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An outbreak of serogroup B:15:P1.16 meningococcal disease, Frederiksborg county, Denmark, 1987–9

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SUMMARY

Epidemiological features of an outbreak of group B:15:P1.16 meningococcal disease (MD) in Frederiksborg county, Denmark, 1987–9, were investigated. The study comprised 149 cases notified during the outbreak and the two preceding years; 115 were confirmed by the isolation of *Neisseria meningitidis*. In 1989 the incidence had increased to 14·1 per 100000 population. Among group B strains, B:15:P1.16 accounted for 80% (77/97). The overall mortality rate was 10% (15/149). Regarding cases due to group B:15:P1.16 strains a significant time–space clustering, which exclusively occurred within the 10–19 years age group, was demonstrated. The link between cases within clusters was indirect or unknown, except for ten patients with contact to one particular school. The prophylactic measures used included administration of rifampicin to household contacts. During the outbreak the proportion of secondary cases was high (6–15%). All secondary cases occurred outside the household indicating that the household had been protected.

INTRODUCTION

In developed countries meningococcal disease (MD) occurs most frequently as sporadic cases caused by group B meningococci [1]. Epidemics and outbreaks associated with particular meningococcal strains occur from time to time. During the epidemics in Iceland in 1976–7 and on the Faroe Islands around 1981, the majority of strains belonged to group B type 15, subtype P1.16 (B:15:P1.16). During the same period the northern part of Norway had a prolonged epidemic due to group B:15:P1.16 meningococci with peaks in 1975 and 1978 [2]. An outbreak in Gloucestershire between October 1981 and March 1986 also involved cases of group B:15:P1.16 MD [3].

During 1980–5, the annual incidence of MD in Denmark was about 3·4 per 100000 population; in 1986 an increase to 5·5 per 100000 was noted. While the incidence in most parts of the country then remained at this elevated level, the incidence in Frederiksborg county continued to increase during 1987–9. This increase was associated with clusters of group B:15:P1.16 cases among teenagers.

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The purpose of our study is to describe the epidemiological features of this outbreak with a view to an assessment of the efficiency of prophylactic measures for the prevention of secondary cases of group B MD. For comparison the investigation comprised data from the immediately preceding period 1985–6.

MATERIALS AND METHODS

Study population

In the present study a case of MD was defined as a patient with MD in the form of meningitis and/or septicaemia. A co-primary case was defined as MD in a patient's direct contact in whom onset of disease occurred within 24 h after that of the index case. A secondary case was defined as MD in a patient's direct contact in whom onset occurred later than 24 h after that of the index case.

Cases were identified through the national notification system for communicable diseases as well as through the files of the Institution of Medical Officers of Health in Frederiksborg county and of the national reference laboratory at the Neisseria Department, Statens Seruminstitut. All patients with MD during the period 1 January 1985–31 December 1989, and with a permanent address in Frederiksborg county, were included.

The diagnosis of MD was verified by isolation of *Neisseria meningitidis* from the cerebrospinal fluid (CSF), blood or petechial skin lesions, demonstration of Gram-negative diplococci by direct microscopy of CSF, detection of meningococcal antigen in CSF by counter-immunoelectrophoresis, demonstration of meningococcal antibodies in serum (meningococcal antibody test, MAT) [4], or by clinical criteria. A clinical diagnosis required that the patient had typical signs of meningitis or septicaemia accompanied by a haemorrhagic rash. A case was considered confirmed if meningococci were isolated by culture from CSF and/or blood; if the diagnosis was based on other criteria, it was considered probable.

Prophylactic measures

In Denmark prophylactic measures against MD include information to relevant risk groups about early signs of illness and eradication of pharyngeal carriage of meningococci by giving rifampicin to all persons with household-like contact with the index case (600 mg twice daily for 2 days to adults). If more than one case of MD occurs within 1 month within the same well-defined group of persons, prophylactic treatment with rifampicin is recommended to that group of persons. Finally, vaccination against MD is recommended when an outbreak caused by serogroups A or C is recognized. On each occasion the definition of the target group has to be considered.

