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Outbreak of meningococcal disease in western Norway due to a new serogroup C variant of the ET-5 clone: effect of vaccination and selective carriage eradication

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SUMMARY

A new sulphonamide resistant (SR) C:15:P1.7,16 meningococcal strain, a variant of the ET-5 clone, dominated in an outbreak of 22 cases in western Norway commencing in 1995. The first eight patients were 15–21 years old from the Nordhordland area, initiating a carrier study in the local high schools. Carriage of SR serogroup C meningococci was detected by routine methods and treated with a single dose of ofloxacin 400 mg. Of 20 treated carriers, 14 harboured the outbreak strain C:15:P1.7,16. Vaccination of 4000 children, adolescents and close contacts of patients was also performed. After the intervention, 14 additional cases of meningococcal disease occurred, 8 due to the outbreak strain. However, incidence rates dropped from 180 to 30 per 100000 per year in the student population, but increased from 0 to 13 in the rest of the population in Nordhordland. Carriage eradication is not generally recommended in Norway. However, tracing and treating meningococcal carriage may have reduced transmission and disease in this outbreak situation.

INTRODUCTION

The Norwegian epidemic of serogroup B meningococcal disease started in 1974. The annual incidence rate has varied between 4 and 8 per 100000, with a declining trend between 1988 and 1998. The highest incidences have been registered in the coastal areas of western and northern Norway [1–5]. Serogroup B meningococci have caused 65–85% of the cases [5]. The proportion of serogroup C meningococcal disease has increased in recent years and this serogroup presently causes 20–30% of the cases, while less than 4% of the cases are caused by serogroups other than B or C [3, 4].

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During the winter months of 1995–6, eight patients living in Nordhordland, just north of Bergen in western Norway, were hospitalized with systemic meningococcal disease. A new *Neisseria meningitidis* strain characterized as C:15:P.7,16 was isolated from 7 of these 8 patients. The outbreak occurred in a rural area of 800 km² with 27000 inhabitants, and was followed up with information, carriage eradication of the putative outbreak strain and a vaccination programme.

Carriage eradication of meningococci following single cases and outbreaks of meningococcal disease has been an issue for discussion regarding effectiveness, fear of overuse of antibiotics and expenses related to tracing carriers [6]. The aims of our study

were to evaluate a simple and rapid carrier identification strategy, to study the effect of a single dose of ofloxacin on the individual carrier state and to investigate whether selective carriage eradication in combination with vaccination affected the outbreak in Nordhordland.

MATERIAL AND METHODS

Setting

The *Neisseria meningitidis* strain C:15:P1.7,16, was defined as the outbreak strain. All cases caused by this strain and resident in Nordhordland or in the surrounding communities were defined as outbreak cases (Fig. 1, Table 1). Seven cases caused by other meningococcal strains that occurred in Nordhordland and Askøy at the time of the outbreak were included in the study.

The first 8 patients with meningococcal disease in this serogroup C outbreak were 15–21 years old and 5 were students at local high schools (Fig. 1, Table 1). We therefore decided to perform a carrier study that included all 1400 students (13–21 years old) at the 3 junior and 3 senior high schools in Nordhordland.

Tonsillopharyngeal specimens were obtained from 1120 of the 1400 students (80%). Follow-up specimens were obtained 1 and 6 weeks later from the 20 students suspected to carry the outbreak strain (see below), and 6 weeks later from 53 untreated meningococcal carriers and 60 non-carriers. These were selected because they were classmates of the 20 suspected carriers of the outbreak strain. The swabbings were performed by 2 medical doctors and 3 laboratory technicians, using a standardized procedure [7].

After 2 years, in 1998, a follow-up carrier study was performed in the same three senior high schools. Tonsillopharyngeal specimens were obtained from 680 volunteers of 982 students (69·2%).

Bacteriology

The throat swabs were inoculated immediately onto chocolate agar plates, containing vancomycin (3 g/l), colimycin (12·35 mg/l), trimethoprim lactate (5 g/l), and amphotericin B (10000 U/l). Within 2–5 h the agar plates were incubated at 37 °C, in 5% CO_2 and 80% humidity. The plates were read on two subsequent days. Meningococcal isolates were identified by oxidase reaction, Gram-stain microscopy, fermentation of glucose, maltose, sucrose and lactose, and serogrouping by agglutination, using antisera (Difco Laboratories, Detroit, MI, USA). Susceptibility to sulphonamides were examined by Etest (AB Biodisk, Solna, Sweden), and minimum inhibitory concentration (MIC $\geqslant$ 16 mg/l recorded as sulphonamide resistance (SR) [8]. Single colonies were picked for characterization. However, if two morphologically different oxidase positive colonies were detected on the same agar plate, both colonies were characterized. All students with SR serogroup C isolates were considered as possible carriers of the outbreak strain.

