23-valent non-conjugated pneumococcal vaccine. The serotype was reported for 29 isolates of *S. pneumoniae* from children aged < 5 years. Of these, serotypes 6, 14 and 18 were most common, and 90% were serotypes contained in a candidate heptavalent conjugate vaccine [9].

Geographical variation

Analysis of individual factors was undertaken to attempt to explain interlaboratory variations in incidence. Blood culture sampling rate ($P < 0{\cdot}0001$) and hospital episode rate ($P = 0{\cdot}02$) were associated with increased incidence, whereas vaccine uptake rate had no association with incidence ($P = 0{\cdot}54$). There was also an association between incidence and the type of blood culture system used by the individual laboratories ($P = 0{\cdot}05$). The multivariable analysis showed that only the effect of blood culture sampling rate ($P = 0{\cdot}008$) remained significant after adjusting for the other factors. Blood culture system ($P = 0{\cdot}27$) and admission rate ($P = 0{\cdot}40$) were only significant on their own due to their association with blood culture sampling rate. After adjusting for blood culture sampling rate, the remaining variation between laboratories was only of borderline significance ($P = 0{\cdot}05$).

For the 22 laboratories which reported incidence of invasive pneumococcal infection by age and sex, a further analysis was carried out. The age and sex factors were included in the model and had highly significant effects on incidence ($P < 0{\cdot}0001$). For eight laboratories, data on blood culture testing rates was

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Table 1. *Invasive pneumococcal disease in the 24 laboratories in South and West England; incidence of infection, blood culture sampling rates and number of cases per 1000 blood cultures taken*

Area/laboratory	Number of cases	Catchment population	Incidence/ 100000	Total number of blood cultures	Number of blood cultures/ 100000 population	Cases per 1000 blood cultures
Bristol – Royal Infirmary	56	274000	20·4	9929	3624	5·6
Bristol – Frenchay	35	227000	15·4	6060	2670	5·8
Winchester	30	217000	13·8	3962	1826	7·5
Gloucester	39	315000	12·3	6567	2085	5·9
Hereford	21	175000	12·0	3037	1735	6·9
Isle of Wight	15	125000	12·0	2277	1822	6·6
Barnstaple	16	140000	11·4	2316	1654	6·9
Yeovil*	12	112000	10·7	—	—	—
Bristol – Southmead	26	250000	10·4	6982	2793	3·7
Exeter	32	315000	10·2	7165	2275	4·4
Southampton	46	450000	10·2	14016	3115	3·3
Swindon	27	265000	10·2	6381	2408	4·2
Dorchester	21	207000	10·1	3443	1663	6·1
Portsmouth/Haslar	53	533000	9·9	12946	2429	4·1
Truro	34	370000	9·2	7707	2083	4·4
Cheltenham	19	213000	8·9	4509	2117	4·2
Bath	36	410000	8·8	7082	2345	5·1
Bournemouth/Poole	41	466000	8·8	8923	1915	4·6
Salisbury	13	160000	8·1	3004	1877	4·3
Plymouth	35	438000	8·0	10815	2469	3·2
Taunton	24	317000	7·6	6226	1964	3·8
Torbay	18	250000	7·2	4194	1678	4·3
Weston-Super-Mare	7	102000	6·9	2046	2006	3·4
Basingstoke	12	230000	5·2	3204	1393	3·7

* No information on number of blood cultures.

