Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995

Alan P Johnson, David C E Speller, Robert C George, Marina Warner, Gil Domingue, Androulla Efstratiou

Abstract

***Objective*—To assess the prevalence of antibiotic resistance and serotype distribution among pneumococci in England and Wales in 1990 and 1995.**

***Design*—Observational surveys in March 1990 and March 1995. During two weeks in each survey period all pneumococci isolated in public health laboratories in England and Wales were collected and assessed for sensitivity to antibiotics and the distribution of serogroups or serotypes.**

***Setting*—The network of public health laboratories throughout England and Wales.**

***Subjects*—1127 individual patient isolates of *Streptococcus pneumoniae* obtained during the two surveys.**

***Main outcome measures*—Sensitivity or resistance to a range of antibiotics; serogroup or serotype.**

***Results*—The prevalence of intermediate or full resistance to penicillin increased from 1.5% in 1990 to 3.9% in 1995 and resistance to erythromycin increased from 2.8% to 8.6%. About 92% of isolates belonged to serogroups or serotypes included in the currently available pneumococcal vaccine.**

***Conclusion*—Resistance to penicillin and erythromycin has increased among pneumococci in England and Wales. Continued surveillance to assess further increases in the prevalence of pneumococcal resistance to antibiotics is essential.**

Introduction

During the past three decades antibiotic resistant pneumococci have been reported world wide.[1,2] To assess trends in the prevalence of resistance in England and Wales the Public Health Laboratory Service assessed antimicrobial resistance and serogroup or serotype distribution of all pneumococci isolated in the nationwide network of public health laboratories during defined periods in 1990 and 1995.

Methods

During two weeks in March 1990 and March 1995, 52 public health laboratories submitted all isolates of *Streptococcus pneumoniae* to the Central Public Health Laboratory. After receipt isolates were confirmed as pneumococci, serogrouped or serotyped, and tested for antibiotic sensitivity as described.[3] Sensitivity or resistance to antibiotics was determined according to published criteria.[4,5] Data were analysed and compared by the χ^2 test.

Results

A total of 1127 single patient isolates were studied (544 in 1990, 583 in 1995). The age distribution of patients in the two surveys was similar (P=0.82), roughly one third being under age 10 and one third being aged 60 or over. In 1995 there was a significant increase in the proportion of pneumococci isolated from the ear (P<0.05) but no significant change in the proportions of isolates from other sites.

In 1990 eight isolates (1.5%) submitted by six different laboratories exhibited either intermediate or full resistance to penicillin (table 1). Six of the isolates showed intermediate resistance to cefotaxime. In the 1995 survey 23 isolates (representing 3.9% of the study

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Table 1—*Antibiotic resistance of pneumococci in 1990 and 1995 surveys*

Antibiotic	1990 (n=544 isolates)		1995 (n=583 isolates)	
	Range of minimal inhibitory concentrations (mg/l)	No (%) of isolates resistant	Range of minimal inhibitory concentrations (mg/l)	No (%) of isolates resistant
Penicillin	0.007-2.0	5 (0.9)† 3 (0.6)‡ 8 (1.5)§	0.007-4.0	11 (1.9)† 12 (2.0)‡ 23 (3.9)§
Cefotaxime	0.007-1.0	6 (1.1)† 0‡ 6 (1.1)§	0.007-2.0	13 (2.2)† 4 (0.7)‡ 17 (2.9)§
Ceftriaxone		Not determined	0.007-2.0	12 (2.1)† 2 (0.3)‡ 14 (2.4)§
Cefuroxime	0.007-8.0	7 (1.3)	0.007-8.0	20 (3.4)
Ampicillin	0.007-2.0	6 (1.1)	0.007-8.0	16 (2.7)
Chloramphenicol	0.5 to >16.0	8 (1.5)	0.5-32.0	8 (1.4)
Erythromycin	0.125 to >16.0	15 (2.8)	0.125 to >16.0	50 (8.6)
Tetracycline	0.125 to >16.0	27 (5.0)	0.125 to >16.0	30 (5.1)
Trimethoprim	0.25 to >16.0	98 (18.0)	0.25 to >16.0	105 (18.0)
Rifampicin	0.03-1.0	0	0.03-0.25	0
Vancomycin	0.125-2.0	0	0.125-2.0	0
Clindamicin	0.06 to >8.0	3 (0.6)	0.06 to >8.0	11 (1.9)
Fusidic acid	0.5 to >16.0	530 (97.4)	0.5 to >16.0	578 (99.1)

† Proportion of isolates with intermediate resistance.
‡ Proportion of isolates with full resistance.
§ Proportion of isolates with either intermediate or full resistance.