SR isolates were further characterized by a dot–blot method with monoclonal antibodies against the A, B, C, W and Y polysaccharide antigens, the 2a, 4, and 15 serotype antigens and the P1.2, P1.7, P1.12 and P1.16 serosubtype antigens [9]. Isolates not reacting with the monoclonal serogroup reagents were designated nongroupable (NG). The genotypes of all C:15, B:15 and NG:15 isolates ($n = 55$) were determined by multilocus enzyme electrophoresis, as previously described, using variation in 14 enzyme loci [7] and by restriction fragment length polymorphism analyses (RFLP). DNA was extracted from a loopful of meningococcal cells essentially as described [10], except for lysozyme treatment at 37 °C for 2 h only. Digestion of the chromosomal DNA was performed using the restriction enzyme *Hae*III (New England Biolabs, Herts, UK) according to the manufacturer's recommendations. Fragments were separated by electrophoresis in 0·7% agarose gel at 40 V for 18 h.

Intervention

All children aged 2–5 years ($n = 1070$) and adolescents aged 13–21 years ($n = 3330$) in Nordhordland were offered a single intramuscular injection of meningococcal polysaccharide vaccine A+C® (Pasteur Mérieux, Lyon, France) containing 50 μg each of serogroup A and C capsular polysaccharide. All participants (or their parents) received written information about the outbreak and the vaccine prior to vaccination. Children aged 6–12 years have had a low incidence of meningococcal disease in Norway, and were not offered vaccine.

In the six high schools, vaccination and the tonsillopharyngeal swabbings were performed concomitantly on two subsequent days in February 1996. After the initial serogrouping of meningococci, and examination of susceptibility to sulphonamide, a single oral dose of 400 mg ofloxacin was offered to all carriers of SR serogroup C isolates.

Table 1. *Meningococcal disease cases associated with the C:15:P1.7,16-outbreak in and around Nordhordland, September 1995–April 1998*

Case no.	Admission date	Age	Sex	Occupation	Residence	Meningococcal strain	*C:15*-clone*	Disease category§	Outcome	Association
1	30.09.95	18	M	Worker	NH†	C:15:P1.7,16	*	1		
2	10.10.95	21	M	Conscript‡	NH	C:15:P1.7,16	*	—		Friend of case 3
3	14.10.95	19	M	Unemployed	NH	C:15:P1.7,16	*	3		Friend of case 2
4	25.12.95	15	M	Student	Askøy	C:15:P1.7,16	*	1		Sporting activities in NH
5	01.01.96	15	M	Student	NH	C:15:P1.7,16	*	4		Grandson of case 11
6	02.01.96	15	F	Student	NH	C:15:P1.7,16	*	3		
7	03.02.96	18	F	Student	NH	C:2a:P1.5,2		2		
8	06.02.96	17	F	Student	NH	C:15:P1.7,16	*	2		
Mid-February 1996: mass vaccination, throat swabbing and eradication of C:15:P1.7,16 carriage										
9	30.03.96	14	M	Student	Askøy	B:15:P1.7,16		4		Neighbour & second cousin of case 4
10	20.05.96	17	M	Student	NH	C:15:P1.7,16	*	2	Death	Fathers of cases 5 & 6: workmates
11	11.08.96	75	F	Pensioner	Bremanger	C:15:P1.7,16	*	4	Death	Grandmother of case 5
12	17.08.96	18	M	Student	NH	B:15:P1.5,2		4		
13	26.10.96	8	F	Student	NH	B:15:P1.7,16		4		
14	04.11.96	29	M	Worker	NH	C:15:P1.7,16	*	4		Uncle of case 15
15	05.11.96	2	M	Kindergarten	Bergen	C:15:P1.7,16	*	2	Death	Nephew of case 14
16	02.12.96	1	M	At home	NH	B:NT:P1.2		4		
17	26.01.97	3	F	At home	NH	C:15:P1.7,16	*	1		Her sister was a C:15-carrier
18	16.02.97	19	M	Worker	NH	B:15:P1.7,16		4		
19	17.02.97	22	M	Worker	NH	B:		4		
20	16.03.97	16	M	Student	Bergen	C:15:P1.7	*	4		Visited relatives in NH
21	17.03.97	11	M	Student	Bergen	C:15:P1.7,16	*	4		Not known
22	04.04.98	45	F	Worker	Bergen	C:15:P1.7,16	*	3		Husband from NH

* The outbreak clone.

