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Systemic pneumococcal disease in Norway 1995–2001: capsular serotypes and antimicrobial resistance

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SUMMARY

A total of 4624 pneumococcal isolates from episodes of systemic pneumococcal disease were received at the Norwegian Institute of Public Health during the period 1995–2001. All isolates were serotyped and tested for susceptibility to benzylpenicillin, lincomycin, erythromycin, tetracycline and trimethroprim–sulphamethoxazole. The proportion of strains resistant to these antimicrobial agents remained stable at a low level, ranging from 0·1% for benzylpenicillin to 2·5% for erythromycin. The distribution of serotypes was also stable over the 7 years: serotypes 1, 4, 9, 14, 7, 6 and 23 were the most frequent, representing 70·5% of isolates. Overall, 95·8% of the isolates were of serotypes/groups included in the current 23-valent polysaccharide vaccine, 52·2% were of serotypes/groups included in the 7-valent conjugated vaccine and 85·5% were of serotypes/groups included in the 11-valent conjugated vaccine.

INTRODUCTION

Streptococcus pneumoniae is a leading cause of bacteraemia and meningitis worldwide. Even when optimal antibiotic treatment is provided, the case fatality rate among cases of systemic pneumococcal disease remains high [1, 2]. Systemic pneumococcal disease is most common in young children and the elderly. Splenectomized and immunocompromised persons are at markedly increased risk for severe pneumococcal disease [3]. Benzylpenicillin has been the drug of choice for treatment of systemic pneumococcal disease, since its introduction in the 1940s. However, penicillin-resistant and multidrug-resistant isolates have been increasingly frequently recovered from patients and carriers in several countries [4]. Emergence of multidrug-resistant pneumococci emphasizes the importance of vaccination as a means to prevent pneumococcal disease. Vaccination might also reduce carriage of resistant strains and even contribute to lowering the introduction of such strains into areas with little resistance [5].

At least 90 different serotypes of pneumococci have been described, based on differences in the antigenic structure of their capsular polysaccharides [6]. Since 1984, a vaccine containing 23 different pneumococcal capsular polysaccharides has been available in Norway. It is recommended for high-risk groups, such as splenectomized patients and the elderly [7, 8]. Due to poor antibody response to the polysaccharides, the 23-valent polysaccharide vaccine is not recommended for children younger than 2 years of age. In recent years, pneumococcal conjugated vaccines

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have been developed, in which capsular polysaccharides are covalently linked to a carrier protein; such vaccines also induce an antibody response in children younger than 2 years of age. A 7-valent conjugated vaccine is now available, and 9-valent and 11-valent vaccines are undergoing clinical trials [5, 9].

In this paper, we review the pneumococcal disease situation in Norway, using retrospective data on systemic pneumococcal isolates collected at the Norwegian Institute of Public Health during the period 1995–2001. The incidence rate of systemic disease, the age and sex distribution of the patients, the distribution of serotypes and the susceptibility of the isolates to antimicrobial agents are presented. These data are intended to inform a discussion on the place of the new conjugated vaccines in preventing systemic pneumococcal disease in the Norwegian population.

MATERIALS AND METHODS

Bacterial isolates

Systemic pneumococcal disease has been a notifiable disease in Norway since 1977. All clinical microbiology laboratories in Norway routinely submit pneumococcal isolates from normally sterile body sites to the Norwegian Institute of Public Health (NIPH) for further characterization. Isolates from approximately 80% of the notified cases of systemic pneumococcal disease are received at the NIPH. This study includes a total of 4624 strains received during the period 1995–2001. All isolates were confirmed as *S. pneumoniae* by the optochin-sensitivity test, and if necessary, by bile solubility [10]. For patients with meningitis from whom both blood and cerebrospinal fluid (CSF) isolates were received, only the CSF isolate was included in the analysis.

Data on age and sex distribution of the Norwegian population in 1995–2001 were obtained from Statistics Norway.

