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Frequencies of pneumococcal types causing serious infections in patients admitted to the Radcliffe Infirmary, Oxford, 1969–77

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SUMMARY

During a $7\frac{1}{2}$ year period pneumococci were isolated from body fluids of 124 patients at the Radcliffe Infirmary, Oxford – 72 with pneumonia, 26 with meningitis and 26 with other serious infections. Eighty-one (65 %) of the patients were over 50, and 33 (27 %) were over 70 years old. Of the 124 pneumococcal strains 104 (84 %), including 23 (79 %) of those from patients who died, belonged to types included in the vaccines successfully used in South Africa and in Papua New Guinea. The relative frequencies of types in the Oxford series and in a larger British series agreed closely with those found in a recent survey of 3644 bacteraemic pneumococcal infections in 10 American cities. Any polyvalent pneumococcal vaccine licensed for use in the United States is thus likely to be relevant to the situation in Britain.

INTRODUCTION AND METHODS

In the 1930s, when type-specific antisera were the only effective means of treating pneumococcal infections, the Quellung or capsule-swelling procedure for typing *Streptococcus pneumoniae* strains (Neufeld, 1902) acquired great clinical importance. It fell into disuse, however, when antisera were superseded by more potent antibacterial agents that were not type-specific in their actions – the sulphonamides and then penicillin. For a time the marked and reliable sensitivity of pneumococci to penicillin *in vitro* suggested that they might soon cease to be a serious medical problem; but despite the striking success of penicillin and other antibiotics in the treatment of many cases of pneumococcal infection, such hopes have not been fulfilled. As has often been pointed out, notably from Philadelphia by Austrian (Austrian & Gold, 1964; Austrian, 1968, 1975, 1977*a* and *b*), serious infections due to this species are still common and, particularly among some groups of patients, still have a high mortality rate. The recent emergence of pneumococcal strains resistant to penicillin and to other antibiotics (Hansman *et al. 1971; Appelbaum et al. 1977) has emphasized the importance of a preventive* rather than a purely therapeutic approach to pneumococcal infections. Since the

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most hopeful approach to prevention is by type-specific immunization, pneumococcal typing has recovered some of its former importance.

In the past 15 years, and especially since the U.S. National Institute of Allergy and Infectious Diseases turned its attention to the matter in 1967, considerable progress towards prevention has been made, along 3 main lines: (*a*) identifying groups of people most at risk from pneumococcal infections; (*b*) determining which pneumococcal types most commonly cause serious infections; and (*c*) developing and testing vaccines containing the capsular polysaccharides of those types. Studies in the United States have confirmed the reasonable assumption that people over 50 years old and those with various chronic debilitating diseases have an increased risk of dying if they develop bacteraemic pneumococcal infections, and therefore are most in need of protection against this possibility (Austrian & Gold, 1964; Kaiser & Schaffner, 1974). Such studies have also shown that the great majority of serious pneumococcal infections are caused by a minority of pneumococcal types. In all, 86 pneumococcal types are known, but the Danish nomenclature (Lund, 1970*a*) groups antigenically related types together and uses only 46 type or group numbers (1 to 48, omitting 26 and 30 for historic reasons). Strictly, therefore, one should refer for example to type 1 or type 2, but to group 6 or 7; but it is an increasingly common practice, which will be followed here, to refer to all 46 as types. Austrian & Gold (1964) found that 6 of these 46 types were between them responsible for 63 % of 529 bacteraemic pneumococcal infections, and that only a limited number of the other 40 types contributed to the remaining 37 %. On the basis of these and similar findings, polyvalent vaccines containing polysaccharides of up to 15 types have been developed and used in field trials. Given to young adults employed in South African gold mines, among whom pneumococcal pneumonia is a common disease, such vaccines achieved by comparison with unvaccinated control groups a decrease of 82 % in the incidence of bacteraemic infections caused by the types included in the vaccine (Austrian *et al.* 1976). These were types 1–4, 6–9, 12, 14, 18, 19 and 25. A similar degree of protection was achieved in a trial in Papua New Guinea (Riley *et al.* 1977), using a vaccine which contained all but two (types 9 and 19) of the types used in South Africa, and three additional types (5, 23 and 46).