Epidemiological markers

Serological grouping was performed by means of a co-agglutination test using rabbit antisera against *N. meningitidis* groups A, B, C, W-135, 29E, X, Y and Z coated on protein A-rich *Staphylococcus aureus* cells as carriers [5]. Serological typing and subtyping were performed by a whole-cell ELISA using monoclonal antibodies as described by Abdillahi and Poolman [6]. The monoclonal antibodies were kindly provided by J. T. Poolman, RIVM, The Netherlands. The *in vitro*

susceptibility to sulphonamide was determined by a plate dilution method. Strains for which the MIC was 8 μg/ml or more were considered sulphonamide-resistant. Susceptibility to rifampicin was determined by an agar disk diffusion method using 20-h pre-diffusion and a disk content of 10 μg rifampicin. The inhibition zone of resistant strains is zero.

Statistical methods

The following statistical methods were employed: χ^2 test for trend, Fisher's exact test and Knox method [7] to test for time–space clustering. The Knox method requires specification of critical values for time and space to define closeness. The test involves a comparison of the observed number of pairs close in time and space, which can be regarded as a Poisson's variable, with the expected number, which is the product of the proportion of pairs close in time with the number of pairs close in space. In this study, two cases were defined to be adjacent in time if they occurred within 31 days, and adjacent in space if they occurred within the same municipality. The assumption that there was no association between time and space was tested.

RESULTS

Prevalence of meningococcal disease (MD)

Frederiksborg county is situated north of the metropolitan area of Copenhagen and has about 340000 inhabitants. It is a suburban community with some rural areas.

In Frederiksborg county, a total of 149 cases of MD were identified during the period 1985–9. One hundred and twelve confirmed cases were identified through both the national notification system for communicable diseases and the laboratory reporting system established at the Neisseria Department. Another 31 cases, 3 confirmed and 28 probable, were identified only through the notification system for communicable diseases, 4 probable cases only through notifications to the Public Health Officer, and 2 probable cases only at the Neisseria Department. Out of the 34 probable cases the diagnosis in 13 was rendered probable by MAT, in 5 by counterimmuno-electrophoresis, in 8 by direct microscopy of CSF, and in 8 the diagnosis was based on clinical criteria only.

Table 1 shows the annual numbers of confirmed and of probable cases of MD in Frederiksborg county and incidences per 100000 population in Frederiksborg county as well as in the rest of Denmark. Since 1986 the incidence in Frederiksborg county has continued to increase, while the incidence in the rest of Denmark has remained at an elevated level although with a decreasing tendency. In 1989, the incidence in Frederiksborg county reached 14·1 per 100000 population.

The seasonal pattern is demonstrated in Fig. 1. No remarkable seasonality was observed, although it could be noted that more cases tended to occur during winter and fewer during summer time.

Prevalence of N. meningitidis *B:15:P1.16*

From 112 (97%) out of 115 confirmed cases of MD the Neisseria Department received meningococcal isolates for determination of epidemiological markers.

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Table 1. *Meningococcal disease in Frederiksborg county and in the rest of Denmark 1985–9*

Year	No. of cases in Frederiksborg county			Incidences per 100000	
	Confirmed	Probable	Total	Frederiksborg county	The rest of Denmark
1985	7	3	10	3·0	3·5
1986	18	4	22	6·5	5·4
1987	24	9	33	9·7	5·4
1988	31	5	36	10·6	4·6
1989	35	13	48	14·1	4·6
Total	115	34	149		

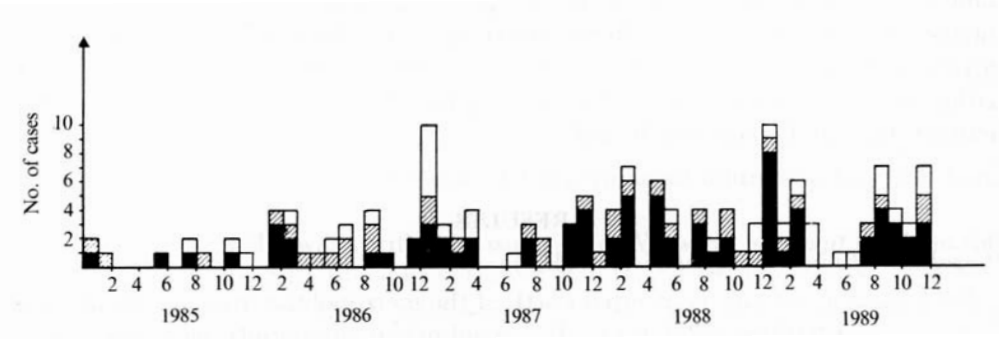

Fig. 1. Seasonal pattern, meningococcal disease, Frederiksborg county, Denmark, 1985–9. ■, B:15:Pl.16; ▨, confirmed cases, non. B:15:Pl.16; □, probable cases.