Serotyping

Pneumococcal typing was performed by the quellung reaction using antisera produced by Statens Serum-institut (Copenhagen, Denmark). All strains were serogrouped. Strains isolated from children aged between 0 and 5 years were also typed using factor sera, to identify types within groups. From patients with multiple isolates of the same type during the same disease episode, only one isolate was included in the analysis.

Antimicrobial susceptibility

The drug susceptibility pattern of the strains was tested using the disc diffusion method for benzylpenicillin (applying 1 μg oxacillin discs), lincomycin, erythromycin, tetracycline and trimethroprim–sulphamethoxazole (Neo-Sensitabs, Rosco Diagnostics, Taastrup, Denmark) on PDM medium with 5% horse blood incubated overnight at 35 °C in 5% CO_2. Inducible clindamycin resistance in erythromycin-resistant isolates was not tested. Isolates showing reduced zone sizes for any one of these antibiotics were tested further using the E test method (AB Biodisk, Solna, Sweden) on PDM medium with 5% horse blood in 5% CO_2, to determine the minimal inhibitory concentrations (MICs) against benzylpenicillin, erythromycin, chloramphenicol, doxycycline, cefotaxime and clindamycin. Isolates with MIC values of $\leqslant 0{\cdot}06\,\mu$g/ml and $\geqslant 2\,\mu$g/ml were defined as penicillin sensitive and penicillin resistant respectively. Isolates with MIC values $\leqslant 1\,\mu$g/ml and $\geqslant 4\,\mu$g/ml were defined as sensitive and resistant to erythromycin, doxycycline and clindamycin respectively [11]. Isolates with chloramphenicol MICs of $\leqslant 4\,\mu$g/ml and $\geqslant 8\,\mu$g/ml were recorded as sensitive and resistant respectively. Finally, strains with cefotaxime values of $\leqslant 0{\cdot}5\,\mu$g/ml and $\geqslant 2\,\mu$g/ml were likewise recorded as sensitive and resistant [12]. For control purposes we used *S. pneumoniae* TIGR4 (NIPH 7/87) [13], ATCC49619, and NIPH 76/00; these strains are wild type, penicillin intermediately sensitive and penicillin-resistant isolates respectively.

RESULTS

Incidence rates of systemic pneumococcal infections

All cases of systemic pneumococcal disease are reported to the Norwegian Notification System for Infectious Disease (MSIS). Data from MSIS show that Norway, with a population of 4·5 million, as at the end of 2001, has experienced a steady increase in incidence rates of systemic pneumococcal disease, from 6/100 000 in 1989 to approximately 20/100 000 in 1996 [14]. Annual numbers of reported cases are given in Figure 1. From 1996 the incidence has remained stable at approximately 19–20/100 000. Nearly half of the cases occurred in individuals aged 65 years or more.

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Fig. 1. Numbers of cases of systemic pneumococcal disease in Norway reported to the Norwegian Notification System for Infectious Diseases from 1989 to 2001.

During the study period from 1995 to 2001, a total of 5890 cases were reported to MSIS.

Incidence of systemic pneumococcal disease by age and gender

A total of 4624 isolates, representing 78·5% of all reported cases, was received at the NIPH and included in the analysis. The anatomical site of isolation of the organisms is presented in Table 1. Of the strains received, 4319 were collected from blood cultures, 292 from CSF and 13 from other normally sterile body sites. The number of CSF isolates remained stable in absolute numbers during the 7 years, representing 5·3–7·1% of the total number of isolates. The number of isolates collected followed a seasonal pattern, with a reduced incidence of disease during the summer months (data not shown).

Of the 4624 strains received, 2206 (47·7%) were from individuals aged >65 years, 325 (7·0%) were from children aged ⩽5 years and 2086 (45·1%) were from the 6–65 years age group. For seven patients (0·2%) the age was not available. The age range of the patients was from 0 to 101 years, median 63 years, mean 57 years.