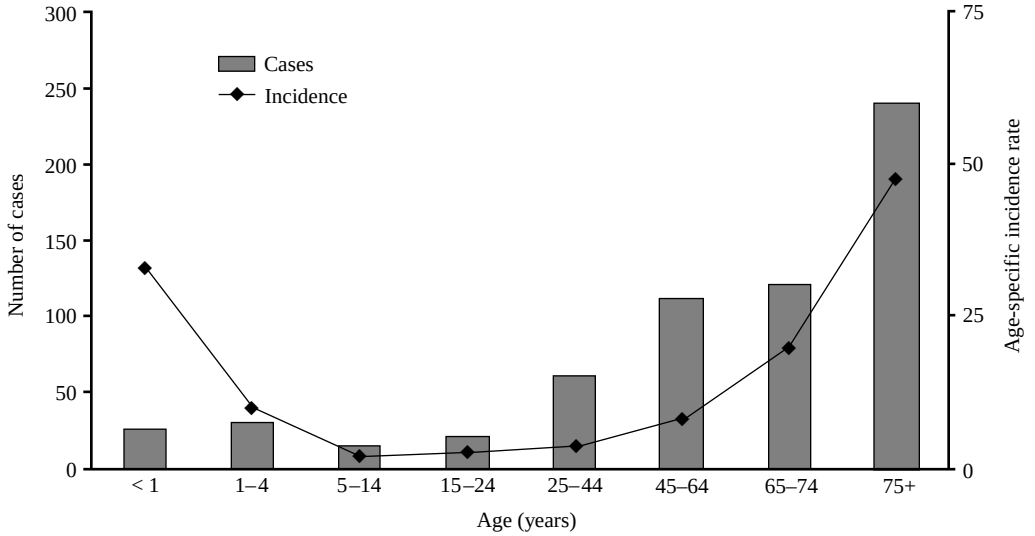

Fig. 1. Number of infections and incidence per 100000 population according to age group for 624 patients (two laboratories excluded).

also available by age and sex. As this only accounted for a minimal amount of further variation, and as the data was not available for most laboratories, it was not included in the final model. After adjusting for geographical age and sex differences, but not for blood culture sampling rate differences, there

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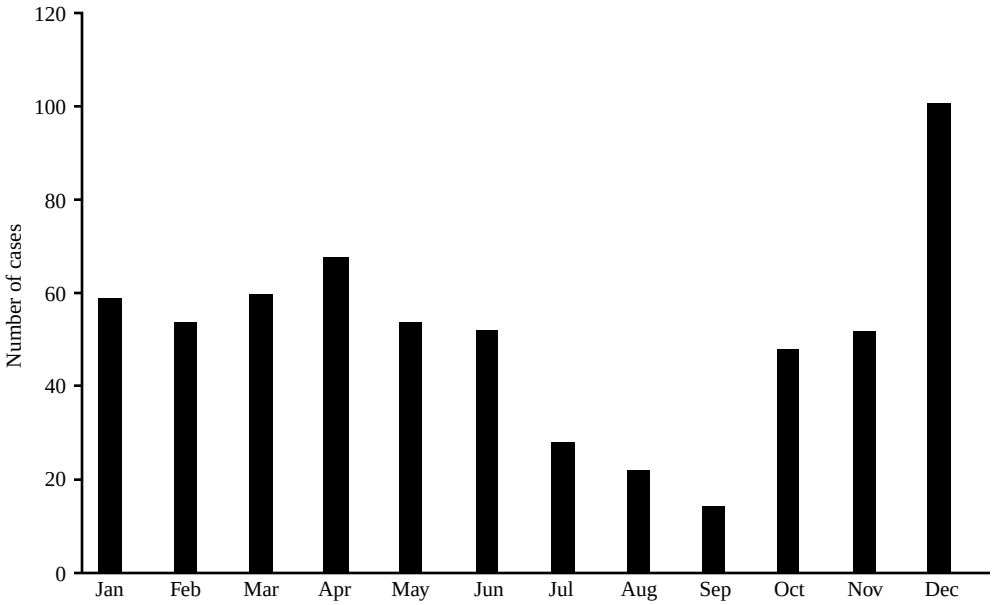

Fig. 2. Seasonal variation of invasive pneumococcal infections – number of cases by month for 612 patients.

Table 2. *Serotype distribution for 209 isolates of* S. pneumoniae, *listed in order of decreasing frequency*

	All patients		Children < 5 yr	
Serotype	Number of isolates (total = 209)	(%)	Number of isolates (total = 29)	(%)
14	42	20·1	10	34·5
6	20	9·6	4	13·8
9	19	9·1	2	6·9
4	18	8·6	1	3·4
19	17	8·1	2	6·9
1	17	8·1	1	3·4
7	14	6·7	0	0
23	12	5·7	2	6·9
18	10	4·8	5	17·2
3	7	3·3	0	0
8	6	2·9	0	0
20	5	2·4	0	0
Other*	22	10·5	2	6·9

* Serotypes 5, 10, 11, 12, 15, 16, 17, 22, 29, 31, 38.

remained significant variation in incidence of invasive pneumococcal infection between laboratories ($P < 0{\cdot}0001$). Blood culture sampling rate was then included in the model. This was highly significant ($P < 0{\cdot}0001$). Overall, an increased blood culture sampling rate was associated with a higher incidence (Pearson's correlation coefficient 0·583). After adjusting for age, sex and blood culture sampling rate, the statistical significance of the laboratory variation was reduced considerably ($P = 0{\cdot}019$). This effect can be seen in Table 1, where the incidence varies fourfold (5·2–20·4), but the cases per 1000 blood cultures varied just over twofold (3·2–7·5).

