Epidemiology of systemic pneumococcal infections in western Europe

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In no European country is pneumococcal infection, including meningitis, a notifiable disease. Therefore, there are no overall data regarding pneumococcal infection; the data that are available are scattered and come mainly from the northern European countries and France. Most are from national reference centres (Réseaux National de Santé Publique [EPIBAC], Saint Maurice, France; the Public Health Laboratory Service Communicable Disease Surveillance Centre, London, United Kingdom; the National Public Health Institute, Helsinki, Finland; the World Health Organization Collaborating Center for Reference and Research on pneumococci, Copenhagen, Denmark and the Swedish Institute for Infectious Disease Control, Stockholm, Sweden) and are drawn from voluntary reports. Others are the results of limited and frequently cooperative studies. The shortage of clinical data contrasts sharply with the large amount of data on the epidemiology of resistance.

CLINICAL EPIDEMIOLOGY

Invasive infections: Table 1 (1-7) summarizes variations in incidence of invasive pneumococcal disease per 100,000 inhabitants by country and partially by year. Except for the low values in 1997 in Sweden (3), the average rate is approximately 10/100,000 inhabitants. The average rate masks a significant increase in incidence in Denmark from 1992 (9).

Table 2 (1,2,4,5,7-10) reveals the variation in the incidence of pneumococcal septicemia by age. The incidence is bimodal, with one peak before two or five years of age, depending on the series, and another in persons 65 years of age and older, with a gradual increase after age 65 years – for example, the incidence is 70/100,000 in adults older than 85 years in France (Figure 1). The Finnish data on children younger than age 16 show a growing increase in the incidence rate between

TABLE 1
Incidence of invasive pneumococcal disease per 100,000 inhabitants determined by blood culture, cerebrospinal fluid culture and other methods

Country, time period (reference)	Overall incidence	Vaccine coverage
Denmark, 1989 to 1994 (1)	10 to 19	84%
Sweden, 1964 to 1980 (2)	7.5	—
Sweden, 1987 (septicemia) and 1990 (3)	3.2 10.2	96.7%
Finland, 1983 to 1992 (4)	9.1	95%
France, 1991 to 1996 (15)	8 to 10.6	84% to 89.5%
England and Wales (7)	9.3	95%

1983 and 1994 from 53/100,000 before age two years to 110/100,000 with no rational explanation (9).

Fedson et al (11), in a forthcoming article, report a significant increase in pneumococcal incidence rates in 1996 – 47/100,000 in Sweden, 80/100,000 in Denmark and 62/100,000 in Norway (personal communication). This corresponds to published rates in North America. Despite comparable collection techniques, the same trend is not reported in France, where the rate has been stable since 1991 (Figure 2). In Sweden, opinions are divided. Some believe that there is an actual increase (12), while others believe the increase has been artificially created by a spontaneous increase in strains sent to the reference centres (13), especially because penicillin-resistant strains are more common (7).

Table 3 shows the incidence of pneumococcal meningitis by country. The incidence rates are even more similar between them from one country to another – around 1/100,000 cases

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TABLE 2
Incidence of pneumococcal septicemia per 100,000 inhabitants by age

Country	Time period (reference)	Age groups						
		All ages	Five years or younger	Five to 14 years	15 to 64 years	65 years or older	75 years or older	85 years or older
Finland	1985 to 1992 (4)	—	—	—	6.2	27.1	35.8	44.5
Finland	1985 to 1989 (8)	—	24.2	8.9	—	—	—	—
Denmark	1989 to 1994 (1)	—	13 to 23	—	—	27 to 55*	—	—
France†	1991 to 1995 (5)	8.3	15.2 to 16.9	1.5 to 3	4.2 to 5.7	22.5 to 28.3	—	0
	1996 (6)	8.3	12	—	—	29	—	70
Sweden	1964 to 1980 (2)	6.1	—	—	—	40 to 47	—	—
Finland			< 2 years	≤ 16 years				
	1983 to 1992 (9)	—	53	10.5	—	—	—	—
	1993 (9)	—	70	20	—	—	—	—
	1994 (9)	—	110	30	—	—	—	—
Belgium	1983 to 1994 (10)	8.3	—	—	—	—	—	—
England and Wales			< 1 year					
	1982 (7)	4.1	14	—	—	—	12	—
	1986 (7)	—	18	—	—	—	14	—
	1992 (7)	8.7	34	—	—	—	36	—

*Older than 60 years of age; †Bacteremia and meningitis with bacteremia

Figure 1) *Streptococcus pneumoniae* bacteremia incidence per 1,000,000 inhabitants in France by age group. Data from reference 5

Figure 2) *Streptococcus pneumoniae* bacteremia in France from 1991 to 1995. Data from reference 5

per year (range 0.6/100,000 in England-Wales to 2.1/100,000 for Asians living in the North East Thames region of England [14]). Children have an increased incidence of pneumococcal meningitis (8); children younger than six months of age have an incidence rate of 7.1/100,000, children younger than one year 6.8/100,000, children younger than two years 4.7/100,000, children younger than five years 2.1/100,000, and children younger than 16 1/100,000 (the adult rate). Since the *Haemophilus influenzae* type b vaccine came into widespread use, pneumococcus has become the leading cause of purulent meningitis in France (Figure 3), as in other countries. In adults, the incidence increases beginning at age 65 years (5,7). As with septicemia, the sex ratio favours men in all European countries.