The incidence of pneumococcal disease by age and gender is shown in Figure 2. Total of 2349 strains (50·8%) were recovered from females and 2272 (49·1%) from males. The incidence rates of systemic disease were calculated using the age distribution in the population in 2001. The rates were highest among small children (0–2 years of age) yielding 18·6/100 000 and among the elderly (>65 years of age) reaching 46·6/100 000. The incidence rate of systemic disease was higher among males (14·7/100 000) than among females (11·0/100 000) in the earliest years of life (0–5 years). The incidence rate among people aged 6–65 years was similar for the two genders (8/100 000), while among people aged >65 years, it was once again higher for males (51·1/100 000) than for females (43·4/100 000).

Table 1. *Site of isolation of the systemic pneumococcal strains from Norway, 1995–2001*

	No. of isolates (relative frequency, %)		
Year	Total	Blood	CSF
1995	573	534 (93·2)	36 (6·3)
1996	703	653 (92·9)	50 (7·1)
1997	662	626 (94·6)	35 (5·3)
1998	665	628 (94·4)	36 (5·4)
1999	684	634 (92·3)	48 (7·0)
2000	643	595 (92·5)	45 (7·0)
2001	694	649 (93·5)	42 (6·1)
Total	4624	4319 (93·4)	292 (6·3)

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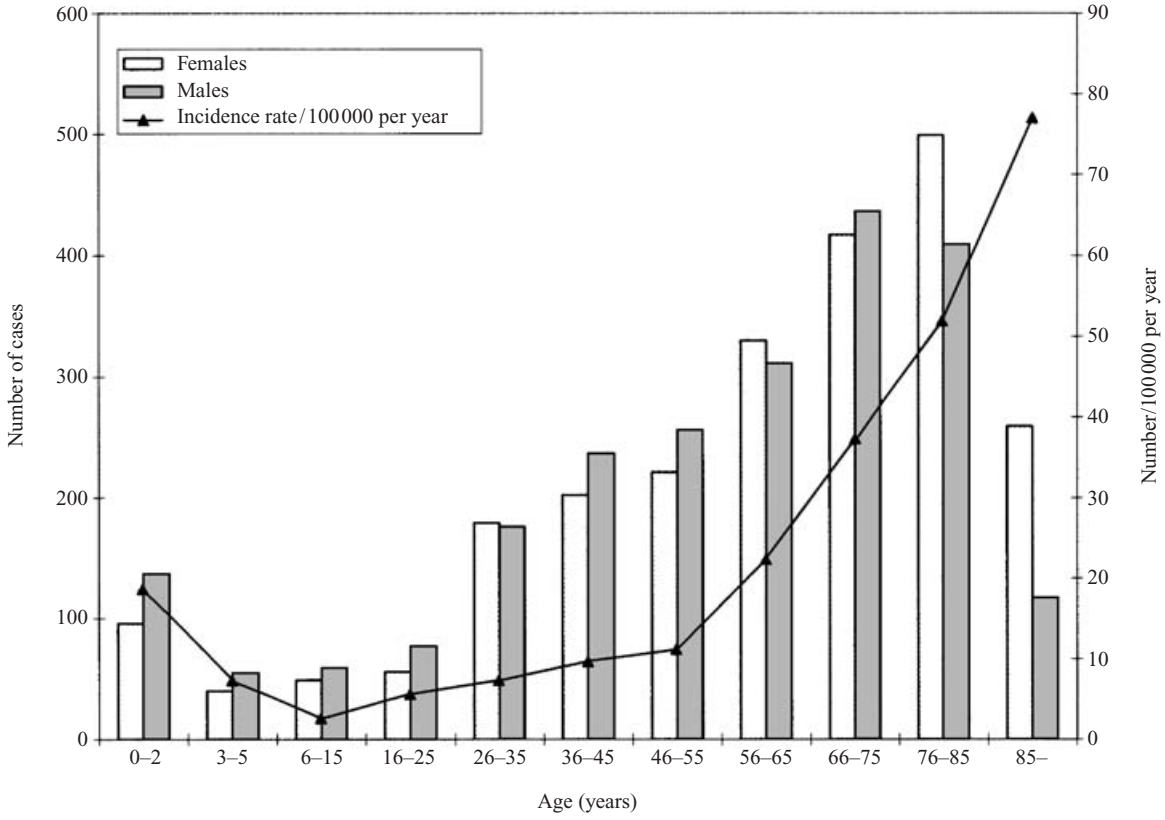