DISCUSSION

The overall incidence (10·3 per 100000) of invasive pneumococcal infection in South and West England during 1995 was similar to that reported for 1989–92 by Aszkenasy and colleagues [2]. The overall incidence is also comparable to that reported for similar time periods in Finland [6], Sweden [4] and California, USA [10]. By comparison the incidence in Denmark, in 1994, was significantly higher (18 per 100000) [5].

The true incidence of invasive pneumococcal infection in South and West England may be considerably higher than reported here. Under-ascertainment of cases of pneumonia and septicaemia will occur because some patients, especially the elderly, may not have blood cultures taken after admission to hospital or are managed in the community. Also, because of treatment with penicillin before admission to hospital, some cases of pneumococcal meningitis will not be culture-confirmed and therefore not included in our survey.

In agreement with many other reports on invasive pneumococcal infections [2, 6, 7, 10–12], this study shows a marked age-related variation in incidence

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with extremes of age being most susceptible. The sex-related and seasonal variation in incidence have also been reported previously [2, 6, 10, 12–15].

The most important finding of this study is the marked variation in incidence of infection between the individual laboratories within the region. This was not accounted for by differences in age or sex of the patients, hospital admission rates, vaccine uptake rates within the community, nor type of blood culture system used in the laboratory, but was largely due to variations in blood culture sampling rates.

Even after incorporating the variable blood culture sampling rates into the final model, some variation between laboratories remained. One possible explanation for this is differing clinical practices and protocols for blood culture sampling, especially in the elderly. Data on overall blood culture sampling rates, by age and sex, was only available for eight laboratories. This only accounted for a minimal amount of variation, but could have been more significant if all laboratories had provided this data. Another possible explanation is the effect of any clustering of infection. The statistical model assumes that cases occur randomly. If a cluster of infections in Winchester had contributed to the high rate of cases per 1000 blood cultures, and if this laboratory was excluded from analysis, there would be no significant variation between the remaining laboratories. Data collection for several years would be necessary to exclude this possibility.

The finding that apparent variations in incidence of invasive pneumococcal infection were largely due to variations in blood culture sampling rates is important for investigators to consider when comparing both geographical and temporal changes in the incidence of infection. Breiman and colleagues [7] attributed much of the increase in pneumococcal bacteraemia, over a 12-year period in South Carolina, to increased blood culture sampling. However, Hedlund and colleagues [4] reported a significant increase in incidence of invasive infection in Sweden without a corresponding increase in blood culture sampling rates.

The people most at risk of invasive pneumococcal infection, and with the highest mortality, include those at extremes of age or with impaired immunity, especially those without a functioning spleen. These are the people who would benefit most from effective vaccination, but current non-conjugated vaccines are not suitable for children under 2 years because of poor antibody responses in this age group. In the UK, the 23-valent non-conjugated pneumococcal vaccine is recommended for patients in defined at-risk groups [16] but is not recommended for routine use in otherwise healthy elderly people.

In our study, 97% of the isolates were of serotypes included in the current 23-valent pneumococcal vaccine; serotype 14 was the most common accounting for 20% of isolates. The most common serotypes found in this study were similar to the commonest serotypes found in other recent studies in Denmark [5], Finland [6, 11] and Sweden [4].

Reduced susceptibility or full resistance to penicillin occurred in 2·3% of our isolates which is lower than the average (3·9%) for England and Wales in 1995 [17], but resistance to erythromycin (7·6%) was similar to the national prevalence (8·6%). Resistance to both antibiotics has been rising steadily in recent years [17]. Reduced susceptibility or resistance to penicillin was considerably higher (14–17%) in recent reports from USA, [10, 18], but is reported to remain low ($<$ 1–1·5%) in Scandinavian countries; [4–6, 19]. The variation in prevalence of resistance to erythromycin is less marked, ranging from 2–3% in Sweden and Norway to 10% in USA.

In common with other reports, we do not have information on differing clinical practices and protocols for blood culture sampling, especially in the elderly, in the hospitals in our region. However, this study and others suggest that higher rates of blood culture sampling offer one explanation for higher pneumococcal disease rates. This has implications for clinical practice in that higher diagnostic rates should result in more selective antibiotic prescribing and less pressure on the development of antibiotic resistance. Also, high and consistent ascertainment is important to provide an improved estimate of the true rate of invasive pneumococcal infection, a requirement for future vaccine evaluation studies. The continuing high morbidity from this disease, and the increasing resistance worldwide in *S. pneumoniae* to the antibiotics commonly used for treatment, emphasize the urgent need for effective vaccines.

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