† The four outbreak communities in Nordhordland.

‡ Resident in NH, but conscript in Kongsberg.

§ Disease categories on admission to hospital: 1, meningitis; 2, septic shock; 3, meningitis and septic shock; 4, bacteraemia without meningitis, without shock.

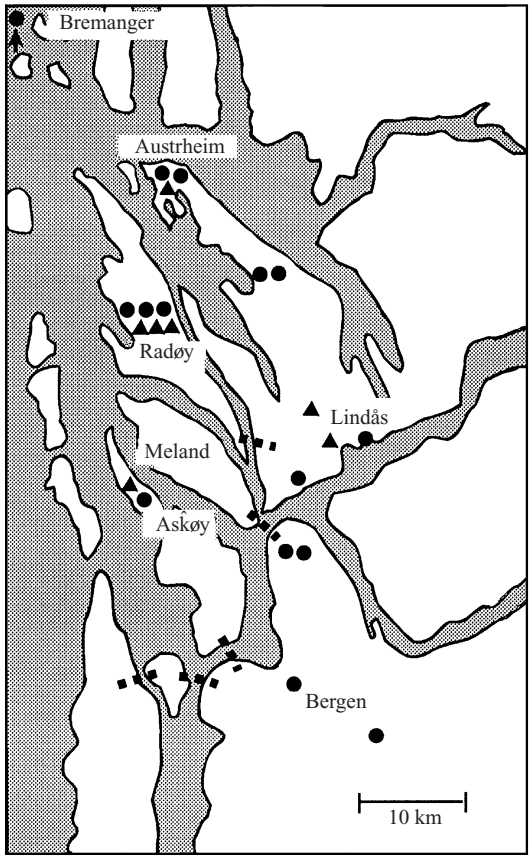

Fig. 1. Geographical distribution of meningococcal disease during an outbreak in and around Nordhordland, 1995–8. Cases caused by *Neisseria meningitidis* C:15:P.1.7,16 ● or other strains ▲. Main bridge ■ ■ ■.

Statistics

Incidence rates of meningococcal disease were calculated as the number of new patients divided by the population at risk per 100000 per year. McNemar's χ^2 test with continuity correction was used to test the significance of the observed difference in incidence rate before and after the intervention, in the student population and the rest population of Nordhordland, respectively. A P-value $\leqslant 0{\cdot}05$ was considered statistically significant.

RESULTS

Patients with meningococcal disease

Twenty-two bacteriologically verified cases of systemic meningococcal disease occurred between September 1995 and April 1998 as part of a local outbreak in the Nordhordland area (Fig. 1, Table 1). The outbreak strain C:15:1.7,16, including one C:15:1.7 strain, was isolated from 15 patients, C:2a:P1.5,2 was isolated from 1 patient and serogroup B meningococci were isolated from 6 patients, including 3 patients with the Norwegian epidemic strain B:15:P1.7,16.

The 15 patients with C:15:P1.7,16 infection (10 males and 5 females) belonged to the age groups < 12 years (3 patients), 13–19 years (8 patients) and > 20 years (4 patients). Seven of these cases occurred before the intervention with vaccination and carriage eradication took place (Table 1). Three of the 15 patients died, all after the intervention.

The first case, an 18-year-old male worker living in Nordhordland, presented in September 1995 (Table 1). The second case was a 21-year-old male conscript from Nordhordland. He fell ill a few days after having been on a 1-wk leave at home. No additional cases occurred in the military camp. Four days later an unemployed 19-year-old male was admitted to hospital. Cases 2 and 3 had mutual friends and had attended the same party a few days prior to onset of illness. The next 4 patients were students, of whom 3 were 15-year-old and 1 was 18-year-old (cases 4–6, 8). Case 4 lived in a municipality close to Nordhordland and had attended sporting activities in the area.