Fig. 2. Incidence rates, age and sex distribution of systemic pneumococcal disease in Norway 1995–2001.

Capsular types of systemic pneumococcal isolates

The serotype distribution of pneumococci isolated from blood or CSF from all patients is presented in Table 2. The most common serotypes/groups in order of frequency were 1, 4, 9, 14, 7, 6 and 23, accounting for 70·5% of the systemic isolates. The seven most common serotypes/groups causing disease among patients aged >65 years were 14, 4, 9, 1, 23, 6 and 3, accounting for 68·4% of the cases. Serotypes 4 and 9 were more prevalent among people older than 65 years, while serotypes 18 and 6 were more prevalent among children aged up to and including 5 years.

Isolates received from children (0–5 years) were serotyped by factor sera to differentiate between types within the groups (Table 3). The most common serotypes were 14, 6B, 1, 18C, 19F, 23F and 7F, representing 70·2% of the cases in this age group.

Serotypes 6, 4, 14, 18, 23, 7 and 9 were the most frequent serotypes isolated from CSF; accounting for 60·3% of the CSF-positive cases (data not shown). The highest incidence rate of CSF-positive cases was seen among patients aged 0–1 year (6·1/100 000).

We found little year-to-year variation in the serotype distributions. Table 4 shows a slight but steady

Table 2. *Serotype/group distribution of systemic pneumococcal disease isolates*

Serotype/group	No. of isolates (relative frequency, %)		
	All	Age 0–5 years	Age >65 years
1	846 (18·3)	36 (11·1)	224 (10·5)
4	525 (11·4)	13 (4·0)	242 (11·3)
9	470 (10·2)	20 (6·2)	228 (10·7)
14	469 (10·1)	56 (17·2)	269 (12·6)
7	342 (7·4)	18 (5·5)	111 (5·2)
6	330 (7·1)	55 (16·9)	173 (8·1)
23	276 (6·0)	21 (6·5)	174 (8·1)
3	244 (5·3)	7 (2·2)	153 (7·1)
19	206 (4·5)	32 (9·8)	111 (5·2)
18	150 (3·2)	36 (11·1)	57 (2·7)
22	142 (3·1)	6 (1·8)	85 (4·0)
12	108 (2·3)	1 (0·3)	43 (2·0)
8	62 (1·3)	1 (0·3)	23 (1·1)
33	60 (1·3)	3 (0·9)	32 (1·5)
10	54 (1·2)	3 (0·9)	30 (1·4)
16	47 (1·0)	2 (0·6)	18 (0·8)
15	44 (1·0)	4 (1·2)	25 (1·2)
35	43 (0·9)	3 (0·9)	27 (1·3)
11	41 (0·9)	1 (0·3)	31 (1·4)
Others	165 (3·6)	7 (2·1)	84 (3·7)
Total	4624 (100)	325 (7·0)	2140 (46·3)

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Table 3. *Serotype distribution of pneumococci isolated from systemic pneumococcal disease in patients aged 0–5 years*

Serotype	No. of isolates	Frequency (%)
14	56	17·2
6B	42	12·9
1	36	11·1
18C	34	10·5
19F	22	6·8
23F	20	6·2
7F	18	5·5
9V	16	4·9
4	13	4·0
6A	13	4·0
19A	10	3·1
3	7	2·2
22F	6	1·8
9N	4	1·2
10A	3	0·9
15C	3	0·9
33F	3	0·9
35F	3	0·9
Other types*	16	4·9
Total	325	100

* Others include type 38 and 16F (two isolates each); 8, 21, 11A, 12F, 15B, 18A, 18B, 23B and 24F (one isolate each), and three non-typable strains.

increase in serotype 12, from 1·0 to 4·9% and a peak of serotype 1 to 23·3% in 1997, followed by a decline in the more recent years.