It is expected that vaccines similar to those used in South Africa and in Papua New Guinea will soon be licensed for general use in the United States (Austrian, 1977*b*). Little information has so far been available about their relevance to the British situation. The findings presented in this paper were collected at the Radcliffe Infirmary, Oxford during a 7½ year period from December 1969 to June 1977. Throughout this period capsular typing, using the capsule-swelling procedure and antisera obtained from the Statens Seruminstitut, Copenhagen, Denmark, was carried out on all pneumococci isolated from blood, cerebrospinal fluid or other body fluids of patients admitted to the Infirmary. Most of the strains were typed in this laboratory, but some – especially in the first two years, when the range of typing sera held in Oxford was adequate only for the commoner types – were typed in the Cross-Infection Reference Laboratory, Central Public Health Laboratory, Colindale, by courtesy of Dr M. T. Parker.

FINDINGS

Pneumonia (72 *cases*, 16 *fatal*)

Pneumococci were isolated from the blood of 69 patients; one of these, a 45-year-old man, had one attack of pneumonia due to a type 1 pneumococcus and 2 months later another attack due to a type 7 strain, and from now on he is counted as two patients. Two others had pneumococci isolated from pleural fluid but not from blood. Thus the total number of patients with pneumonia was 72. Their age and sex distribution and the pneumococcal types responsible for their illnesses are shown in Table 1. Pneumococcal types which were included in the vaccines tested in South Africa and Papua New Guinea as described above are given their own columns in Tables 1 and 2: both there and in the rest of this paper they are indicated by the term 'vaccine types'. It can be seen that 64 (89 %) of the 72 strains, including 13 (81 %) of the 16 patients who died, belong to 'vaccine types'.

At least 12 patients in this group had underlying diseases – leukaemia (5 cases, 2 fatalities at 85 and 95 years old) myeloma (4 cases), diabetes (2 cases, one fatality at 72 years old probably due to a cerebral haemorrhage), and a reticulosis (one case). Only one of these 12, a man aged 37 years with chronic lymphatic leukaemia, was less than 50 years old.

Meningitis (26 *cases*, 11 *fatal*)

Pneumococci were isolated from cerebrospinal fluid specimens, and in some cases from blood cultures also, from 26 patients with meningitis. The age and sex distributions of these 26 and the pneumococcal types responsible for their illnesses are shown in Table 2. Apart from the inclusion of 4 small children the age distribution of the meningitis patients, with 16 (73 %) of 22 adults over the age of 50 years, is similar to that of the pneumonia patients, for whom the equivalent figures are 54 (76 %) of 71 adults. Ten of the 16 meningitis patients over the age of 50 years died, whereas only 14 of the 54 pneumonia patients in that age group and only 1 of the 10 younger meningitis patients died. The predominance of males was more marked among the meningitis patients (see Tables 1 and 2). The most striking difference between the two series as regards pneumococcal types is the absence of type 1 strains from the list of strains causing meningitis, whereas they caused 15 of the 72 cases of pneumonia. Nineteen (73 %) of the 26 pneumococcal strains from patients with meningitis, including 8 (73 %) of the 11 from patients who died, belong to 'vaccine types'.

Two of the 26 meningitis patients had diabetes – a man aged 66 years who recovered from his meningitis, and a woman aged 63 years who died. The only other patient with a known chronic underlying disease was a 4-year-old boy with nephrotic syndrome, who developed his meningitis shortly after being admitted to hospital with acute appendicitis. His pneumococcus belonged to type 6 (as did that of a 3½-year-old boy also with nephrotic syndrome who was admitted to the Infirmary for acute abdominal symptoms after the end of this survey and was found to have pneumococcal peritonitis). The 19-year-old man developed meningitis as a complication of a severe head injury.

Table 1. *The* 72 *cases of pneumonia*

Age in years	Total no.	Sex M:F	Number fatal	Number of cases due to 'Vaccine types' 1	3	4	5	6	7	8	12	14	18	19	23	Other types (*type nos.*)
8	1	1:0	0										1			
20–29	7	4:3	0	3	1				1	1					1	
30–39	3	1:2	0	1	1											1 (*17*)
40–49	7†	4:3	1	1	1	1	1		2*			1				
50–59	14	7:7	1	3	3*	1		1	1	3	1	1				
60–69	18	14:4	4	4*	3	2*		1*	1	1		2	1			3 (*11**, *20*, *38*)
70–79	15	6:9	5	1	3***	2*	1	1*				2		2	1	2 (*10*, *28*)
80–95	7	4:3	5	2**	2*				1							2 (*16**, *22**)
Total	72	41:31		15	14	6	2	3	6	5	1	6	2	2	2	8
Fatalities		7:8	16	3	5	2		2	1							3

† Including twice the man who had 2 attacks (see text).
*, ** and *** indicate 1, 2 and 3 fatalities respectively.