Serotype distribution varies from one country to the next or from one year to the next, but 85% to 95% are contained in the 23-valent vaccine. In France, 85.6% of serotypes are contained in a heptavalent vaccine conjugate for meningitis (15).

Pneumonia: Pneumococcal pneumonia is considered the leading cause of community-acquired pneumonia (16), even though the diagnosis may not be definitive. This contrasts with invasive infections, where the diagnosis is made after isolation of pneumococcus from a normally sterile site, mainly blood and cerebrospinal fluid. Incidence rates vary according to the diagnostic method used (eg, blood culture, protected bronchial sampling with or without brushing, bronchial aspiration, expectoration, indirect methods such as pneumolysin antibody testing or testing for antigens in urine, serum or expectoration). This leads to great variation in the results of epidemiological studies. The difficulty is heightened by the poor performance of diagnostic tests; approximately 50% of pneumonias have a definite microbiological diagnosis. Incidence can be assessed by prospective studies (17,18,19) or from discharge codes (code 480 to 486, International Classification of Disease [of World Health Organization-9]) for patients hospitalized in institutions taking in the majority of patients for a

TABLE 3
Incidence of pneumococcal meningitis

Country, author (reference)	Year	Incidence per 100,000	Vaccine coverage	Mortality rate (%)
Sweden				
Burman (2)	1964 to 1980	1.4	—	33
Berg et al (35)	1987 to 1989	1.2	100	24
Kragsbjerg et al (36)	1981 to 1992	1	96.4	16
England (North East Thames Region)		0.8 (Caucasians)	90	22
Urwin et al (14)	1990 to 1993	2.1 (Asians)		
Wales and England				
Aszkensay et al (7)	1982 to 1992	0.6	—	—
Finland				
Sanklampen et al (4) (> 16 years)	1983 to 1993	0.9	95	—
Eskola et al (8) (< 16 years)	1985 to 1995	7.1 (< 6 months)		
		2.1 (< 5 years)		
		6.8 (< 1 year)		
		1 (< 16 years)		
		4.7 (< 2 years)		
France				
Mehl-Auget (6)	1991 to 1995	0.86 to 1.10	85.6*	25

*With a heptavalent vaccine conjugate

Figure 3) Bacterial meningitis in France from 1987 to 1995. Data from reference 5. S pneumoniae *Streptococcus pneumoniae*; **H influenzae** *Haemophilus influenzae*; **L monocytogenes** *Listeria monocytogenes*; **N meningitidis** *Neisseria meningitidis*

given population (20,21). Pneumococcal infections can be calculated on the basis of specific groups of patients to whom ratios found in the literature are applied (20,21). For example, at least 80% of pneumococcal-positive blood cultures are associated with pneumonia; 5% to 30% (15% to 20% in general) of pneumococcal pneumonia is accompanied by a positive blood culture. Therefore, it is possible to determine the approximate number of cases of pneumococcal pneumonia hospitalized per year if the number of cases septicemia in that country correlated to the population is known.

Table 4 (17-23) summarizes the rare studies of pneumonia incidence. There is a great variation in the data concerning pneumonia of all etiologies combined; in particular, the inci-

dence in England is low (the methodology in this study did not include chest x-rays) (17). The Finnish studies were based on clinical and radiological criteria (18,19). The French study was based in part on pneumonia diagnoses in hospital, which generally included an x-ray on admission (20). In those patients older than 60 to 65 years of age, the incidence rate rises significantly.

The incidence of pneumonia increases with age (Figure 4), especially beginning at age 60 years, as found in Finland, Holland and France. In general, pneumonia-related mortality also varies according to age, as well as out-patient (3% on average) or in-patient (9% on average; more than 25% in bacteremic-associated cases) management. *Pneumococcus* is rarely spon-

TABLE 4
Incidence per 100,000 inhabitants per year of community-acquired pneumonia*

Country, year (reference)	All etiologies		Pneumococcal	
	Global incidence	In-patients	Global incidence	In-patients
Great Britain 1987 (17) [†]	470	103	169 [‡]	
Sweden 1987 (22)	1000		—	
Finland 1982 (18)	1160	540	300 [§]	126 [§]
1982 to 1984 (19)	1150 [§]	700 [§]	220	
France 1995 to 1996 (20)	795	168 (550 [¶])	252	50 (220 [¶])
Spain 1983 (23)		77		
Holland 1991 (21)**	—		137	23 (202 [¶])

*Some data are calculated from the genuine data in the article; [†]Patients 16 years of age or older; [‡]36% were diagnosed by blood or other cultures, or antigen detection; [§]30% of etiologies assumed to be pneumococcal (data calculated, not cited in article); [¶]Patients older than 60 years of age;

**Patients older 50 years of age

taneously declared as the etiological agent associated with death; of 15,840 pneumonia deaths in France in 1995, only 2.8% were pneumococcal origin as indicated on the death certificate. Ninety-five per cent of the deaths occurred after age 60 years; 45% were in the 80 to 89 year age group (20). The incidence of pneumococcal pneumonia was higher in cases of

comorbidity (19% compared with 4% [24]). In western Europe as a whole, Fedson et al (11) estimates the annual number of hospitalized cases of pneumonia of all etiologies combined to be 575,300 in subjects older than 65 years of age. Pneumococcus was found to be responsible for 172,590 to 287,650 cases. The annual number of deaths was found to be 76,500 (11).