Table 2—*Serogroup or serotype distribution of pneumococci in 1990 and 1995 surveys*

Serogroup or serotype	1990 (n=544 isolates)		1995 (n=583 isolates)	
	No of isolates	%	No of isolates	%
1	12	2.2	17	2.9
3	58	10.7	41	7.0
4	5	0.9	6	1.0
6	83	15.3	76	13.0
7	12	2.2	8	1.4
8	6	1.1	3	0.5
9	36	6.6	44	7.5
10	8	1.5	12	2.1
11	29	5.3	27	4.6
14	29	5.3	42	7.2
15	9	1.7	17	2.9
16	13	2.4	6	1.0
17	7	1.3	6	1.0
18	18	3.3	16	2.7
19	74	13.6	131	22.5
20	7	1.3	3	0.5
22	12	2.2	8	1.4
23	69	12.7	62	10.6
31	5	0.9	13	2.2
33	17	3.1	4	0.7
Non-typable	5	0.9	16	2.7
Other†	30	5.5	25	4.3

† Includes serogroups or serotypes 2, 5, 12, 13, 21, 24, 28, 29, 32, 34, 35, 37-42.

population) showed intermediate or full resistance to penicillin (table 1). This increase was significant ($P<0.02$). Full resistance to cefotaxime and ceftriaxone was noted in only 0.7% (four) and 0.3% (two) of the isolates respectively. The 23 penicillin resistant isolates were from 18 laboratories, 14 laboratories submitting one such isolate.

In 1990 five isolates showing intermediate penicillin resistance belonged to serotype 23F whereas the three fully resistant isolates belonged to serotypes 6B, 9V, and 23F. Of the 23 isolates showing intermediate or full resistance to penicillin in 1995, nine belonged to serotype 9V and the others to serotypes 6B, 19A, 19C, 19F, and 23F.

The prevalence of erythromycin resistance increased from 2.8% (15 isolates referred from 10 laboratories) in 1990 to 8.6% (50 isolates from 29 laboratories) in 1995 ($P<0.001$) (table 1). Of the 29 laboratories submitting erythromycin resistant isolates in the second survey, 16 submitted one such isolate and seven submitted two. The erythromycin resistant isolates in 1990 belonged to serogroups or serotypes 3, 5, 6, 9, 14, 19, and 22 whereas those in 1995 belonged to serogroups or serotypes 3, 6, 14, 15, 19, and 23.

There were no significant changes in the prevalence of resistance to other antibiotics (table 1). Resistance to vancomycin or rifampicin was not detected in either survey. In 1990 nine isolates (1.7%) were resistant to three or more antimicrobial agents whereas in 1995, 11 isolates (1.9%) were multiresistant. In both surveys multiresistant isolates belonged to serogroups 6, 9, 19, or 23.

In the two surveys 37 serogroups or serotypes were noted, 27 occurring in both surveys. The seven most common in both were 3, 6, 9, 11, 14, 19, and 23 (table 2). In each survey about 92% of the isolates belonged to serogroups or serotypes included in the currently available 23 valent pneumococcal vaccine.[6] Similarly, in each survey roughly 73% of isolates from children aged 2 or less belonged to serogroups or serotypes included in a nine valent conjugate vaccine currently undergoing development for use in children.[7] Conjugate seven valent and five valent vaccines are also being evaluated,[7] and roughly 66% of isolates from children aged 2 or less belonged to serogroups or serotypes proposed for inclusion in the five valent vaccine.

Discussion

The two surveys showed a significant increase in the prevalence of intermediate or full resistance to penicillin. As noted previously,[8] however, resistance to cefotaxime or ceftriaxone— which may be the drugs of choice for meningitis caused by pneumococci with reduced sensitivity to penicillin—is still fairly rare. Of potentially greater relevance was the increase in the prevalence of resistance to erythromycin to 8.6% in 1995. Erythromycin is widely used for pneumococcal infections in patients who are allergic to penicillin or who are infected with penicillin resistant organisms. In addition, erythromycin resistant pneumococci show cross resistance to the related macrolides clarithromycin and azithromycin,[9,10] which are extensively used for empirical treatment of community acquired respiratory infection.

The trend of increasing resistance to β lactams and macrolides is consistent with reported data on sensitivity testing of blood and cerebrospinal fluid isolates of pneumococci in England and Wales. In these isolates the prevalence of penicillin resistance increased from 0.3% of 2667 isolates in 1989 to 2.5% of 2751 isolates in 1994 and the prevalence of erythromycin resistance increased from 3.3% of 2522 isolates in 1989 to 11.2% of 2689 isolates in 1994.[11,12] Increasing rates of antibiotic resistance among pneumococci have also been noted in individual hospitals in the United Kingdom.[13,14] Interestingly, there was no significant change in the prevalence of resistance to a range of other antimicrobial agents, including tetracycline, chloramphenicol, and trimethoprim. Furthermore, these surveys and other studies[15] show that vancomycin resistance has not emerged in pneumococci, which is important given that rifampicin or vancomycin may be useful for treating cephalosporin resistant pneumococcal meningitis in children.[16]

Continued surveillance of antimicrobial resistance and serotype distributions in *S pneumoniae* is essential if clinicians are to make rational decisions about the management and prevention of pneumococcal infection.