The outbreak strain was isolated from 8 additional patients after the intervention. A 17-year-old student (Table 1, case 10) who had refused swabbing and vaccination, died from meningococcal septicaemia in May 1996. The grandmother (case 11) of case 5, living north of the outbreak area in the neighbouring county, died of meningococcal septicaemia due to the outbreak strain. A 29-year-old male (case 14) and his 2 year old nephew (case 15) were admitted to hospital with meningococcal disease 1 day apart. The child died. Further, a 3-year-old child (case 17), who had been vaccinated with the A + C polysaccharide vaccine 10 months earlier, also contracted the disease. After the admission of case 17, a mutual close contact of several of the patients was found to harbour the outbreak strain. The last 3 registered cases all occurred in the city of Bergen; 2 were students and 1 was a worker. One of the students had visited relatives in Nordhordland 3 days before he was admitted to hospital. The worker's husband, who comes from Nordhordland, carried the outbreak strain.

Extended characterization of all the C:15:P1.7,16 patient strains showed that they belonged to the clone ET-5, which has been responsible for the epidemic in Norway since the mid 1970s [7]. However, since the capsular serogroup of the outbreak strain differed from previous serogroup B epidemic ET-5 strains, the

Table 2. *No.* (%) *of tonsillopharyngeal carriers of* Neisseria meningitidis *among healthy students in Nordhordland, 1996 and 1998*

	1996		1998	
N. meningitidis strain	Among 1120 students	With the C:15-clone	Among 680 students	With the C:15-clone
Sulphonamide-resistant				
C:15:P1.7,16	13 (1·2%)	13	0	
C:15:P1.7	1 (0·1%)	1	0	
C:2a:P1.2	3 (0·3%)		0	
B:15:P1.16	2 (0·2%)		3 (0·4%)	
B:4:P1.12	0		3 (0·4%)	
NG:15:P1.7,16	22 (2·0%)	15	3 (0·4%)	3
NG:15:P1.7	17 (1·5%)	6	7 (1·0%)	1
NG:15:P1.16	0		2 (0·3%)	
NG:2a:P1.2	4 (0·4%)		0	
Other*	7 (0·6%)		9 (1·3%)	
NG:NT:NST†	15 (1·3%)		0	
Sulphonamide-sensitive	153 (13·6%)		105 (15·4%)	
No meningococci	883 (78·8%)		548 (80·6%)	

* C:NT:NST, B:15:NST, B:2a:P1.2, B:4:NST, B:NT:NST, NG:15:NST, NG:4:NST, Y, W.
† NG, non-groupable; NT, non-typable; NST, non-subtypable, with the monoclonal antibodies used.

isolates were further analysed by RFLP. The outbreak ET-5 strains differed by one or more fragments, 3–10 kbp in size, from other ET-5 strains tested, including two other C:15:P1.7,16 strains ET-5 recovered from mid-Norway in 1995 (data not shown).

Meningococcal carriage among students

In the carrier study in February 1996, 1120 (80%) of the 1400 students in the junior and senior high schools in Nordhordland volunteered for tonsillopharyngeal swabbing, excluding patients with systemic meningococcal disease. Among the participating students, 233 (20·8%) carried meningococci and 80 (7·1%) carried SR strains. Eighteen students (1·6%) carried SR serogroup C meningococci (Table 2), compared with 3/943 (0·3%) found in a randomly selected Norwegian population during a non-epidemic period [7]. Thirteen students (1·2%) carried C:15:P1.7,16 strains, 1 carried a C:15:P1.7 strains, 21 (1·9%) carried NG:15:P1.7,16 strains and 18 (1·6%) carried NG:15:P1.7 strains.

Among the 55 carrier strains characterized by RFLP analyses in this study, at least 13 different patterns were observed. All C:15 carrier strains ($n = 14$) were identical to the outbreak strain, as well as 21 (55%) of the NG:15 strains ($n = 39$). Thus, the outbreak strain pattern was identified in strains from 35 carriers in 5 schools.

Two students initially carried NG:15:P1.7,16 isolates, but a serogroupable C:15:P1.7,16 isolate was found in the follow-up specimens 6 weeks later. Three students were concomitant carriers of two seemingly different SR strains, isolated from 2 morphologically different colonies of their primary cultures. These students carried both groupable and non-groupable meningococcal strains with the same serotype and serosubtype, and one of them carried the outbreak strain.

No clustering of carriage of the C:15:P1.7,16 strain was found in the classes of the meningococcal disease cases. The 14 carriers of C:15 strains (10 males and 4 females) attended 10 different classes in the 3 senior high schools, none was found in the junior high schools (Table 3). In the 3 senior high schools, 20 carriers of NG:15:P1.7,16 meningococci (9 males and 11 females) attended 14 different classes, and 7 carriers of NG:15:P1.7 strains (3 males and 4 females) attended 6 different classes. In the 3 junior high schools, 2 female carriers of NG:15:P1.7,16 strains, and 10 carriers (6 males and 4 females) of NG:15P1.7 strains, attended 3 different classes.