Table 2. *The annual number of confirmed cases of meningococcal disease from whom meningococcal isolates were available, Frederiksborg county 1985–9*

Year	Number of isolates belonging to				
	group B			other groups	Total
	B:15:P1.16	Others	Total		
1985	4	2	6	1	7
1986	9	6	15	3	18
1987	17	4	21	1	22
1988	20	7	27	4	31
1989	27	1	28	6	34
Total	77	20	97	15	112

Ninety-seven strains (87%) were group B, 10 (9%) group C, and 5 (4%) belonged to other serogroups. Table 2 shows the annual number of confirmed cases of MD in Frederiksborg county from whom isolates were available. Among group B strains, B:15:P1.16 was most prevalent (77/97, 80%). The frequency of group B:15:P1.16 cases related to the total number of confirmed cases was significantly higher during 1987–9 than during 1985–6. All group B:15:P1.16 strains except 5 were resistant to sulphonamide. The remaining 20 group B strains belonged to a variety of types and subtypes.

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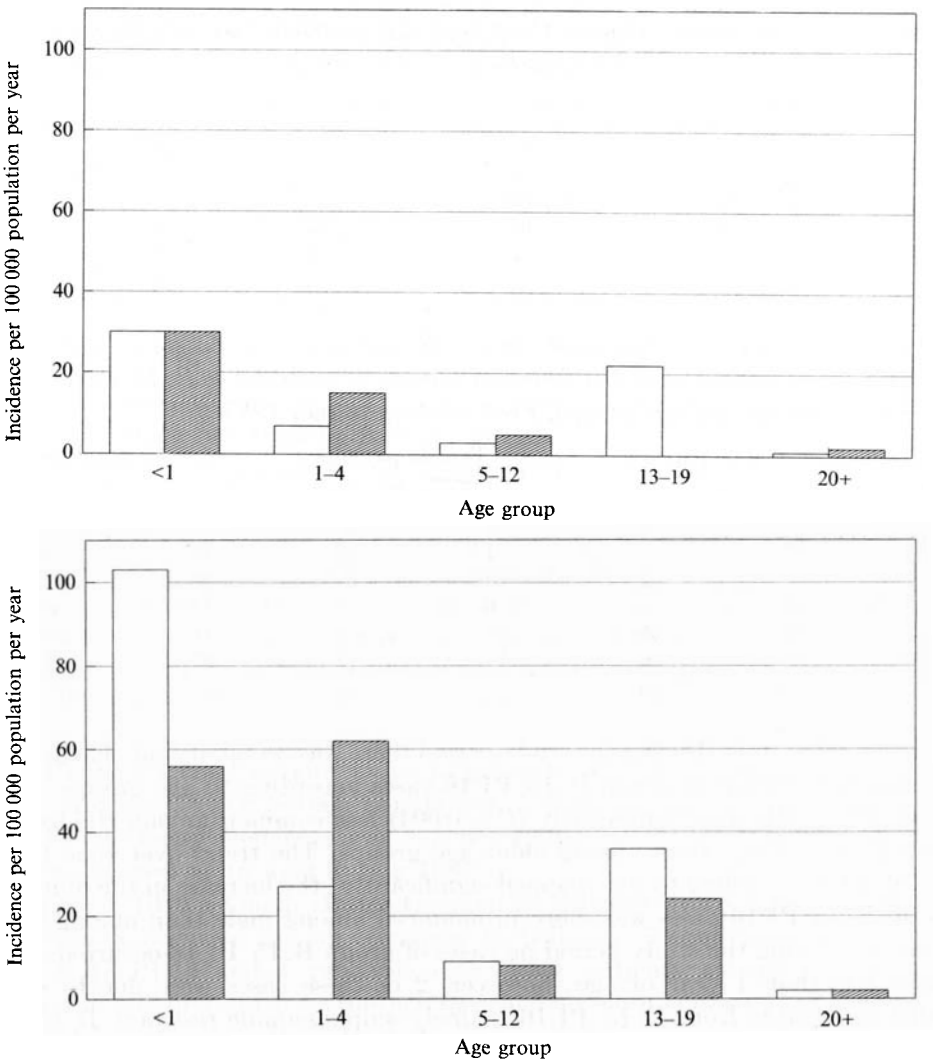

Fig. 2 (*a*, *b*). Incidence of meningococcal disease, confirmed cases, distributed on sex and age groups during the periods 1985–6 (*a*) and 1987–9 (*b*), Frederiksborg county, Denmark. □, Male; ▨, female.