The current 23-valent vaccine would cover 95·8% of the pneumococcal serotypes isolated from all age groups in the study period. The 7-valent conjugated vaccine would cover up to 52·2% in all age groups. The coverage would be higher among children <2 years of age, among whom 72·7% of the cases were caused by serotypes included in this vaccine. The 11-valent conjugated vaccine would cover 85·5% of the pneumococcal serotypes/groups isolated in all age groups during the study period. For this vaccine, the coverage was similar in all age groups. The calculated vaccine coverages in individual age groups are shown in Table 5.

Antimicrobial susceptibility

The results from the antimicrobial susceptibility testing are shown in Table 6. A total of 51 (1·1%) of the 4624 strains showed reduced susceptibility to penicillin, and 5 were found resistant. The most resistant strain, with a benzylpenicillin MIC of 16 μg/ml, was recovered from a child arriving from Romania. This strain was also resistant to erythromycin, doxycycline and clindamycin. The other four strains resistant to penicillin (MICs 2–4 μg/ml) also showed additional resistance to 2 or 3 drugs. The five strains resistant to penicillin were serotypes 23F, 9V and three were type 14.

Of the 4624 strains, 2·5% showed resistance to erythromycin, 2% to doxycycline, 0·9% to clindamycin, 0·5% to chloramphenicol and only 0·1% to cefotaxime. We found only slight year-to-year variations regarding to the number of resistant strains, but a moderately increased circulation of resistant strains was seen in the years 1998 and 1999 (Table 6).

Table 4. *Annual variation in the most prevalent serotypes/groups of pneumococci isolated from cases of systemic disease in Norway, 1995–2001*

Serotype/ groups	Relative frequencies of serotypes (%)*						
	1995	1996	1997	1998	1999	2000	2001
1	12·7	22·5	23·3	21·5	17·3	16·0	14·0
4	15·2	10·8	10·1	12·0	10·2	10·1	11·5
9	10·6	10·0	8·6	8·6	10·5	10·6	12·2
14	10·6	11·4	11·5	9·8	8·6	9·5	9·7
7	10·3	7·1	6·6	5·0	6·4	8·7	8·1
6	6·8	6·3	6·6	6·0	8·6	8·4	7·1
23	6·3	6·5	4·7	6·9	6·1	6·2	5·0
3	5·6	3·6	3·8	6·0	7·2	7·2	3·9
19	4·0	4·6	4·8	4·4	5·1	3·9	4·3
18	3·5	3·4	3·8	3·2	3·7	3·0	2·3
22	4·4	2·8	3·8	2·7	1·9	2·8	3·3
12	1·2	1·0	1·5	1·7	2·5	3·4	4·9
Others	8·7	10·1	10·9	12·3	11·8	10·3	13·7

* Per cent of the total numbers of pneumococci analysed per year.

DISCUSSION

Worldwide, the pneumococcus is a common cause of systemic disease, especially among young children and the elderly. An increase in pneumococcal disease incidence has been observed in several Scandinavian countries and in Scotland in recent years [15–18]. Norway has also experienced a steady increase in pneumococcal disease, from an incidence rate of 6/100 000 in 1989 to a stable incidence around 19/100 000 since 1996. The increased occurrence of pneumococcal disease, observed in Scandinavia and Scotland, has mainly been caused by a rise in the incidence of bacteraemia, while the numbers of meningitis cases have remained stable. The increase could be

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Table 5. *Potential coverage of the different pneumococcal vaccines in Norway*