Vaccination and ofloxacin treatment

Concomitantly with throat sampling and carriage eradication in 1996, vaccination was offered to all 2–5-year-old children ($n = 1070$), all 13–21 year old

Table 3. *No. of carriers with sulphonamide resistant meningococcal isolates by high schools in Nordhordland, 1996 and 1998*

	Study 1996						Study 1998		
	Senior high schools			Junior high schools			Senior high schools		
N. meningitidis	I ($n = 149$)	II ($n = 319$)	III ($n = 282$)	IV ($n = 177$)	V ($n = 147$)	VI ($n = 45$)	I ($n = 132$)	II ($n = 241$)	III ($n = 307$)
C:15:P1.7,16	5	2	6	—	—	—	—	—	—
C:15:P1.7	—	1	—	—	—	—	—	—	—
C:2a:P1.2	—	2	1	—	—	—	—	—	—
C:NT:NST	—	1	—	—	—	—	—	—	—
B:15:P1.16	1	1	—	—	—	—	1	—	2
B:15:NST	1	—	—	—	—	—	—	—	—
B:2a:P1.2	—	1	—	—	—	—	—	—	—
B:4:P1.12	—	—	—	—	—	—	—	2	1
B:4:NST	—	—	—	—	—	—	—	—	1
B:NT:NST	1	—	1	—	—	—	—	—	—
NG:15:P1.7,16	5	10	5	—	1	1	—	2	1
NG:15:P1.7	2	3	2	8	2	—	2	3	2
NG:15:P1.16	—	—	—	—	—	—	2	—	—
NG:15:NST	—	—	—	—	—	—	—	—	1
NG:4:NST	—	—	—	—	—	—	—	—	1
NG:2a:P1.2	—	4	—	—	—	—	—	—	—
NG:NT:NST*	5	3	7	—	—	—	—	—	—
Y	—	1	1	—	—	—	—	—	—
W	—	—	—	—	—	—	1	3	2
Total	20	29	23	8	3	1	6	10	11

* NG, non-groupable; NT, non-typable; NST, non-subtypable; with the monoclonal antibodies used.

Table 4. *Incidence rates per 100000 per year of C:15-meningococcal disease before and after intervention in Nordhordland**

	Before intervention (12 months)	After intervention (12 months)	Significance-test†	
			χ^2_{mc}	*P*-value
13–21 year olds	$(6/3330) \times 100000 = 180$	$(1/3330) \times 100000 = 30$	2·3	= 0·1
Other ages	0	$(3/23670) \times 100000 = 13$	11·1	< 0·001

* Cases resident outside Nordhordland excluded.
† NcNemar's χ^2 test with continuity correction.

adolescents ($n = 3330$), and to close contacts and friends of patients. The overall vaccination coverage of the target populations was 82%. Vaccination coverage was 95% in the age group 2–5 years, 99·8% in the age group 13–15 years but only 50% in the age group 16–21 years.

Ofloxacin treatment was given to 20 students initially identified as carriers of SR serogroup C meningococci, 14 of them were later identified as carriers of the C:15:P1.7,16 outbreak strain. The outbreak strain was not detected in the follow-up specimens 1 and 6 weeks after treatment. However, one prior carrier of the outbreak strain harboured a non-serogroupable and non-serotypable meningococcal strain. One case caused by the outbreak strain occurred among the 4000 vaccinees (Table 1, case 17) but none among the 20 students treated with ofloxacin.

In Nordhordland, the incidence rate of meningococcal disease dropped from 180 to 30 per 100000 per

year in the student population after the intervention, but increased from 0 to 13 per 100000 per year in the rest of the population (Table 4). The incidence rate in the student population before and after the intervention was not significantly different ($\chi^2_{mc} = 2{\cdot}3$ and $P = 0{\cdot}1$). The incidence rate in the rest population of Nordhordland before and after the intervention was significantly different ($\chi^2_{mc} = 11{\cdot}1$ and $P < 0{\cdot}001$).

In the follow-up study 2 years later (1998), 132 (19·2%) of the 680 students examined were meningococcal carriers, 27 (4·0%) carried SR meningococci but none carried SR serogroup C meningococci. Twelve (1·7%) carried NG:15 strains, of whom four carried the outbreak strain, as identified by DNA fingerprinting. Three of these isolates were NG:15:P1.7,16 and one was NG:15:P1.7 (Table 2).