Distribution according to age and sex

The difference in distribution according to age groups between confirmed and probable cases was significant ($P = 0{\cdot}004$) (Table 3). The proportion of cases confirmed bacteriologically was high in the age groups < 1 and > 20 years and low within the 5–12 years age group. There was no significant difference in the distribution of confirmed and probable cases according to sex.

The distributions of confirmed cases according to age and sex within the periods 1985–6 and 1987–9 are shown in Fig. 2a and b, respectively. The incidences for all age groups increased; the increase was most marked for children less than 4 years of age and for teenagers.

In Table 4, the distribution according to age and sex for group B:15:P1.16 cases

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Table 3. *Meningococcal disease. Confirmed and probable cases distributed by age, Frederiksborg county 1985–9*

Age (years)	Confirmed cases	Probable cases	Total
< 1	12	1	13
1–4	22	9	31
5–12	12	11	23
13–19	45	12	57
> 20	24	1	25
Total	115	34	149

Table 4. *Number of confirmed cases of meningococcal disease from whom meningococcal isolates were available and number of cases due to B:15:P1.16 strains distributed on sex and age groups, Frederiksborg county 1985–9*

Age (years)	Male patients		Female patients		All patients	
	Total	B:15:P1.16	Total	B:15:P1.16	Total	B:15:P1.16
< 1	7	—	4	3	11	3
1–4	7	7	15	10	22	17
5–12	6	5	6	3	12	8
13–19	30	25	14	11	44	36
> 20	9	6	14	7	23	13
Total	59	43	53	34	112	77

is shown separately. During the study period there was no significant change in the annual distribution of group B:15:P1.16 cases according to age groups. Group B:15:P1.16 MD was significantly ($P = 0{\cdot}004$) less common among children less than 1 year of age than among older age groups. The trend over time for the distribution according to sex changed significantly; the increase in the number of group B:15:P1.16 cases was more pronounced among male than among female patients. During the study period no cases of group B:15:P1.16 occurred among males less than 1 year of age; however, 2 of these cases were due to strains indistinguishable from B:15:P1.16, namely sulphonamide-resistant B:15:NST meningococci.

Mortality rate

The overall mortality rate was 10% (15/149); for patients with group B:15:P1.16 MD the mortality rate was 14% (11/77). Meningococci were isolated from CSF only in 54 and from blood (or blood plus CSF) in 55 of 112 confirmed cases from whom isolates were available for determination of epidemiological markers. Out of 77 group B:15:P1.16 cases 43 (56%) had bacteraemia in contrast to 12 out of the 35 (34%) other cases. This difference is significant ($P = 0{\cdot}027$ (one-sided test)). The mortality in patients with bacteraemia (11/55) was significantly higher than that in patients without bacteraemia (3/54) ($P = 0{\cdot}02$). Of the 3 lethal cases in the group of patients without bacteraemia 2 were caused by group B:15:P1.16 strains and one by a group B:NT:NST strain. The statistical analysis showed no difference between the mortality rate in patients with group B:15:P1.16 bacteraemia (8/43) and that in other patients with bacteraemia (3/12). The age-distribution for the 11 lethal cases due to group B:15:P1.16

meningococci was remarkable. For patients below 20 years of age the mortality was 8% (5 lethal cases) and for patients more than 20 years of age it was 45% (6 lethal cases).

The outbreak

During 1985 and 1986, only sporadic cases occurred in Frederiksborg county. Fig. 3 shows the geographical distribution within the county of group B:15:P1.16 cases during 1987–9. A clear tendency to clustering of cases among teenagers was seen. The localization of the clusters changed over time.

The first cluster appeared in 1987 in Hillerød municipality, in which the main town of the county is situated. During January–April 6 cases occurred: 5 confirmed B:15:P1.16 cases and 1 probable case (4 teenagers, 3 of whom had contact with one particular school; in 2 patients the contact was through a weight-lifting club, which had training facilities at that school). The attack rate was 18 per 100000 population, and the age-specific attack rate of group B:15:P1.16 in teenagers was 111 per 100000 population.