EPIDEMIOLOGY OF RESISTANCE

Antimicrobial-resistant *Streptococcus pneumoniae* is a genuine pandemic. Resistance varies widely from one country to another in Europe. It is very high in Spain (greater than 40%) and France (greater than 40% in 1996), and rare in northern Europe. Table 5 (15,25-32) summarizes the data on the differences, with surprisingly diametrically opposed rates for countries bordering each other such as Belgium and France. Antibiotic prescribing habits definitely play a major role, in particular the overconsumption of antibiotics in young children (over 60% of pneumococcal otitis cases in France are resistant to penicillin). Resistance to macrolides varies from one country to another; it was low in Spain when pneumococcus with reduced susceptibility to penicillin emerged (31) but was already higher in France (greater than 25%) (15). The increase in resistance to macrolides in Belgium parallels an increase in the consumption of this family of antibiotics (27). The low incidence in Italy is apparently due to the preference for intravenous administration of cephalosporins (29). The resistant strains consist mainly of serotypes 23, 6, 9 and 14 in most countries. Epidemic strains, such as strain 23, have been described in Spain, Iceland and the United States.

The very common resistance in meningeal and ear, nose and throat infections is becoming increasingly frequent in France, about 30% for septicemia and pneumonia (15,33). The

Figure 4) Annual incidence of all cases of community-acquired pneumonia and suspected pneumococcal pneumonia in France by age group. Data from reference 20; S pneumoniae *Streptococcus pneumoniae*

TABLE 5
Global epidemiology of resistance

Country (reference)	Number of strains	Years	Percentage of resistance		
			Percentage reduced susceptibility to penicillin or resistant	Percentage resistant to macrolides	Pneumococcal serotypes with reduced susceptibility to penicillin
France (15)	825	1984	0.5	18.9	
	1470	1990	12	26.2	23E, 14, 6V, 19, 9B
	4078	1996	42.8	51.2	23, 14, 9, 6, 19, 15
England and Wales (25)	544	1990	1.5	2.8	23F, 6B, 9B
	583	1995	3.9	8.6	9V, 6B, 19A, C and F, 23F
Sweden (26)	500	1990	0.002	—	—
Belgium (27)	301	1984	0	— (less than 5%)	
	540	1990	4.1	17	
	641	1993	2.3	21.5	23, 19, 14, 9, 15
Holland (28)	—	1995 to 1996	1.1	—	14, 20, 19, 9, 15
Germany (30)	110	1992 to 1994	4	—	—
Italy (29)	312	1993	5.5	3.8	—
Spain (31)	68	1984	11.7	2.9	—
	85	1990	60.0	9.4	—
Switzerland (32)	351	1993 to 1994	7	6	6, 7, 19, 14, 1

constant, gradual development of resistance in countries such as Spain and France, and Hungary and Poland (34) suggests that resistance will spread to neighbouring countries.

CONCLUSIONS

Invasive pneumococcal infections are a genuine public health problem in Europe because of their frequency and the development of multiple antibiotic resistance. Unfortunately, they are not notifiable diseases, and their epidemiology is not known in a uniform, accurate way. Rates of invasive infections are comparable in different countries; the average rate is 10/100,000, of which approximately 1/100,000 are meningitis. The average figures hide disparities from one country to another, with an increase reported in the northern European countries, Denmark in particular. They also hide the bimodal distribution with a high rate before the age of two years, especially for meningitis, and an increasing rate in persons older than 65 years of age, in a quasilinear fashion. The data regarding pneumonia are more disparate, but all point to the prominence of pneumococcus, a large number of hospitalizations and a mortality rate (about 10%). The heaviest toll is in persons older than 60 years of age, particularly those over 80 years of age.

The epidemiology of resistance is distributed unevenly and is disturbing because of its rate. The high level of resistance in France or Spain leads to the fear that this situation is irreversible as history has shown for the resistance of *Staphylococcus aureus* to penicillin. Just beginning in other countries, resistance must be surveyed regarding the risk of increase in the future. Awareness of this epidemiology definitely implies that a policy for antibiotic use, in particular in children, and a

vaccination policy with perhaps, in the future, the eradication of the carriage of multiresistant strains through vaccination with a conjugate vaccine, could be a hope (37). In the meantime, vaccine prevention must remain or become a major objective.

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