DISCUSSION

A new C:15:P1.7,16 meningococcal strain caused an outbreak of meningococcal disease, initially geographically localized to the Nordhordland area in western Norway. From September 1995 to April 1998, 22 cases with systemic meningococcal disease occurred in Nordhordland and the surrounding areas (Fig. 1, Table 1). In contrast, only two patients had been hospitalized with such disease from Nordhordland in the preceding 5 years. The new C:15:P1.7,16 outbreak strain caused 15 of the 22 notified cases, and serogroup B meningococci caused 6. Since 1974 the majority of meningococcal disease in Norway has been caused by serogroup B strains, but the proportion of serogroup C strains has increased in the last decade in common with the situation in Europe and in North America [2–5, 11–13]. Serogroup B meningococci mainly cause sporadic cases, whereas serogroup C meningococci often cause outbreaks and associated cases, as observed here [11].

The outbreak strain C:15:P1.7,16 has evolved from the typical Norwegian epidemic SR serogroup B clone; B:15:P1.7,16 [5], but has acquired the serogroup C capsule. Of note, the Norwegian B clone has been unusual in causing a high incidence among teenagers [1], and the first 7 patients in this outbreak were aged 15–21 years. Accordingly, the control measures including information, vaccination and meningococcal carriage eradication were aimed primarily at the student population, as well as young children and close contacts of patients.

The reason for this outbreak is not clear. It may have been due to a new highly epidemic meningococcal strain. None of the patients complained about symptoms of any other infectious disease prior to the onset of their meningococcal disease. However, compared with the low incidence in the preceding years, the seven patients whose disease was caused by other strains, could indicate involvement of some infectious co-factor (Table 1) [14].

Of the 1400 students in the local high schools in Nordhordland, 1120 (80%) volunteered for tonsillopharyngeal swabbing in 1996. Meningococcal isolates were initially characterized by sulphonamide susceptibility and serogrouping. These tests were applied because they are readily available and of low cost. Results are available within 2–3 days after swabbing, enabling early specific therapy. However, the sensitivity of the methods may be hampered by three main problems. Firstly, single swabbings do not detect all carriers [15–17]. By the follow-up swabbing after 6 weeks, meningococci were isolated from 34 of 53 untreated meningococcal carriers, and from 7 of 60 previous non-carriers. These figures may reflect a natural variation of carriage or in part be due to limited sensitivity of one single swabbing. Secondly, the study was not designed to identify multiple strain carriers, as mainly single colonies among morphological similar colonies were selected for further characterization. Four double strain carriers were identified. Thirdly, serogrouping by agglutination is more difficult to perform on carrier isolates than on systemic isolates, probably due to less or no capsule material, as experienced here [2]. Further characterization of the carrier isolates confirmed that 14 of the 20 treated students harboured the outbreak strain, and only 6 carriers of other strains were given treatment. Thus, the simple routine methods chosen identified all proven carriers with the serogroupable outbreak strain, which was in line with the aims of our study.

The outbreak strain seemed to differ only by serogroup from the prevailing Norwegian epidemic strain B:15:P1.7,16 [5], which could imply that this new strain was due to a capsule switch of this strain [18]. Further characterization revealed that the outbreak strain belonged to the ET5-complex, but that it differed by one or more fragments of 3–10 kbp in size from other ET5-complex strains, including the B:15:P1.7,16 strain and two previously identified C:15:P1.7,16 strains (data not shown). This property was subsequently used to identify the outbreak variant among the C:15-carrier strains and the non-groupable

carrier strains sharing one or more serotype or serosubtype epitopes with the outbreak strain.

Of 39 NG:15 strains, 21 were genetically identical to the outbreak strain. Though non-groupable strains are often thought of as non-pathogenic, they may change into capsulated variants and cause disease [13]. In contrast to the strategy of another recent study [19], carriers of non-groupable strains were not treated with ofloxacin, because such strains may represent an important source for induction of immunity against meningococci in carriers [20], and because the capsular on-off mechanisms are poorly understood and documented. More knowledge about these mechanisms is necessary for a clearer understanding of the epidemiology of meningococcal disease and for future intervention strategies.