In August 1987, a second cluster which lasted until December 1987 started in Karlebo. Six cases occurred: 4 due to group B:15:P1.16, 1 due to sulphonamide-resistant group B:NT:P1.16, and 1 probable case, all among teenagers. The overall attack rate was 32 per 100000 population, and the age-specific attack rate of group B:15:P1.16 in teenagers was 261 per 100000 (the case due to group B:NT:P1.16 was included).

In 1988 a third cluster including 8 cases occurred in Hørsholm: 7 due to group B:15:P1.16 (5 teenagers) and 1 due to group C:4:P1.1 (teenager). The overall attack rate was 34 per 100000 population, and the age-specific attack rate for B:15:P1.16 among teenagers was 225 per 100000. It seems that the event of clustering moved south-west during 1987–8.

Finally, in 1989 a fourth cluster emerged in Hillerød. During January–March 1989, 6 cases occurred among teenagers in Hillerød: 5 confirmed cases due to group B:15:P1.16 and 1 probable case. Four patients attended the school involved in the first cluster. Another patient had close contact with 2 patients among the students at the school through a skate-boarding club. The overall attack rate was 18 per 100000 population, and the age-specific attack rate for group B:15:P1.16 in teenagers was 174 per 100000 population.

In conclusion, the possible link between cases within clusters was unknown or indirect, except for the 10 patients who had contact with one particular school. The index case occurred in September 1986, 3 cases were associated with the first cluster in 1987, 1 case occurred in 1988 and, finally, 5 cases (the fourth cluster) were identified in January–March 1989. The pupils attended different classes. There are 11 schools for teenagers in Hillerød; 7 are public and 4 are private schools. Only one other school in Hillerød experienced more than 1 case of MD, namely 1 case in January 1987 and a second one in January 1989. However, this latter patient was considered to belong to the outbreak mentioned above since there was only 1 day between the onset of disease in this patient and a close friend attending the school involved. The recrudescence in January–March 1989 resulted in the administration of rifampicin chemoprophylaxis to all pupils and adults at this school and to the siblings of the pupils. This measure is an extension of the

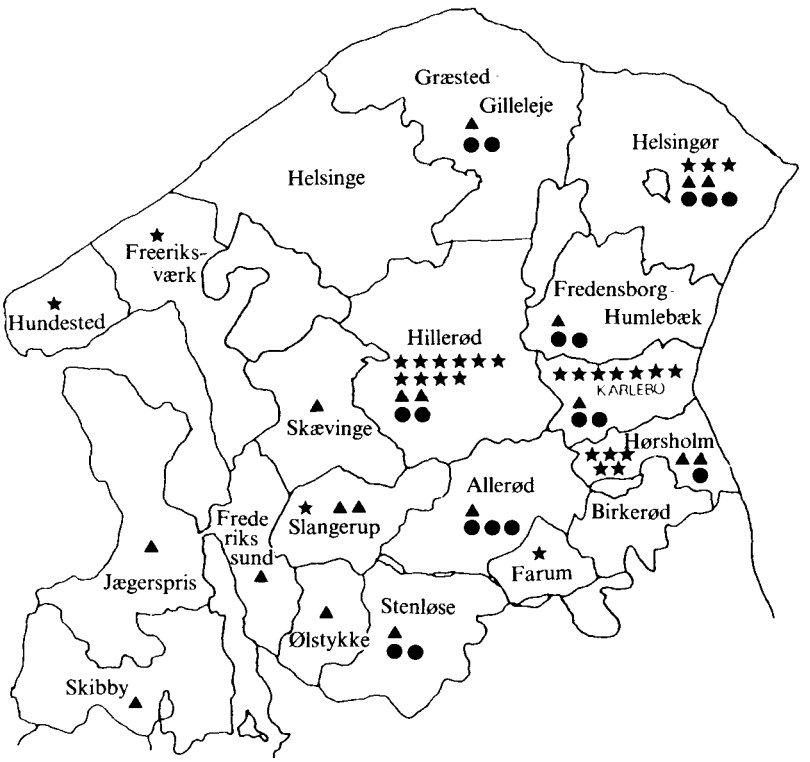

Fig. 3. Municipalities in Frederiksborg county, Denmark. Distribution of meningococcal disease due to group B:15:P1.16, 1987–9, for selected age groups. ▲, 0–4 years; ★, 13–19 years; ●, other age groups.