Table 2. *The 26 cases of meningitis*

Age in years	Total no.	Sex M:F	Number fatal	Number of cases due to 'Vaccine types' 3	4	6	7	8	9	12	18	23	Other types (*type nos.*)
4–12	1	1:0	0						1				
1½–4	3	3:0	0			1					2		
19	1	1:0	0						1				
28	1	0:1	0										1 (*11*)
40–49	4	3:1	1		1*								3 (*22*, *31*, *33*)
50–59	5	3:2	3	2	1*								2** (*39*, *48*)
60–69	6	5:1	3	1*		2*	1	1*		1			
70–79	3	1:2	3					1*			1*	1*	
80–85	2	1:1	1	1									1* (*34*)
Total	26	18:8		4	2	3	1	2	2	1	3	1	7
Fatalities		8:3	11	1	2	1		2			1	1	3

* and ** indicate 1 and 2 fatalities respectively.

Table 3. *Age and sex distribution of the* 124 *patients*

Age in years	Male	Female	Total
Under 5	9	2	11
5–19	4	2	6
20–39	6	8	14
40–49	7 (2)*	5 (1)	12 (3)
50–59	12 (2)	9 (2)	21 (4)
60–69	23 (6)	4 (2)	27 (8)
70–79	10 (2)	13 (6)	23 (8)
80–95	6 (5)	4 (1)	10 (6)
Total	77 (17)	47 (12)	124 (29)

* Figures in parentheses are numbers of fatalities.

Of the 16 cases of meningitis in patients over 50 years old 14 occurred in January–June. Of the 10 cases in younger patients, however, 5 occured in January–June and 5 in July–December. No great seasonal differences were found among the patients with other types of infection.

Other localized infections (9 *cases, none fatal*)

This heterogeneous group includes:

(*a*) Three young children with septic arthritis of the hip – 2 boys aged 9 weeks and 9 months with pneumococcal types 7 and 4 respectively isolated from their blood, and a girl aged 8 months with a type 14 strain isolated from joint fluid.

(*b*) A 9-month-old diabetic boy with otitis media and with a type 23 strain isolated from his blood.

(*c*) A 10-year-old boy with a brain abscess from which a type 1 strain was isolated.

(*d*) Three young females with intra-abdominal infections – a 5-year-old girl with peritonitis and with a type 1 strain isolated from her peritoneal fluid and her vagina; a 10-year-old girl with a pelvic abscess from which a type 1 strain was isolated; and a 21-year-old woman with salpingitis and peritonitis and with a type 3 strain isolated from her peritoneal fluid.

(*e*) A 73-year-old man with cellulitis of his leg and clinical septicaemia and with a type 7 strain isolated from his blood.

The main features of this group are the youth of most of the patients, the absence of fatalities and the fact that all of the pneumococcal strains belonged to vaccine types (type 1, 3 cases; type 3, one case; type 7, 2 cases; type 14, 2 cases; and type 23, one case).

Febrile bacteraemic illnesses without localized infections (17 *cases,* 2 *fatal*)

Three of these patients were young children – 2 boys aged 14 months and 18 months and a girl aged 18 months – who had febrile illnesses without any known underlying diseases. All 3 recovered. The remaining 14 patients were a 16-year-old boy, a 32-year-old man and 8 other men aged 57 to 83 years; and 4 women aged 26, 48, 72 and 79 years. Most of these were diagnosed clinically as

Table 4. *Summary of type frequencies*

'Vaccine types'		Other types	
	Number of cases (fatalities)		Number of cases (fatalities)
Type 3	21 (7)	Type 11	3 (1)
1	19 (3)	10	2
14	10	20	2
4	9 (4)	22	2 (1)
7	9 (1)	15	1 (1)
8	8 (2)	17	1
6	7 (3)	24	1
18	7 (1)	28	1
23	5 (2)	31	1
5	2	33	1
9	2	34	1 (1)
12	2	37	1
19	2	38	1
2	1	39	1 (1)
		48	1 (1)
Total	104 (23)		20 (6)

septicaemic, and 12 of them had underlying chronic diseases: leukaemia (3 cases), carcinoma of lung (2 cases, one of them a 64-year-old man who died of his infection), diabetes (2 cases), alcoholism (2 cases), chronic hepatitis with thrombocytopaenia (1 fatal case, the 48-year-old woman), nephrotic syndrome (the 16-year-old boy) and chronic bronchitis (1 case). The pneumococci isolated from the 3 young children belonged to types 14, 18 and 1 respectively; and those isolated from the 14 older patients to types 2, 3 (2 cases, one fatal), 6, 8, 10, 11, 14 (2 cases), 18, 20, 23 (fatal), 24 and 37. Thus vaccine types were responsible for 12 (71 %) of the 17 cases and for both fatalities.