Antibiotic eradication of meningococcal carriage has been generally eschewed in Norway, in part due to fear of development of resistant bacteria [6]. Furthermore, since 1974, the majority of meningococcal disease caused by both serogroup B and C meningococci, has been sporadic [3, 4]. Tracing and treating meningococcal carriage has therefore not been recommended in the national guidelines for follow up of single meningococcal patients [21]. However, Kristiansen and colleagues have proposed an alternative follow-up strategy, including selection of the disease causing strains by RFLP and treatment of carriers of these strains, among contacts of all patients [22]. This strategy is considered laborious and expensive and the impact on the overall epidemiological situation is unclear [7]. According to the national guidelines, selective carriage eradication should only be performed in outbreak situations with associated patients, as reported here [4, 21].

Ofloxacin was chosen for eradication of meningococcal carriage because it has been shown to be highly effective. In a previous meningococcal outbreak in a college in western Norway, all meningococcal carriers were treated with ofloxacin. Ofloxacin eradiated the initial isolates in 97·2% of the carriers for 33 days, the carriage rate of meningococci was consequently reduced from 21·4% to 3·7%, and no further cases occurred in the student population [23]. Furthermore, in an unpublished study of 15 meningococcal carriers, we isolated no meningococci 1–2 h after administration of ofloxacin. However, ofloxacin is not recommended for use in children.

Mass vaccination with a meningococcal polysaccharide A+C vaccine was performed concomitantly with selective carriage eradication. Vaccination was aimed at 2–5-year-old children and 13–21-year-old adolescents, since about 70% of all meningococcal disease in Norway occur within these age groups [1–4]. Children aged 6–12 years have had low incidence of meningococcal disease in Norway, and were therefore not offered the vaccine. Vaccination compliance was high in children and young teenagers, but low in the most affected age group (16–21-year-olds). The proportion of non-students was 25% in this age group, which may have contributed to this effect.

Due to selective carriage eradication and due to methodological problems, as discussed, probably only a proportion of all carriage of the outbreak clone in the Nordhordland population was eradicated by our interventions. Therefore, it is not surprising that outbreak-clone cases did not come to a complete halt. Subsequently, 14 additional cases of meningococcal disease (2–75-year-old) occurred, of which 8 were caused by the outbreak strain (Fig. 1, Table 1). One 3-year-old child fell ill 10 months after vaccination, which was considered as a vaccine failure. It is known that the meningococcal A+C polysaccharide vaccine does not generally induce a long-lasting immunity in children under 3 years of age, especially against serogroup C meningococci [24]. Despite the low vaccination coverage in the 16–21 years age group, the outbreak strain caused only one additional case in this group; a student who had refused both swabbing and vaccination. This suggested that carriage eradication of the outbreak strain in this population contributed to reduced transmission and disease in this initially most affected age group.

During the period 1996–8, meningococcal A+C polysaccharide vaccine has been given to children reaching the age of 2 and to all new students attending the junior high schools in Nordhordland. In the follow-up carrier study in 1998, the serogroupable outbreak strain was not isolated from any of the participating students. However, 4 of 13 NG:15 meningococcal isolates were classified as being the outbreak strain, as evaluated by RFLP. Thus, the non-capsular variant of the disease-causing meningococcal clone was still present in the outbreak area Nordhordland in 1998. However, no meningococcal disease case has occurred in Nordhordland since February 1997. The outbreak strain has not been isolated from any patients in Norway since April 1998.

Local outbreaks of meningococcal disease are very unpredictable; they may wane rapidly or they may

last in localized areas as in the Stroud area in Gloucestershire [25]. It is therefore not possible to evaluate precisely the impact of carriage eradication and vaccination on the source of this outbreak. However, after the intervention the incidence rate dropped markedly in the student population, and the new cases occurred mainly in different age groups than those targeted. In similar outbreaks, selective carriage eradication and vaccination should be considered, in order to limit the spread of the pathogenic strain and to reduce the use of antibiotics [26]. Simple routine methods can be used for tracing carriers. Household contacts and close contacts of patients should still be the main target groups for intervention.