Table 5. *Number of expected and observed pairs of cases of meningococcal disease within municipalities in Frederiksborg county 1985–9*

Population tested	Number of cases	Number of pairs		
		Observed	Expected	
Group B:15:P1.16 cases	77	30	13	$P < 0{\cdot}001$
and probable cases	111	53	31	$P < 0{\cdot}001$
age group 10–19 years	37	19	9	$P < 0{\cdot}005$
age group 0–4 years	20	1	0·3	NS
age group 10–19 years excluded	40	2	2	NS

official recommendation for the use of chemoprophylaxis. No case of MD relating to that school occurred later in 1989 or in 1990.

For about 70% of the total number of the MD cases information about socio-economic affiliation was available. No tendency to accumulation of MD cases in lower socio-economic groups was found.

The Knox method for testing time–space clustering (see Materials and methods) was applied. The analysis demonstrates (Table 5) that for cases due to group B:15:P1.16 strains a clustering could be demonstrated and that clustering exclusively occurred within the 10–19 years age group.

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Table 6. *Meningococcal disease in Frederiksborg county 1985–9*

Year	Total number of cases	Secondary cases among direct contacts outside the household	
		Number	Percent of total
1985	10	0	0
1986	22	0	0
1987	33	4	12
1988	36	2	6
1989	48	7	15
1985–1989	149	13	9

Secondary cases

No co-primary cases and 13 secondary cases were registered (Table 6). The secondary cases accounted for 9% of the total number of MD cases. No secondary case occurred among household contacts; 2 secondary cases occurred among relatives outside the household; 3 among schoolmates; 6 among friends, 1 was a nursery room-mate and 1 was an indirect contact via a day-care institution. All except one pair of cases were due to group B:15:P1.16 strains. Three secondary cases had received rifampicin prophylaxis 16 days, 22 days and $3\frac{1}{2}$ months, respectively, before the onset of illness. The meningococci isolated from all 3 patients were fully susceptible to rifampicin. The proportion of secondary cases was significantly higher during the outbreak (1987–9) as compared to the period with only sporadic cases (1985–6) ($P = 0{\cdot}037$).

DISCUSSION

The Danish surveillance system for MD is based upon the collaboration between the Department of Epidemiology and the Neisseria Department, Statens Seruminstitut, and the Institution of Medical Officers of Health. After serological characterization of a meningococcal isolate, copies of laboratory results are currently referred from the Neisseria Department to the Department of Epidemiology. If the patient (at that time) has not yet been notified, the actual clinical department is requested to fill in the notification form. At a national level the Department of Epidemiology has to inquire for notifications on about 20% of all bacteriologically verified cases. Patients with MD are also registered in the National Patient Registry. For the whole country the number of notified cases accounts for about 75% of the number of cases registered in the Patient Registry. This means that almost all bacteriologically verified cases of MD and about 75% of probable cases of MD are registered in the notification system for communicable diseases. In addition, it is known that more than 90% of the isolated strains are referred to the Neisseria Department; the present study is therefore considered to give a faithful picture of the outbreak of MD in Frederiksborg county.

Since 1974 the prevalence of group B MD has increased from 27 to about 70% of bacteriologically verified cases in Denmark. Among the group B meningococci

the prevalence of serotype 2b decreased from 38% to zero during the period 1974–83, while that of serotype 15 increased from zero to 60% during the same period [2]. An increase in the prevalence of B:15:P1.16 MD during the 1970s has also been reported from Norway, Iceland, England and Wales, the Netherlands and the Faroe Islands [2]. In the present study group B:15:P1.16 strains constituted on the average 80% of the group B strains (range 60–90%) (Table 2).