Synopsis of the 124 *patients and their pneumococci*

The age and sex distributions of the 124 patients – 72 with pneumonia, 26 with meningitis and 26 with other infections – are shown in Table 3. Of the 124, 81 (65 %) were over 50 and 33 (27 %) over 70 years old. Of the 29 who died, 26 (90 %) were over 50 and 14 (48 %) over 70 years old. There was a 77:47 excess of males over females, most of which occurred among the young children and among those aged 60–69 years: but the proportion of fatal cases was higher among females.

Table 4 shows the frequencies of pneumococcal types. Two of the 16 'vaccine types', type 25 and 46, were not encountered in this series. The remaining 14 accounted for 104 (84 %) of the 124 cases, including 68 (84 %) of the 81 among patients over the age of 50 years, and also for 23 (79 %) of the 29 fatalities.

DISCUSSION

This survey was restricted to patients who were admitted to the Radcliffe Infirmary with serious pneumococcal infections or developed them while in the

Infirmary. This is a general hospital, dealing mainly with acute medical or surgical problems; it has paediatric wards, but the local specialist geriatric wards are in other hospitals and served mainly by another bacteriological laboratory. Consequently the survey probably underestimates the true predominance of elderly patients among those in the Oxford area who developed serious pneumococcal infections.

It also certainly gives an incomplete picture of the frequency of pneumococcal pneumonia in the Infirmary during the 7 year period, since only those with positive cultures from blood (or, in 2 cases, pleural fluid) were included. According to Austrian (1968) 'bacteraemia can be demonstrated only in a fourth to a third of all pneumococcal pneumonias', but 'blood culture provides the safest and simplest readily available technique for establishing the presence of pneumococcal infection'. Isolation of pneumococci from the respiratory tract, in life or at autopsy, is far from being conclusive evidence of their causal role in pneumonia. Consequently blood culture has been the main source of information about frequencies of pneumococcal types as causes of pneumonia in the United States; and the choice of types for inclusion in the polyvalent vaccines has been based on the results of culturing blood and other body fluids. For the purpose of producing comparable British data, countercurrent immunoelectrophoresis and other techniques for the detection of pneumococcal antigens in body fluids would have been inappropriate, even if they had been readily available during the early years of the survey.

Among the pneumococci isolated from 3644 patients with bacteraemic pneumococcal infections in 10 American cities during the years 1967–75 (Austrian *et al.* 1976), types 8, 4, 1, 14, 3 and 7 were the 6 commonest types, in that order of frequency, and between them were responsible for 49·6 % of the infections. The next 10 types in order of frequency – types 12, 6, 18, 9, 19, 23, 5, 20, 22 and 11 – were responsible for a further 35·6 %, giving a total of 85·2 % caused by 16 types. (These were not quite the same 16 as the 'vaccine types' listed above as having been used in the vaccine trials in South Africa and Papua New Guinea before the results of the American survey were available. Types 11, 20 and 22 were not among the 'vaccine types', and type 23 was used only in Papua New Guinea. Conversely, 'vaccine types' 2, 25 and 46 were not among the first 16 in the American series). Comparison of the American findings with those recorded in Table 4 shows that the 6 commonest types were the same in the two series (though not in the same order) and that they were responsible for 76 (61 %) of the 124 Oxford cases. Furthermore, of the types that occupied the next 10 places in the American series, 9 were each responsible for 2 or more cases in the Oxford series and the 10 together were responsible for 34 (27 %) of the 124 cases, giving a total of 110 (89 %) caused by the 16 types that had caused 85·2 % of the 3644 American cases. This close similarity between the situations in America and Britain is confirmed by an unpublished Public Health Laboratory Service study of 369 pneumococcal isolates received in the Cross-Infection Reference Laboratory, Colindale, during the two years June 1969 to May 1971 (personal communication, Dr M. T. Parker). These isolates came from patients in various parts of England and Wales (including 30 of the 124 Oxford patients who are the subject of the present paper). 167 of

the 369 patients had severe pneumonia (mostly bacteraemic), 141 had meningitis and 61 had other serious infections (septicaemia, peritonitis, arthritis, etc.). The 16 commonest pneumococcal types, in order of frequency, were 3, 1, 14, 8, 6 = 19, 23, 18, 5 = 7, 9, 4 = 12, 11 = 20, and 24. The first four of these were among the first six in the American and the Oxford series, and the first fifteen were among the first sixteen in the American series. The six types that were responsible for 49·6 % of the American and 61 % of the Oxford cases were responsible for 170 (46 %) of the 369, and the sixteen types that were responsible for 85·2 % of the American and 89 % of the Oxford cases were responsible for 314 (85 %) of the 369. This agreement is the more remarkable because this American series consisted entirely of bacteraemic patients, whereas patients with positive cultures from other body fluids were included in the two British series.