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REFERENCES

1. Bøvre K., Gedde-Dahl TW. Epidemiological patterns of meningococcal disease in Norway 1975–1979. NIPH Ann 1980: **3**: 9–22.
2. Bøvre K. Meningococcal disease in Norway. Antonie van Leeuwenhoek 1985; **52**: 208–12.
3. Lystad A, Aasen S. The epidemiology of meningococcal disease in Norway 1974–91. NIPH Ann 1991; **14**: 57–66.
4. Iversen BG, Aavitsland P. Meningococcal disease in Norway 1992–1995. Epidemiology and fatality. Scand J Infect Dis 1996; **28**: 253–9.
5. Bøvre K, Frøholm LO, Gaustad P, Holten E, Høiby EA. Some agent characteristics and their coexistence related to occurrence and severity of systemic meningococcal disease in Norway, winter 1981–82. NIPH Ann 1983; **6**: 75–84.
6. Jones DM. Control of meningococcal disease. BMJ 1989; **298**: 542–3.
7. Caugant DA, Høiby EA, Magnus P, Eng J, Frøholm LO. Asymptomatic carriage of *Neisseria meningitidis* in a randomly sampled population. J Clin Microbiol 1994; **32**: 323–30.
8. Sánchez ML, Jones RN. E-test, an antimicrobial susceptibility testing method with broad clinical and epidemiological application. Antimicrobic Newsl 1993; **8**: 1–8.
9. Wedege E, Høiby EA, Rosenqvist E, Frøholm LO. Serotyping and subtyping of *Neisseria meningitidis* isolates by co-agglutination, dot-blotting and ELISA. J Med Microbiol 1990; **31**: 195–201.
10. Caugant DA, Sandven P, Eng J, Jeque JT, Tønjum T. Detection of rifampicin resistance among isolates of *Mycobacterium tuberculosis* from Mozambique. Microbiol Drug Resist 1995; **1**: 321–6.
11. Cartwright K. Meningococcal carriage and disease. In: Cartwright K, ed. Meningococcal disease. New York: John Wiley & Sons, 1995: 115–46.
12. Jackson LA, Schuchat A, Reeves MW, Wenger JD. Serogroup C meningococcal outbreaks in the United States. An emerging threat. JAMA 1995; **273**: 383–9.
13. Whalen CM, Hockin JC, Ryan A, Ashton F. The changing epidemiology of invasive meningococcal disease in Canada, 1985 through 1992. JAMA 1995; **273**: 391–4.
14. Moore PS, Hierholzer J, Dewitt W, et al. Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. JAMA 1990; **264**: 1271–5.
15. Pether JVS, Lightfoot NF, Scott RJD, Morgan J. Carriage of *Neisseria meningitidis*: investigations in a military establishment. Epidemiol Infect 1988; **101**: 21–42.
16. Cartwright KAV, Stuart JM, Jones DM, Noah ND. The Stonehouse survey: nasopharyngeal carriage of meningococci and *Neisseria lactamica*. Epidemiol Infect 1987; **99**: 591–601.
17. Olcen P, Kjellander J, Danielsson D, et al. Culture diagnosis of meningococcal carriers: yield from different sites and influence of storage in transport medium. J Clin Pathol 1979; **32**: 1222–5.
18. Swartley JS, Marfin AA, Edupuganti S, et al. Capsule switching of *Neisseria meningitidis*. Proc Natl Acad Sci USA 1997; **94**: 277–82.
19. Bevanger L, Bergh K, Gisnås G, Caugant DA, Frøholm LO. Identification of nasopharyngeal carriage of an outbreak strain of *Neisseria meningitidis* by pulsed-field gel electrophoresis *versus* phenotypic methods. J Med Microbiol 1998; **47**: 993–8.
20. Reller LB, Mac Gregor RR, Beaty HN. Bactericidal antibody after colonization with *neisseria meningitidis*. J Infect Dis 1973; **127**: 56–62.
21. Lystad A. Principles and practice of control of meningococcal disease in Norway. NIPH Ann 1980; **3**: 103–7.
22. Kristiansen BE, Jenkins A. Preventing the spread of meningococcal infection: strategies for chemoprophylaxis. Dis Manage Health Outcomes 1997; **1**: 230–40.
23. Gilja OH, Halstensen A, Digranes A, Mylvaganam H,

Aksnes A, Høiby EA. Use of single-dose ofloxacin to eradicate tonsillopharyngeal carriage of *Neisseria meningitidis*. Antimicrob Agents Chemother 1993, **37**: 2024–6.
24. Zollinger WD. New and improved vaccines against meningococcal disease. In: New generation vaccines. New York: Marcel Decker Inc, 1997: 469–89.
25. Cartwright KAV, Stuart JM, Noah D. An outbreak of meningococcal disease in Gloucestershire. Lancet 1986; **ii**: 558–61.
26. Begg N. Outbreak management. In: Cartwright K, ed. Meningococcal disease. Chichester: John Wiley & Sons, 1995: 285–305.