Few outbreaks of MD due to group B have been reported. In 1971–4 an outbreak in Bolton, England, was caused by sulphonamide-susceptible group B type 2 strains; this outbreak was characterized by a high attack rate in young children 6–11 months of age [8]. At the same time, 1972–3, group B meningococci predominated in an outbreak in Devon, England, in which about 2/3 of the patients were under 10 years of age [9]. During the period 1981–6 Gloucestershire, England, experienced an outbreak due to group B:15:P1.16 meningococci. Seventy-one percent of the patients were between 10 and 24 years of age [3]. Both in Norway [10] and on the Faroe Islands [11] the age-distribution of group B:15:P1.16 cases shows two peaks, one comprising young children and one teenagers. The latest reported outbreak started about 1983 in Iquique, Chile, and was due to serogroup B:15:P1.3 strains. Eighty-nine percent of the cases were in patients < 21 years. The male/female ratio was 1:2 [12]. It seems that, in general, cases due to group B:15:P1.16 strains show a tendency to clustering, to affect teenagers as well as young children, and a high incidence of MD sustained for years [2]. The course of the outbreak of group B:15:P1.16 MD in Frederiksborg county is in agreement with the general pattern. In Frederiksborg the number of male patients outnumbered that of female patients, which was also the case in Gloucestershire.

Reported figures on the mortality rate of MD vary between 3 and 11% [3, 10–13]. We found an average mortality rate of 10%; the mortality rate was especially high in patients with bacteraemia (20%) and in patients more than 20 years of age (45%). The accuracy of the clinical diagnosis given by the general practitioner before admission to hospital differs significantly between age-groups. It was found to be low among adults and 0–2-year-old children [14]. This finding might incidate a late admission to hospital of adults with MD with a more severe course of disease as a consequence.

The outbreak in the Gloucestershire district and that in the county of Frederiksborg have much in common: group B:15:P1.16 meningococci dominate; the outbreaks are extended over years; the disease travels slowly through different communities within the district; the contact between cases is indirect. There are also some differences: the peak-incidence in young children is absent and the mortality rate is lower in Gloucestershire [3]. In our study the clustering of cases was exclusively associated with teenage groups. A link between cases within the cluster was demonstrated for 10 patients who had contact with one particular school, partly through common membership of sports clubs. This finding strongly indicates that transmission of the disease occurred outside the household and that in the case of clustering a target group for preventive measures could be defined. It is also remarkable that cases due to the outbreak strain group B:15:P1.16 are prevalent in other Danish counties in which single clusters but no sustained high-level incidence has been noted.

Among household contacts of a patient with MD the attack rate has been found to be 500–800 times higher than that determined for the population in general [15]. According to a Belgian study the estimated secondary attack rate (within 60 days) was 685/100000 among household contacts, 404/100000 among day-care nursery contacts, and 77/100000 among pre-elementary school contacts [16]. In the present study the observed number of secondary cases was zero among household contacts and 13 among other direct contacts. The ratio between the secondary attack rate within households (685/100000) and the secondary attack rate for other direct contacts (77/100000) or the relative risk is assumed to be the same in Denmark as in Belgium. Based on the estimate that there are 4 household contacts per case and K other contacts per case one will expect that the ratio between the number of secondary cases among household contacts and the number of other secondary cases would be $4 \times 685/K \times 77$. The observed nil among household contacts differs significantly from the observed 13 cases among other direct contacts if K is assumed to be 10 ($P = 0{\cdot}0009$) or even 100 ($P = 0{\cdot}019$). This finding indicates that the prophylactic treatment of household contacts has been efficient in the prevention of secondary cases within the household.

On the other hand, the study demonstrates that the existing preventive measures are insufficient for controlling an outbreak among teenagers. During a hyper-endemic period with clustering of cases the percentage of MD secondary cases was high (6–15%). In this situation a liberal definition of the target group for chemoprophylaxis may be a means to combat the spread of the disease. The second cluster (5 cases) at a Hillerød school in January–March 1989 resulted in administration of rifampicin to an open group of persons. This could be the reason why no more cases related to that school occurred in 1989 and 1990.

During the group B:15 epidemic on the Faroe Islands a fall in the incidence of MD was observed after the introduction of rifampicin. The fall was more pronounced in the capital, where the number of prescribed prophylactic doses per case of MD was higher than in the provinces. The authors suggest that the use of rifampicin may have modified the course of the epidemic [11].

Against a wider use of rifampicin must be set the risk of side effects, development of rifampicin resistance, and the problems of defining the group at risk. Resistance to rifampicin has so far not been a problem in Denmark.

In an epidemic situation like that among teenagers in Frederiksborg county, the need for an effective vaccine against group B disease is obvious. Immunization trials are going on in Norway, Cuba and Chile. In Norway a vaccine composed by outer membrane proteins from group B:15:P1.16 is under evaluation in a clinical vaccination trial. It is expected that the code will be broken during the spring of 1991 [17].

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