Table 5 compares the 'vaccine types' with the sixteen commonest types in the American and Public Health Laboratory series and the seventeen types which were each responsible for two or more cases in the Oxford series. (Since 7 types were each responsible for two of the Oxford cases, the commonest 16 types in that series cannot be defined). It is reasonable to expect that if a 16-type vaccine is licensed for use in the United States its composition will be based on the frequencies found in the American series – i.e. 'vaccine types' 2, 25, and 46 will not be included but will be replaced by types 11, 20 and 22. Such a vaccine would be highly relevant to the prevailing situation in Britain. Effective immunization against all of its sixteen types would have protected 110 (89 %) of the Oxford patients, including 71 (88 %) of the 81 over the age of 50 years and 25 (86%) of the 29 who died. These are somewhat higher figures than would have been given by effective immunization against the 16 'vaccine types', as indicated above in the synopsis of the 124 patients and their pneumococci.

Speculations about the proportion of patients who could theoretically be protected by use of a vaccine must of course be tempered by considering the practicability and cost-effectiveness of achieving such protection throughout the relevant population. The present survey provides no information about such matters.

One reason that has been given for doubting the value of immunization against pneumococcal infections is that natural fluctuations in the frequencies of pneumococcal types causing serious infections will render vaccines obsolete within a few years. These natural fluctuations have been studied in Denmark by Lund (Mørch, 1949; Lund, 1970*b*) and in Boston, U.S.A., by Finland & Barnes (1977). Although individual types rise and fall in the order of frequency, these long-term surveys have shown that only a restricted number of types ever reach the upper part of the order. Finland & Barnes listed the types which ever reached the eight top positions as causes of bacteraemic infections in any of fifteen selected years between 1935 and 1974. Only 16 types achieved such positions, and 13 of these were among the 16 that were found to be commonest in the American series that we have discussed above. The three exceptions were types 16 and 25, each of which reached the eighth position on one occasion only and type 2. This last type has had a remarkable history. As its low type number implies, it was one of the first types to be

Table 5. *Comparison of the pneumococcal types used in vaccines in South Africa and in Papua New Guinea with those that were commonest in the American, Oxford and Public Health Laboratory series*

	1	2	3	4	5	6	7	8	9	10	11	12	14	18	19	20	22	23	24	25	46
'Vaccine types'																					
South Africa	*	*	*	*		*	*	*	*			*	*	*	*					*	
Papua New Guinea	*	*	*	*	*	*	*	*				*	*	*				*		*	*
American series (16 commonest types)	*		*	*	*	*	*		*		*	*	*	*	*	*	*	*			
Oxford series (17 commonest types)	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*			
P.H.L.S. series (16 commonest types)	*		*	*	*	*	*	*	*	*		*	*	*	*	*		*	*		

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recognized, and this was beause it was a common pathogen. In each of the first four years of Finland & Barnes' 15 (1935, 1941, 1951 and 1953) it was in one of the top four positions, but from 1953 onwards it never reached the top eight; this Boston experience was paralleled in other countries. Type 2 seems to be the sole example of a lasting change in the range of types commonly causing serious infections.

Whether widespread immunization against some pneumococcal types would itself induce an increase in frequency of other types is a question which can be answered only after long-term experience. Even if it did lead to an increase in frequency of *carriage* of types which do not at present rank as important pathogens, there is no obvious reason for expecting that these types will at the same time become more virulent. Short-term experience in South Africa has supplied no evidence of such an effect (Austrian *et al.* 1976).

A surprising feature of the Oxford series is that the highest proportion of patients with chronic underlying diseases was found in the group with the most successful outcome – those with febrile bacteraemic illnesses but no evidence of localized infection. A possible explanation of this paradox is that patients with such conditions are under close medical supervision, and so are particularly likely to have blood cultures taken early in febrile illnesses and to receive prompt antibiotic treatment.

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