	Age				
Vaccine coverage*	<2 years	<15 years	15–65 years	>65 years	Total
No. of isolates tested	234	422	1984	2211	4617
Covered by the 23-valent polysaccharide vaccine†	97·0 %	95·7 %	96·6 %	95·3 %	95·8 %
Covered by the 7-valent conjugated vaccine‡	72·7 %	59·5 %	43·3 %	58·7 %	52·2 %
Covered by the 11-valent conjugated vaccine§	85·9 %	86·3 %	87·3 %	83·6 %	85·5 %

* For patients >15 years of age factor typing was not carried out. The coverage percentages include all types within a group. For seven patients the age was not known.
† Includes serotypes 1, 2, 3, 4, 5, 6B, 7F, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.
‡ Includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (cross reaction with 6A included).
§ Includes serotypes 1, 3, 4, 6B, 7F, 9V, 12F, 14, 18C, 19F and 23F (cross reaction with 6A included).

Table 6. *Resistance to antibiotics of systemic pneumococcal isolates in Norway, 1995–2001*

		No. of isolates (%) intermediately resistant/resistant to					
Year	No. of isolates	Penicillin	Cefotaxime	Erythromycin	Clindamycin	Chloramphenicol	Doxycyclin
1995	573	3 (0·5)/0	0/0	0/12 (2·1)	0/0	5 (0·9)/3 (0·5)	1 (0·2)/9 (1·6)
1996	703	2 (0·3)/0	0/0	0/10 (1·4)	0/4 (0·6)	6 (0·9)/1 (0·1)	0/11 (1·6)
1997	662	7 (1·1)/1 (0·2)	3 (0·5)/1 (0·2)	1 (0·2)/17 (2·6)	0/4 (0·6)	4 (0·6)/2 (0·3)	2 (0·3)/12 (1·8)
1998	665	7 (1·1)/3 (0·5)	2 (0·3)/2 (0·3)	0/24 (3·6)	0/10 (1·5)	10 (1·5)/4 (0·6)	4 (0·6)/17 (2·6)
1999	684	10 (1·5)/1 (0·1)	3 (0·4)/1 (0·1)	0/18 (2·6)	0/13 (1·9)	3 (0·4)/7 (1·0)	1 (0·1)/19 (2·8)
2000	643	11 (1·7)/0	3 (0·5)/0	1 (0·2)/14 (2·2)	0/5 (0·8)	6 (0·9)/3 (0·5)	1 (0·2)/13 (2·0)
2001	694	11 (1·6)/0	1 (0·1)/0	0/20 (2·9)	0/4 (0·6)	5 (0·7)/3 (0·4)	0/14 (2·0)

a result of more frequent use of blood cultures rather than an actual increase in disease cases [15, 18]. It has also been noted that serotypes 1 and 5 cause a relatively higher amount of pneumococcal disease in European countries than in the United States. Different clinical practice on when to perform a blood culture has been stated as one possible reason for this difference [19].

Extremely high incidence rates of pneumococcal disease have been reported from the native populations in Australia, reaching 2052/100 000 among children <2 years and 178/100 000 among people aged 20–59 years [20], and in Alaska, reaching 74/100 000 [21]. These high incidence rates have been associated with malnutrition, smoking, alcoholism and low socioeconomic status. These associations may also help to explain why males are often more frequently affected by pneumococcal disease than are females.

The age distribution among the Norwegian patients is similar to that found in other countries [18, 22, 23], with the highest incidences among children aged <5 years and the elderly aged >65 years of age. Some studies have reported a higher incidence among males than females in the 35–49 years age group [15, 24]. Our data show, to the contrary, a similar incidence for males and females in that age group, and higher incidences among males than females in the <5 and >65 years age groups.

Pneumococcal infections have been shown to be more frequent during the winter months [18, 25], which is confirmed in our study. A high occurrence of viral infections during the winter has been stated as a risk factor for pneumococcal disease, facilitating both the spread and the invasion of pneumococci. As many as 50–80 % of pneumococcal infections may be associated with antecedent viral infections [26].