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Key messages

- The prevalence of resistance to penicillin and erythromycin among pneumococci in England and Wales increased two and a half-fold and threefold respectively between 1990 and 1995
- Resistance to cefotaxime or ceftriaxone, which may be the drugs of choice for pneumococcal meningitis caused by penicillin resistant pneumococci, is still fairly rare
- Roughly 92% of pneumococcal isolates in England and Wales belong to serogroups or serotypes included in the currently available 23 valent vaccine
- Between 65.1% and 73.9% of pneumococcal isolates from children aged 2 or less belong to serogroups or serotypes included in the five, seven, or nine valent conjugate vaccines under development for use in children of this age group
- Continued surveillance of pneumococcal resistance to antibiotics is essential if clinicians are to make rational decisions concerning the treatment of pneumococcal infections

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Seasonality of birth of patients with childhood diabetes in Britain

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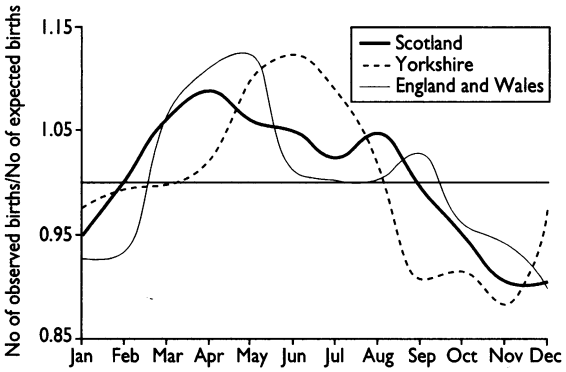
Indirect evidence suggests that early environment is important in the causation of insulin dependent diabetes mellitus.[1] Viral infection is thought to be the most likely trigger. Although biochemical and immunological abnormalities develop several years before the clinical onset of insulin dependent diabetes, the age at which exposure to infection might induce the disease is unclear. The high prevalence of diabetes mellitus in patients with the congenital rubella syndrome shows that the process may be initiated in utero.[1] As most viral infections are seasonal, the pattern of dates of birth of people with diabetes should differ from that of the general population if a significant proportion of cases was caused by intrauterine or perinatal viral infection. We therefore examined seasonality of birth in three large independent populations of children with insulin dependent diabetes in Britain.

Patients, methods, and results

The details of the three registers have been reported previously.[2-4] To ensure that the populations were independent, cases incident in Yorkshire[2] and Scotland[3] were excluded from the population in the British Paediatric Association's study.[4] The analysis was restricted to births during the time common to all three populations—that is, 1974-88. The method of Walter and Elwood was used for analysis of seasonality of month of birth.[5] We adjusted for the seasonality of live births in the general population by constructing pseudocohorts of births on the basis of the number of births during each month of the study. The numbers of live births in England and Wales published by the Office of Population Censuses and Surveys were used for analysis of the data from Yorkshire and the British Paediatric Association's study.[2 4] The numbers of live births obtained from the registrar general for Scotland were used for analysis of the Scottish data.[3]

The Scottish, Yorkshire, and British Paediatric Association registers contained respectively 2258, 1142, and 1265 patients with diabetes born during 1974-88. For each register the monthly pattern of births differed significantly from that in the general population



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Scotland	171	175	212	197	209	187	203	197	197	182	157	171
Yorkshire	96	88	96	98	107	114	110	94	97	72	88	82
England and Wales	92	94	105	133	124	104	103	117	106	107	87	93

Fig 1—*Observed divided by expected number of births each month in three populations with diabetes compared with respective general populations. Numbers are births each month in each diabetic population*

(Scotland, $\chi^2 = 9.7$, $P = 0.002$; Yorkshire, $\chi^2 = 8.7$, $P = 0.005$; England and Wales, $\chi^2 = 3.5$, $P = 0.04$). For each register more patients were born during the spring and early summer and fewer during the winter months compared with the general population (fig 1).

Comment

The seasonal pattern of birth of patients with diabetes mellitus has not, to our knowledge, been reported to differ from that of the general population. Our study has shown abnormal seasonality of birth in three large independent populations with childhood onset diabetes. This is unlikely to be due to chance, and it is difficult to conceive of a bias that might account for the results.

Several important conclusions can be drawn from our observation. Firstly, as seasonality of birth cannot be accounted for by genetic mechanisms, environmental factors must be important in the aetiology of diabetes. Secondly, to induce seasonality of birth these environmental factors must exert their influence in utero or in the first year of life. Thirdly, these environmental factors must, of course, be seasonal in nature.

Our observations are consistent with the hypothesis that the disease process resulting in childhood diabetes is initiated by viral infection early in life. Further studies

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