Limited data regarding the pneumococcal disease situation in Norway have been published earlier [27, 28]. A review of the situation and a mapping of the serotype distribution are essential in order to develop an appropriate immunization policy for different age groups in Norway. Currently, the 23-valent vaccine is recommended for all persons with certain underlying diseases and those 65 years of age or more [7]. This vaccine covers strains with serotypes responsible for 95·8 % of all systemic pneumococcal disease in

Norway and 95·3% of the cases in patients >65 years of age. Similar results have been reported from other countries, where 86–98% of systemic pneumococcal disease is caused by serotypes covered by the 23-valent vaccine [15, 17, 24, 29–31]. The 23-valent vaccine, composed of polysaccharide antigens, does not elicit a satisfactory immune response in children <2 years old, nor in many immunocompromised persons. Even in healthy adults, the level of pneumococcal antibodies induced by the polysaccharide vaccine declines within few years after vaccination [32].

The high incidence of pneumococcal disease among small children emphasizes the importance of considering the introduction of the new 7-valent conjugated vaccine in Norway. Our data showed that the seven most prevalent serotypes in Norway (1, 4, 9, 14, 7, 6 and 23) represent more than 70% of the cases in all age groups. Our serotype distribution was quite similar to that reported from other European countries [15, 17, 22, 24, 31]. The 7-valent vaccine could cover 72·7% (taking into consideration the cross reaction with serotype 6A) of the cases among children age 0–5 years and 52·2% of the cases in all age groups. This relatively low coverage is in particular a result of the lack of types 1 and 7F in the 7-valent conjugated vaccine. The serotype distributions differ geographically. Thus, the 7-valent vaccine covers the seven most common types in the United States, Canada and Oceania, six of the most common types in Europe, five of the most common types in Latin America, but only four of the most common types in Africa and Asia [19]. A conjugated vaccine including additional serotypes would be of great potential value. The 11-valent conjugated vaccine, now undergoing clinical trials, would have covered 85·9% of the cases among small children (0–2 years of age) and 85·5% of all the Norwegian cases. This means that the 11-valent vaccine would probably be very valuable as a replacement for the 23-valent vaccine. A conjugated vaccine will naturally be much more expensive than the polysaccharide vaccine. In Norway so far, the 7-valent conjugated vaccine is only recommended for children with underlying conditions that put them at increased risk of pneumococcal disease, but new immunization guidelines are about to be developed.

Reduced susceptibility to antimicrobial agents in *S. pneumoniae* is considered a significant problem worldwide [33]. Serotypes 23F, 19F, 6B and 14 have been recognized as the most prevalent resistant types. Non-systemic strains from the upper respiratory tract, sinuses and middle ear, and especially strains from young patients less than 15 years old, have a higher frequency of antimicrobial resistance [34, 35]. Conjugated vaccines have shown a capability to reduce the carriage of resistant strains circulating in a population by reducing carriage of bacteria with vaccine serotypes [5]. Norway has a very low frequency of resistant strains [11], probably a result of a relatively restrictive use of antibiotics [36]. Resistant clones circulating in Europe are also seen in Norway, but normally in our setting they only appear as single clinical incidents [37]. Although our study shows no evidence for an increase in the number of resistant pneumococcal strains in Norway, a broader use of conjugated vaccines might be a useful tool to prevent such a development.

In conclusion, our data show a stable incidence of systemic pneumococcal disease in Norway during the period from 1995 to 2001. The occurrence of resistant strains recovered from Norwegian patients has been low, both for benzylpenicillin and other commonly used antimicrobials. The 7-valent conjugated vaccine could have a significant impact on the systemic pneumococcal disease incidence among Norwegian children, but will cover only 72·7% of the cases. Thus, a conjugated vaccine with broader covering of serotypes would be of value. Continuous monitoring of the pneumococcal disease situation, both regarding serotypes and resistance is essential to provide data to inform public health strategy decisions.

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